MAKERERE  UNIVERSITY

OPTIMIZING HIV VIROLOGIC OUTCOMES FOR PREGNANT AND BREASTFEEDING WOMEN AND INFANT TESTING COVERAGE IN SOUTH WESTERN UGANDA

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Dissertation submitted in partial fulfillment of the requirements for the award of the degree of Doctor of Philosophy (PhD) in Health Sciences of Makerere University

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DECLARATION

I, Jane Kabami, hereby declare that the work presented in this dissertation has not been presented for any other degree in any university.

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DEDICATION

I dedicate this book to my beloved husband, Dr Peter Ssebutinde and children: Blessed, Anne Shalom, Shiloh and Emmanuel; My Parents, Mr Ruhamyankaka Donati (RIP) and Beatrice Nyiragatanzi; and my siblings: Sylvia Mugisha, Stavia Natukunda, Lydia Mutesi, Margret Mukanoheri, Emmanuel Ruhamyankaka, Stella Kabageni and Immaculate Kambabazi. Your unconditional love, prayers, and encouragement have been my strength throughout this journey.

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OPERATIONAL DEFINITIONS

Adherence	Defined as how closely the study participants followed their prescribed treatment plan by self-report at the routine clinic visit. It was classified as "adherent" if their record indicated missing ≤ 1 dose of ART per month, as "non-adherent" if their record indicated missing ≥ 2doses of ART per month, and as "unknown" if their record was missing adherence data
Antenatal care	The healthcare and support given to a pregnant woman by healthcare professionals during pregnancy to ensure both the mother and baby are healthy and also prepare for childbirth.
Breastfeeding	This is feeding a baby /infant directly from a woman's breast.
Disclosure	Defined as "participants sharing their HIV status with another person they trust".
Early infant testing - EID	Refers to both the DNA PCR testing of HIV Exposed infants within the first weeks of life to identify early HIV infection, enabling timely access to ART, and includes the final 18-month antibody HIV testing
Mother	A woman who gives birth to, breastfeeds, or takes care of a child from birth to 18months
Perinatal transmission	Transmission that occurs when a pregnant woman with HIV passes the virus to their baby during pregnancy, childbirth or breastfeeding.
POC Viral load testing	Testing was done using the GeneXpert machines at the facilities or near the facilities at the hubs.

Post-natal care	The healthcare and support given to mothers and their newborns in the period following childbirth and typically lasts about 6-8 weeks after delivery.
Pregnancy	The period when a fetus develops inside a woman's uterus and typically lasts around 40 weeks from the 1st day of the last menstrual period.
Reproductive age	The reproductive age for women in this study is between 15 - 45 years of age.
Viral suppression	Defined as HIV viral load results less than 1000 copies/mL
Viral non-suppression	Defined as HIV viral load results greater than 1000 copies/mL

LIST OF ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ANC	Antenatal Care
BL	Baseline testing
CI	Confidence Interval
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPHL	Central Public Health Laboratories
DNA	Deoxyribonucleic acid
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EID	Early Infant Diagnosis
ENHANCED-SPS	Enhanced viral load counseling and Standardized Peer mother Support
eMTCT	Elimination of mother-to-child transmission of HIV
FGD	Focus Group Discussion
HAART	Highly active Antiretroviral Therapy
HEI	HIV exposed infant
HIV	Human Immunodeficiency Virus
HSDP	Health Sector Development Plan
IDI	In-depth interview
MoH	Ministry of Health
MTCT	Mother-to-child transmission of HIV
PCR	Polymerase Chain Reaction

PLHIV	People Living with HIV
PMTCT	Prevention of mother-to-child transmission of HIV
PNC	Postnatal care
RNA	Ribonucleic acid
SD	Standard Deviation
SEARCH	Sustainable East African Research in Community Health
SSA	Sub-Saharan Africa
TDF	Theoretical Domain Framework
TMLE	Targeted Minimum Loss-based Estimation
UNAIDS	The Joint United Nations Program on HIV/AIDS
UNCST	Uganda National Council of Science and Technology
UPHIA	Uganda Population-Based HIV Impact Assessment
UTT	Universal test and treat
VHT	Village Health Team
VL	Viral Load
VS	Viral suppression
WHO	World Health Organization
WLHIV	Women living with HIV

ABSTRACT

Background: Achieving viral suppression among pregnant and breastfeeding women is critical for eliminating vertical transmission of HIV in Sub-Saharan Africa. Adherence to antiretroviral therapy (ART) and disclosure of HIV status are key determinants of viral suppression and play a crucial role in preventing perinatal HIV transmission. However, multiple barriers—including stigma, limited knowledge, and restricted healthcare access—impede these efforts. Peer-led counseling interventions offer a promising approach to improving maternal ART adherence, promoting HIV status disclosure, and enhancing early infant diagnosis by equipping mothers with the knowledge and skills necessary to prevent perinatal HIV transmission. Understanding maternal perceptions of viral suppression is essential for implementing effective strategies to eliminate Vertical transmission of HIV.

Objective: To evaluate the effect of the Enhanced Viral Load Counseling and Standardized Peer-Mother Support (ENHANCED-SPS) intervention on viral suppression among pregnant and breastfeeding women living with HIV in rural Uganda, and assess whether peer-led support enhances completion of infant HIV testing.

Methods: This was an Implementation Science Research study that utilized a before-and-after cluster randomized trial design conducted in two phases. In phase one, we determined the prevalence of viral suppression and identified motivators and barriers to viral suppression among pregnant and postpartum women using retrospective data from the SEARCH trial. Additionally, we examined facility- and community-level barriers and facilitators of viral suppression among women of reproductive age in southwestern Uganda. Based on these findings, we employed the PRECEDE model of health promotion to design the ENHANCED-SPS intervention, which

included enhanced viral load counseling and standardized peer-mother support to address structural barriers and specific needs of the target population.

In phase two, we evaluated the ENHANCED-SPS intervention's impact on viral suppression (primary outcome) and secondary outcomes, including ART adherence, HIV status disclosure, and infant HIV testing. A cluster-randomized trial (NCT04122144) was conducted from September 2019 to October 2021 in 14 high-HIV-prevalence public facilities in rural southwestern Uganda, randomized 1:1 to intervention or standard care. Guided by the PRECEDE model, the intervention included: (1) provider training on viral load counseling (predisposing), (2) standardized peer-mother support with bi-weekly phone counseling (enabling), and (3) point-of-care viral load monitoring with provider-peer feedback (reinforcing). Participants received adherence assessments and tailored plans to address ART and infant testing barriers. Outcomes were analyzed using TMLE to account for missing data, repeated measures, and clustering. Secondary outcomes included ART adherence (≤1 missed dose/month), HIV disclosure, and infant HIV testing (via medical record review). A qualitative sub-study explored women's perceptions of viral suppression using transcribed, coded interviews in Dedoose.

Results: <u>In phase one of the study</u>, among enumerated participants at baseline, HIV testing among 15–45-year-old women was high at 92% and 93% with similar HIV prevalence of 12.6% and 12.3%, in intervention and control communities, retrospectively. Among women living with HIV, with a history of pregnancy/live birth, viral suppression was 42% and 44% at baseline, and 81% and 76% (p=0.002) at year 3, respectively. Overall, by year 3, the intervention communities achieved significantly higher viral suppression (77%) compared to controls (68%, p<0.001) among all 15-45-year-old women living with HIV. Pregnancy/live birth was a predictor of year-3 VS in

control (p=0.016) but not intervention (p=0.43). Younger age was a risk factor for non-suppression in both arms.

In Phase two of the study, a total of 505 pregnant and postpartum women were enrolled between September 2019 and October 2020. The median age was 28 years; 96% were pregnant, 69% had been previously diagnosed with HIV, and 70.0% (95% CI: 65.9–74.1%) were virally suppressed at baseline. After 12 months, viral suppression increased to 94.9% (95% CI: 92.5–97.4%), representing an absolute increase of 24.9% (95% CI: 21.6–28.2%; $p < 0.001$). The intervention yielded significant improvements in viral suppression across all age groups, among both pregnant and postpartum women, and within strata defined by care status and duration of ART use. Despite a 58.9% (95%CI: 27.4-90.3%) improvement from baseline, viral suppression among post-partum women at 12 months was only 75.7%.

ART adherence improved from 68% (95% CI: 62–74%) at baseline to 93% (95% CI: 81–100%) at 12 months, a 25% increase (95% CI: 9–40%; $p = 0.009$), with the largest gains seen in participants aged 15–24 years, those breastfeeding, or those not virally suppressed at enrollment. HIV status disclosure increased from 80% (95% CI: 69–90%) at baseline to 94% (95% CI: 89–99%) after 12 months, a 14% improvement (95% CI: 8–21%; $p = 0.003$); similar trends were observed for disclosure to a spouse or partner.

Among 464 children (234 in the intervention and 230 in the control arm) born to study participants, final HIV testing (antibody rapid test at 18 months) was completed in 94.5% (95% CI: 91.6–97.5%) of cases in the intervention group versus 83.3% (95% CI: 78.4–88.3%) in the control group, yielding an 11.2% difference (95% CI: 5.4–17.0%; $p < 0.001$). While there were no significant differences in the proportions completing the 1st (4–6 weeks) or 2nd (9 months) tests, the 3rd test

(6 weeks post-breastfeeding cessation) was completed at a rate 14.8% (95% CI: 7.9–21.8%; $p < 0.001$) higher in the intervention arm.

In a qualitative sub-study, women living with HIV described viral suppression in the context of achieving good health and ensuring HIV-free infants. They emphasized that adherence to ART was key to attaining viral suppression and noted that engagement with healthcare providers was crucial, despite experiencing barriers such as anticipated stigma, challenges with HIV status disclosure, pregnancy-related distress, and long distances to health facilities.

Conclusion: The multi-component, peer-led ENHANCED-SPS intervention significantly improved viral suppression, ART adherence, and HIV status disclosure among pregnant and postpartum women. The intervention also increased infant HIV testing completion rates, facilitating early diagnosis and timely linkage to care. Despite these successes, viral suppression among breastfeeding women remained suboptimal (75.7%), underscoring the need for additional postpartum interventions. The findings emphasize the importance of culturally sensitive viral suppression education, adherence support, and non-judgmental healthcare environments to enhance maternal and infant health outcomes in HIV care programs.

CHAPTER ONE: INTRODUCTION

1.1.Background

1.1.1. Overview of the burden of HIV

HIV remains a significant public health challenge, with over 39.9 million people living with HIV (PLHIV) globally (1). Sub-Saharan Africa continues to bear the heaviest burden, accounting for nearly two-thirds of global HIV infections. While advancements in antiretroviral therapy (ART) have dramatically reduced HIV-related mortality and improved the quality of life for many individuals, there are still significant challenges, particularly in low- and middle-income countries, where access to treatment can be limited (2, 3). While global new HIV infections have also decreased in recent years, an estimated 1.3 million people were newly infected in 2023, of which 120,000 were among children. Many countries are struggling to meet the targets set by UNAIDS to end the epidemic by 2030 (1, 4). This burden is compounded by the continued challenges in addressing vertical transmission of HIV, as well as rising rates of HIV among young people, particularly in Africa (5). The lack of comprehensive prevention programs for the key and priority populations at risk of HIV, combined with social and economic disparities, means that the fight against HIV is ongoing and demands sustained efforts in prevention and care (6, 7).

The adult HIV prevalence in Uganda remains high at 5.8%, higher among women (7.2%) compared to men (4.3%). This persistent high prevalence is influenced by several factors, including limited access to preventive services for high-risk groups, social stigma, and inadequate awareness of HIV prevention methods (8, 9). Additionally, the significant progress made in expanding access to effective HIV treatment and care has allowed people living with HIV (PLHIV) to live longer, healthier lives (10, 11). However, specific populations such as pregnant and postpartum women and girls (12), men (13-15), and key populations like sex workers continue to

experience disproportionately high rates of infection (8, 16, 17), compared to the general population, due to significant barriers to HIV prevention and treatment. Improving access to HIV testing and sero-status awareness is essential for providing timely and effective HIV prevention, treatment, and care (18).

1.1.2. Global burden of vertical transmission of HIV

In 2023, an estimated 1.3 million pregnant women were living with HIV globally. Approximately 90% of these women live in sub-Saharan Africa (1, 19, 20). Vertical transmission of HIV accounts for the vast majority of the 1.4 million children living with HIV under the age of 15 years, with almost 90% of these children living in sub-Saharan Africa. In 2023, an estimated 57% of all children living with HIV were receiving ART, and 76,000 children under 15 years of age died of AIDS-related causes, declining from 110,000 deaths in 2017 (1, 21-23).

Despite the increase in effective methods to prevent vertical transmission of human immunodeficiency virus type 1 (HIV-1), there were still an estimated 120,000 new pediatric HIV-1 infections in 2023, and over 85% of all the new infections occurred in Sub-Saharan Africa. More than half of these new infections occur after the first six weeks of life during the breastfeeding period (22, 24-26), the majority of whom are not tested until it is too late for optimal antiretroviral therapy (ART) (27). Infants acquiring HIV during pregnancy, delivery, or early postpartum often die before they are recognized as having HIV infection (28).

1.1.3. Eliminating new HIV infections among children

The 2016 World Health Organization (WHO) Consolidated Guidelines on antiretroviral drugs (ARVs) recommend highly active antiretroviral therapy (HAART) for all pregnant and breastfeeding women living with HIV and encourage lifelong ART, thereby improving women's health and reducing transmission to their children and partners (29). All mothers and infants living

with HIV should be started on ART as recommended by the PMTCT guidelines (20, 30). PMTCT coverage for Sub-Saharan African countries in 2023 was reported at 80% which is far short of the 95% global target (1, 31, 32). For effective treatment outcomes, both the mother and the infant should receive ART coupled with other interventions that translate into optimal viral suppression. It is important to note that high maternal viral load (mVL) at the time of delivery remains the major risk factor for vertical transmission of HIV(33, 34).

Optimal viral load suppression in elimination of vertical transmission programs has not been totally achieved due to barriers of viral load monitoring, lack of knowledge about the importance of viral suppression, non-adherence to ART, poor retention in care and follow-up of the mother and infant pair within the prevention of vertical HIV transmission cascade (22, 33, 35). Additionally, many current programs fail to reach mothers who acquire HIV during pregnancy, the postpartum period, or while breastfeeding. Some women are also reluctant to initiate or adhere to antiretroviral therapy (ART) (36-38). To note, the rate of perinatal transmission is significantly higher among women who acquire HIV during pregnancy and postpartum than among those who acquire HIV before pregnancy and is likely related to the high viral loads in plasma and breast milk during acute infection (39).

1.1.4. Importance of viral load monitoring and suppression in pregnancy and breastfeeding

Viral load monitoring during pregnancy is essential for evaluating ART adherence, detecting drug resistance, and assessing the risk of vertical transmission (40, 41). Maintaining an undetectable viral load (<1000 copies/ml) is crucial, but challenges such as cultural and social barriers may hinder suppression (42, 43). In Uganda, newly diagnosed pregnant women start ART immediately, with viral load tested after six months. If viral load is detectable but <1000 copies/ml, adherence support is provided, and testing continues annually. If >1000 copies/ml, VL testing is

recommended after 3months of intensive adherence counseling and ART is adjusted if resistance is found. For women already on ART, viral load is tested at the first antenatal visit. However, routine viral load (VL) monitoring programs face challenges of inadequate coverage, delays in sample collection, testing, and return of VL results; high cost; and low quality of VL testing, which are likely to increase with scale-up of VL testing and ART use (44). Many pregnant women, particularly those newly diagnosed, fail to undergo viral load testing (45). Various factors contribute to persistent maternal viremia, including late ANC engagement, poor adherence, and factors like ethnicity, drug abuse, and low education levels (46, 47).

Studies on viral suppression in pregnancy are challenging to compare due to varying test methods and detection limits. Thus, timely viral load monitoring during pregnancy and close to delivery is critical to ensure effective suppression (48, 49). In Uganda, viral suppression among pregnant and breastfeeding women has remained suboptimal and ranges between 68%-85%, highlighting the gap in utilization of HIV treatment services (8, 9, 30, 50, 51). Viral suppression rates during pregnancy and at delivery are lower than in non-pregnant women in Africa, and in some groups can be as low as 40% among women actively on ART. A detectable VL in a pregnant woman is a medical emergency that requires immediate concerted action to suppress the VL and minimize the risk of mother-to-child transmission. The time to achieve viral suppression varies by VL at treatment initiation (52).

In a study from South Africa, in pregnant women with a median pre-ART VL of 10,000 copies/ml, the median time from ART initiation to VL <1000 copies/ml was 24 days, and to <50 copies/ml was 94 days (20). Factors associated with detectable VL at delivery included higher VL levels at ART initiation, <50% adherence to treatment, shorter duration of ART, and receipt of protease inhibitor (PI)-based regimens (53, 54). Current problems with VL ordering and slow turnaround

times are placing pregnant women at risk. We need augmentations to VL systems that can speed up VL processing, particularly for high-risk groups like pregnant HIV-positive women(24). Offering point-of-care viral load testing could mitigate most of the challenges to viral load monitoring, which is the question addressed in our study.

1.1.5. Vertical HIV transmission prevention gap

Progress in the prevention of vertical transmission of HIV has been substantial. In 2016, the WHO implemented option B+, which recommended lifelong antiretroviral therapy (ART) to all pregnant and post-partum women with HIV, and the current test-and-treat approach recommends ART to all persons with HIV (55-57). The coverage of vertical transmission prevention programs increased from 29% in 2010 to 53% in 2022, but ART coverage among pregnant and breastfeeding women with HIV stagnated at 82% and viral suppression levelled off to slightly over 80% (39, 58-60).
In 2023, 84% of pregnant women living with HIV were receiving ART, a significant increase from 2010 levels when only 55% had access (1, 29). Treatment drop-out rates among women who are pregnant and breastfeeding remain high, estimated above 30%, leading to increased risk of transmission to their children. Eighty-five percent of all new HIV infections among children occurred in sub-Saharan Africa (21, 26, 36). As the risk of HIV transmission in pregnancy and delivery drops, transmission among children is increasingly concentrated in the breastfeeding period (25). Despite the increase in the availability of antiretroviral therapy between 2010 and 2016, coverage during pregnancy and lactation remained 80% way below the global average of 95%, contributing to low levels of viral suppression (27).

Women of childbearing age continue to be disproportionately affected by HIV, and a significant number of pregnant and post-partum women do not receive ART during the pregnancy and post-partum period (57, 61, 62), which increases risks of viral non-suppression, pediatric infections,

and poor maternal health outcomes (58, 63). In Uganda, viral suppression among pregnant and breastfeeding women has remained suboptimal below the UNAIDS 95-95-95 targets and ranges between 68%-80%, highlighting the gap in utilization of HIV treatment services (9, 50, 64, 65). Barriers to viral suppression include health system challenges (staff shortages, delayed viral load results) and structural factors (transport difficulties), which particularly affect women in the perinatal period (66).

Pregnancy presents unique challenges and vulnerabilities for women. For example, fear and stigma of a new HIV diagnosis during pregnancy may affect care engagement and result in challenging disclosure to partners, family, and friends; reliability of ART access, psychosocial factors such as stigma and discrimination, as well as ART adherence influencing viral suppression(67). The rate of perinatal transmission is significantly higher among women who acquire HIV during pregnancy than among those who acquire HIV before pregnancy and is likely related to the high viral loads in plasma and breast milk during acute infection (39).

In addition, pregnant women living with HIV also face multiple barriers related to pregnancy and HIV infection, including reliability of ART access, psychosocial factors such as stigma and discrimination as well as ART adherence influencing viral suppression (67). However, comprehensive HIV treatment services for women of reproductive age can improve treatment coverage and viral suppression (30). In Uganda, comprehensive services for preventing vertical transmission services including early enrolment into HIV care and adherence counselling, have contributed to a remarkable reduction in final vertical transmission of HIV from 20% in 2000 to 3% in 2021 (24, 68). However, there has been a significant increase in vertical transmission over the past 2 years to 5% vertically transmitted infections in 2023. Thus, a lot of work remains to be done in order to achieve the target of zero new infections in children by 2030 (30, 55, 58).

Support and counseling from peers are crucial to addressing barriers to services for preventing vertical HIV transmission in Sub-Saharan Africa (24, 69, 70). Use of community health workers has previously been recommended to increase awareness of viral load status as well as male partner engagement for safe disclosure and optimal ART adherence (27, 70). In particular, peer-mothers, who are lay women with HIV and trained to offer counseling and education on HIV prevention and treatment for pregnant women or mothers with HIV, have been increasingly incorporated in antenatal and postnatal clinics (71, 72).

Peer support and counseling are increasingly being integrated in prevention of vertical transmission programs and have been reported to be crucial in addressing both the global and regional gaps in achieving viral suppression among women on ART (24, 69). Structured peer support initiatives that emphasize increased awareness of viral load status and male partner engagement for safe disclosure have been recommended to optimize virologic outcomes and reduce vertical transmission (27). In addition, mhealth interventions have enhanced health-care service delivery through phone counseling, appointment reminders, and helping to address barriers to adherence and care engagement (73). However, the impact and implementation of these interventions on these outcomes and their generalizability to various settings have not been rigorously evaluated. There is an urgent need to develop and evaluate interventions that combine peer support and mhealth to optimize viral suppression among pregnant and post-partum women with HIV and to progress towards zero new infections in children.

1.2. PROBLEM STATEMENT

Despite substantial progress in expanding antiretroviral therapy (ART) coverage under Uganda's option B+ and the HIV test and treat policy, viral non-suppression remains a critical barrier to eliminating vertical HIV transmission (34, 39, 74). In some settings, viral suppression rates during

pregnancy can be as low as 68% among women on ART, making a detectable viral load during pregnancy a medical emergency that demands immediate action (29, 75). Achieving and maintaining a suppressed viral load (<1,000 copies/mL) during pregnancy and breastfeeding is essential for both maternal health and for the prevention of vertical transmission of HIV (10).

Nearly 90% of pediatric HIV infections occur through vertical transmission during pregnancy, delivery, or breastfeeding, despite the increase in effective methods to prevent vertical transmission (76). In 2023, an estimated 4,700 new pediatric HIV-1 infections were reported, down from 5,700 in 2019, with 49% attributed to mothers who initiated ART but later defaulted or disengaged from care (75). More than half of these new infections occur after the first six weeks of life during the breastfeeding period (22, 24-26), and often die before they are recognized as having HIV infection (28).

In Uganda, between 15%-30% pregnant and breastfeeding women fail to achieve or sustain viral suppression (≥1,000 copies/mL) by delivery or during breastfeeding, undermining Uganda's goals for prevention of vertical transmission of HIV and the global 95-95-95 targets (8). Factors associated with non-suppression include non-disclosure of HIV status, depressive symptoms, and health-system barriers such as stock-outs and limited viral-load counselling and follow-up in rural settings (47, 64). Other studies report that while 85.7% of pregnant women may achieve viral suppression, only 52.4% have a viral load measurement 12 months after initiating ART, falling short of UNAIDS targets (51, 64). Persistent viremia during pregnancy and breastfeeding continues to undermine the progress made in preventing vertical HIV transmission(25, 74, 77). Consequently, vertical transmission rates in Uganda remain high, with estimates of 5700 new infections in 2019 and 4700 new vertical transmission infections in 2023, far from the zero-infection goal. Approximately 84% of new pediatric infections are linked to seroconversion during

late pregnancy, breastfeeding, or treatment abandonment, with 56% occurring during the breastfeeding period vs 44% during pregnancy (75).

Although the uptake of lifelong ART for prevention of vertical transmission is relatively high, it still falls short of the 95% target, and suboptimal adherence remains a major concern, with 15-20% of mothers on ART not achieving viral suppression (31, 33, 77). The current Uganda consolidated guidelines on prevention and treatment of HIV advocate for a comprehensive approach to the elimination of vertical transmission aligned with the UNAIDS 95-95-95 targets, including counseling on viral load testing and monitoring. However, these guidelines have not sufficiently emphasized the utilization of viral load results and the feedback provided to patients. Reported challenges include a lack of knowledge about viral loads, poor adherence, loss to follow-up, poor retention, and insufficient support for HIV status disclosure (22, 24, 33). These challenges contribute to the suboptimal viral suppression among pregnant and breastfeeding women and perpetuate vertical HIV transmission, representing a significant missed opportunity to safeguard the health of women living with HIV and their children. (19, 64). However, the extent of these missed opportunities has also not been quantified, limiting targeted intervention efforts.

Thus, addressing viral non-suppression requires strategies to improve disclosure of HIV status, ART adherence, and retention. Peer support models – notably *peer mother* programs – have shown great promise in this regard. Evidence suggests that peer support and counseling play a crucial role in improving disclosure of HIV status, spousal support, ART adherence, and health provider motivation and awareness (78). Peer mother programs in countries like Uganda have led to lower vertical transmission rates and improved ART adherence. When well-integrated with training and support, these programs provide culturally appropriate education, psychosocial support, and linkage to care, thus improving maternal retention and engagement (79). Structured peer support

initiatives that promote viral load awareness and male partner engagement have been further recommended to enhance maternal and infant outcomes (27). Additionally, mHealth tools like phone counseling and appointment reminders help overcome barriers to care and support service delivery (73).

However, the impact and implementation of these interventions on these outcomes and their generalizability to various settings have not been rigorously evaluated. There is an urgent need to develop and evaluate interventions that combine peer support and mhealth to optimize viral suppression among pregnant and post-partum women with HIV and to progress towards zero new infections in children. This study evaluated the effect of a multi-component intervention of **E**nhanced viral load counseling and **S**tandardized **P**eer-Mother **S**upport (ENHANCED-SPS) on viral load suppression, ART adherence, retention in care, and early infant diagnosis (EID) testing rates in HIV clinics in South Western Uganda.

1.3. JUSTIFICATION

Despite the growing number of people on ART and with the rollout of test and treat in Uganda, there is still limited information on virologic non-suppression and its determinants among the pregnant and postpartum women, whose vulnerability is evident and the main risk factor for HIV infections in children (80). The goal of ART is to reduce the amount of the virus circulating in the mother's blood/viral load, which directly correlates with the risk of transmission to the infants during pregnancy, childbirth, and breastfeeding. The greatest challenge to achieving this goal in Uganda and globally, however, remains retaining mothers on ART, ensuring that they are virally suppressed and their HIV exposed babies receive appropriate testing and care throughout the breastfeeding period (81, 82).

The UNAIDS 2016 – 2021 strategy of Fast-Track to end AIDS prioritized the goal of zero new HIV infections among children, and ensuring mothers are alive and healthy as an essential step toward ending the HIV epidemic by 2030 (25, 29). In 2017, Uganda launched the fast-track initiative to end AIDS by 2030 and focused on consolidation of the progress made in the elimination of vertical transmission programs as its number 3 of the 5-point plan (83). However, Uganda has not yet achieved elimination of vertical transmission to date, with an estimated 4,700 new pediatric HIV infections in 2023 (5% of total new infections), down from 5,700 in 2019, majority from newly infected women (75, 84, 85). Therefore, there is a need to scale up initiatives that advocate for optimal viral suppression to achieve zero new infections in children.

This study evaluated the effect of a multicomponent intervention on viral suppression, incorporating both educational and structural strategies. The intervention aimed to optimize virologic outcomes among pregnant and breastfeeding women by enhancing their understanding of viral suppression and its role in vertical HIV transmission, promoting timely ART adherence, and strengthening the support systems (family and peers) surrounding them, which directly addresses the known barriers to viral suppression.

1.4. RESEARCH QUESTIONS

1. What is the prevalence and predictors of viral suppression among pregnant and breastfeeding women living with HIV among women of reproductive age living with HIV within the SEARCH trial in 32 communities, comparing intervention to control communities in Uganda and Kenya?
2. What is the effect of an enhanced VL counseling and standardized peer mother support (ENHANCED-SPS) intervention on viral suppression among pregnant and postpartum women at 14 public health clinics in Southwestern Uganda?

3. What is the effect of ENHANCED-SPS intervention on adherence to ART among pregnant and postpartum women among pregnant and postpartum women at 14 public health clinics in south western Uganda?

4. What is the effect of ENHANCED-SPS intervention on HIV status disclosure among pregnant and postpartum women among pregnant and postpartum women at 14 public health clinics in south western Uganda?

5. What are the barriers and facilitators to implementing enhanced VL counseling and peer mother support intervention?

6. What is the effect of ENHANCED-SPS intervention on EID among infants born to women living with HIV enrolled in the ENHANCED-SPS trial?

1.5. STUDY OBJECTIVES

1.5.1. General objective: To evaluate the effect of the Enhanced Viral Load Counseling and Standardized Peer-Mother Support (ENHANCED-SPS) intervention on viral suppression among pregnant and breastfeeding women living with HIV in south-western Uganda, and to assess whether peer-led support enhances completion of infant HIV testing.

1.5.2. Specific Objectives

Phase One:

Objective 1: To determine the prevalence and identify the predictors of viral suppression among pregnant and postpartum women living with HIV in 32 communities (comparing 16 intervention to 16 control communities) in the SEARCH trial in Southwestern and Eastern Uganda, and Western Kenya.

Phase Two:

Objective 2: To evaluate the effectiveness of an enhanced VL counseling and standardized peer mother support (ENHANCED-SPS) intervention on viral suppression among pregnant and breastfeeding women living with HIV presenting to care at 14 public health clinics in south-western Uganda.

Objective 3: To evaluate the effect of the ENHANCED-SPS intervention on ART adherence and HIV status disclosure at 12 months compared to SOC among pregnant and breastfeeding women living with HIV presenting to care at 14 public health clinics in south-western Uganda.

Objective 4: To evaluate the effect of the ENHANCED-SPS intervention on infant HIV testing at 18months after birth among infants born to women enrolled in the ENHANCED-SPS trial.

Objective 5: To conduct a qualitative evaluation of the facilitators and barriers of implementing the ENHANCED-SPS intervention.

1.6. STUDY HYPOTHESIS

Research Hypothesis: Objective 1

We hypothesized that viral suppression would be higher among pregnant/post-partum women in the SEARCH intervention arm compared to the control arm due to annual, population-wide testing with rapid linkage to streamlined HIV care.

Research Hypothesis: Objective 2&3

We hypothesized that enhanced viral load counseling and standardized peer mother support would increase viral load suppression by 15% among pregnant and post-partum women living with HIV,

increase ART adherence, HIV status disclosure, and retention of mothers in care, hence resulting in reduced risk of vertical HIV transmission.

Research Hypothesis: Objective 4

We hypothesized that enhanced viral load counseling and standardized peer mother support would increase infant HIV testing by 10 % among infants born to study participants at 18months.

1.7. CONCEPTUAL AND THEORETICAL FRAMEWORKS

1.7.1 Conceptual Framework

The conceptual framework (Figure 1) was developed based on a baseline understanding of factors responsible for non-viral suppression. It identified several individual, facility, and care-related factors and socioeconomic and cultural factors leading directly and indirectly to sub-optimal adherence to ARVs, resulting in sub-optimal viral suppression. This study aimed to investigate all of the identified factors and barriers in order to develop and implement a theory-based intervention to improve viral suppression among pregnant and post-partum women in southwestern Uganda.

1.7.2. Theoretical Framework

We used an implementation science approach to assess baseline understanding of factors responsible for viral non-suppression and design a multicomponent intervention aimed at improving viral suppression among women of reproductive age, particularly pregnant and postpartum women living with HIV (86). This study was designed and planned based on the empirically validated PRECEDE model of behavior change (87). PRECEDE is based on the idea that health promotion strategies are most effective when they are co-created and implemented with the people affected (Figure 2).

It further suggests that health promotion strategies are most effective when they combine: 1) Predisposing factors comprised of knowledge, attitudes, or beliefs that affect behavior; 2) enabling factors that facilitate change by making the behavior easier, and 3) reinforcing factors, which include anticipated consequences following behavior (88).

The PRECEDE model also addresses the implementation science approach (Figure 2.) to health research through identification of a practice-implementation gap (barriers and facilitators), designing theory-based interventions based on the identified barriers (enhanced viral load counseling and peer mother support) and impact assessment/outcome (Viral suppression, adherence, disclosure and retention in care and EID as a secondary outcome).

During phase one of the study, we identified barriers and facilitators of viral suppression from literature review, the SEARCH trial (63), and pre-study discussions with peer-mothers at non-study facilities on the contribution of viral suppression to maternal and child health using PRECEDE the model (Figure 2).

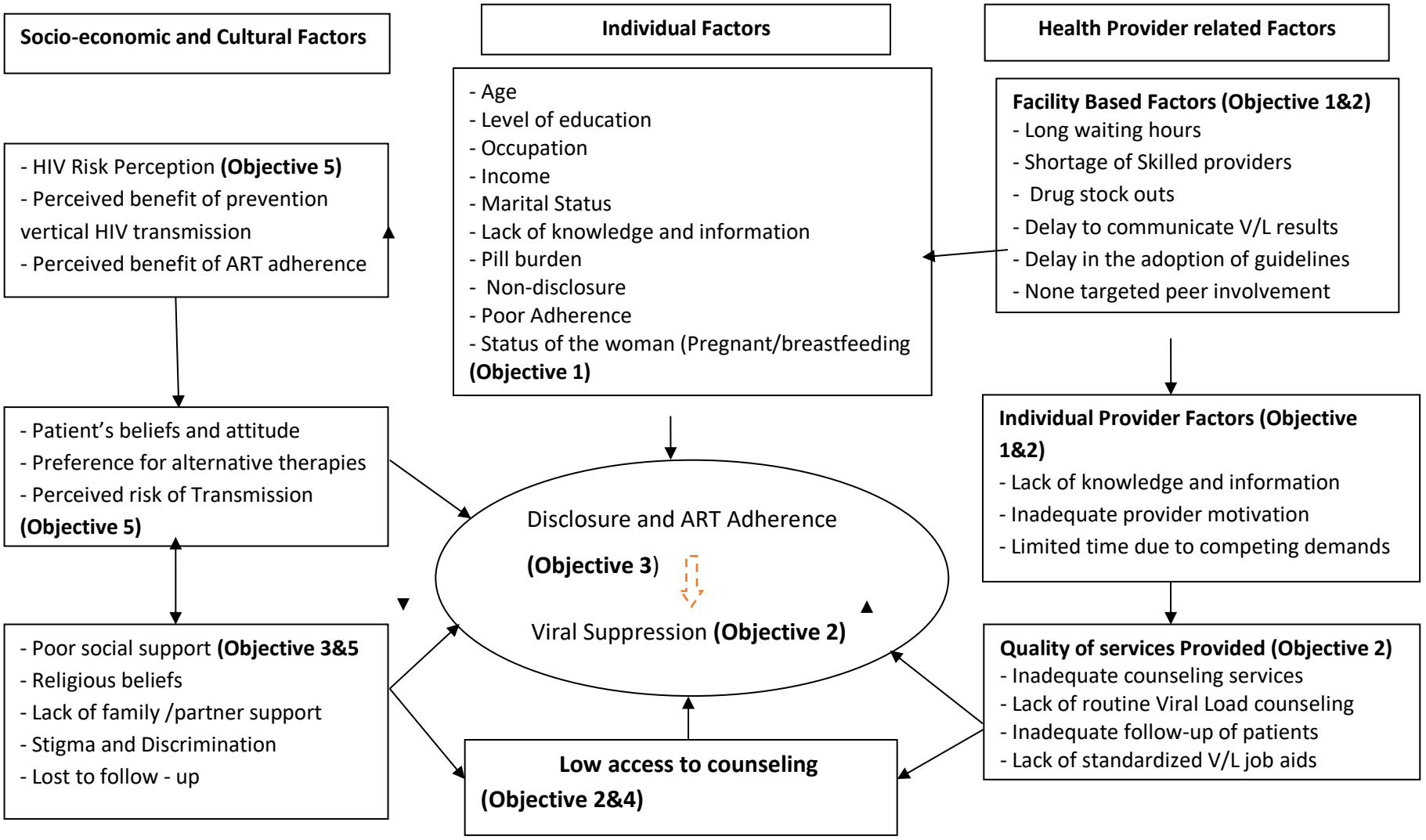


Figure 1: Conceptual Framework

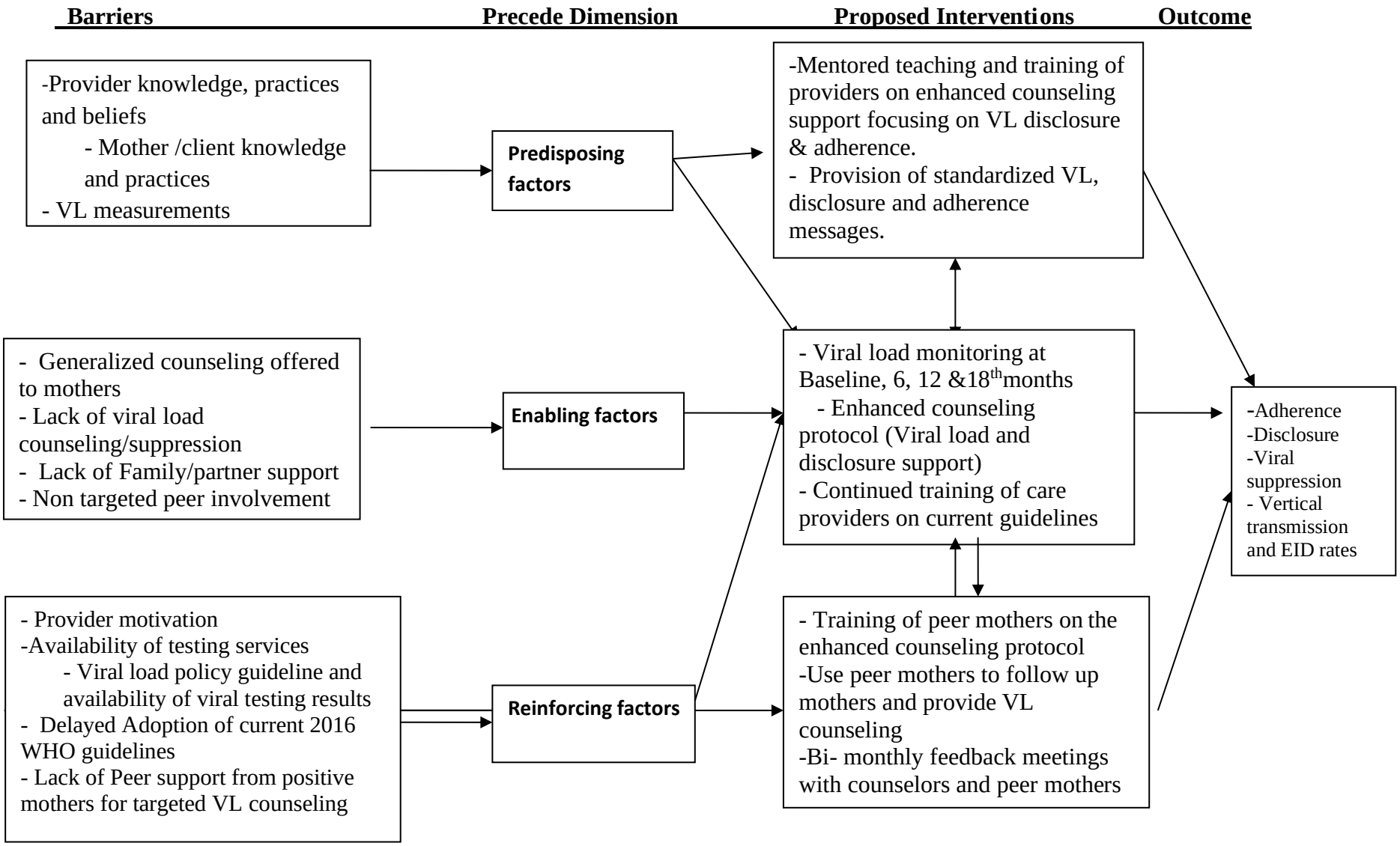


Figure 2. PRECEDE Framework

CHAPTER 2.0: LITERATURE REVIEW

2.1. The burden of HIV/AIDS and antiretroviral therapy coverage in Sub-Saharan Africa.

Globally, 39.9 million people are living with HIV, and an additional 1.3million new HIV infections occur annually, with women and girls accounting for 44% of all new infections (89). The number of people living with HIV on antiretroviral therapy (ART) increased from 7.7 million in 2010 to 30.7 million in 2023. Sub-Saharan Africa (SSA), however, still has the highest burden, with over 20 million living with HIV and accounting for almost two-thirds of the people living with HIV (PLHIV) worldwide (59, 81, 90, 91).

In East and Southern Africa, 20.8 million people are living with HIV, and ART coverage increased from 4 million to 17 million between 2010 and 2023. However, only 65% of children living with HIV are on treatment, and this coverage continues to be much lower than among adults (89). The numbers on ART increased tremendously since the World Health Organization's (WHO's) recommendations to "test and treat all" persons living with HIV (3, 4). Nevertheless, the region is gradually progressing to the UNAIDS 95-95-95 targets; by December 2023, 93% people living with HIV in the region were aware of their status, 83% who knew their status were on treatment, and 78% of those living with HIV had achieved viral suppression (86, 89).

Uganda has registered a tremendous decline in the national HIV prevalence from 7.2% to 5.1% among adults aged 15 to 49 years and a reduction in the number of new infections from 97,000 to 38,000 from 2010 to 2023 (75). Significant regional and gender disparities persist, from 2.3% in West Nile to 8.3% in South Buganda, and higher among females (6.6%) than males (3.6%). This disparity is not different from that seen in the other HIV high-burden countries, where adult HIV

prevalence is still higher than 5%, rendering the majority of all sexually active people at a high risk of acquiring HIV, especially the women (9, 75).

2.2. Current status of Vertical transmission of HIV.

Since 2012, the WHO has recommended triple antiretroviral therapy for the elimination of vertical HIV transmission (92). Multiple countries have implemented and scaled up Option B+ (universal initiation of lifelong ART) to all pregnant and breastfeeding women living with HIV. The steady scale-up and improvement of services to prevent vertical transmission of HIV has reduced the annual number of new infections among children globally by 62% between 2010 and 2023 (91, 92). Additionally, the coverage of vertical transmission prevention programs increased from 29% in 2010 to 53% in 2022, but ART coverage among pregnant and breastfeeding women with HIV stagnated at 82% and viral suppression levelled off to slightly over 80% (39, 58-60, 89). Notwithstanding this success, a significant gap remains in ensuring that mothers and their babies are retained in care throughout the breastfeeding period. This is essential to minimize the risk of transmission during the entire post-partum period, which accounts for the highest number of infections from vertical transmission. Evidence from Swaziland, Malawi, and Uganda suggests that retention in programs that prevent vertical transmission hovers between 50-73% (8, 93).

Despite the current evidence that triple ART is effective and many countries, including Uganda are implementing option B+, prevention of vertical transmission programs have not been able to achieve the goal of elimination. The vertical transmission rate in Uganda, including the breastfeeding period, has remained high at 3.05% and 5.04%, at 6 weeks and 18 months post-partum, respectively, according to the Ministry of Health programmatic report 2023 (19, 62, 69, 94). There has been a significant decline in the number of new infections due to vertical

transmission from 20,000 in 2010 to 4,700 in 2023. Despite this improvement, the target of zero new infections among the children has not been achieved, and targeted efforts are still needed.

Recent studies have reported viral suppression rates of 85.7% among pregnant women who were retained in care compared to the 95% suppression target (47, 64). Viral suppression rates for mothers not retained in prevention of vertical transmission programs are significantly lower compared to those who are retained, with rates potentially ranging from 60% to 80% (95, 96). Women who had disclosed to their partners were four times more likely to achieve viral suppression compared to those who did not disclose (31, 66, 69, 95, 97). Young women between 15-24 years remain at risk of non-suppression according to the current MoH performance review report, with the suppression rates of 75% (8, 85).

Designing targeted interventions that focus on young women and those who have not disclosed their HIV status, as well as newly diagnosed pregnant and breastfeeding women, is critical to achieving viral suppression and eliminating vertical transmission (98). This study will evaluate the impact of enhanced VL counseling and peer mother support as interventions to improve viral suppression and retention in care among pregnant and breastfeeding women living with HIV.

2.3 Evolution of policies and guidelines for prevention of vertical transmission.

The evolution of Prevention of vertical transmission has been dynamic and a critical component of global efforts to reduce HIV transmission. Initially, the focus was on providing antiretroviral therapy (ART) during labor, but advancements over time led to earlier interventions, including during pregnancy and breastfeeding. In the 2000s, the use of single-dose nevirapine for pregnant women and their newborns was introduced, significantly reducing transmission rates (99). In 2013, Uganda introduced Option B (triple therapy) for pregnant and breastfeeding women living with

HIV. By 2013, comprehensive treatment regimens for pregnant women, including lifelong ART for those living with HIV, became standard (100, 101). The global strategy for prevention of vertical HIV transmission now includes universal HIV testing, ART for all pregnant women with HIV, and safe infant feeding practices, contributing to the significant decrease in new pediatric HIV infections globally (39, 76).

Table 1:Evolution of the different PMTC guidelines

Year	WHO Recommendations on the prevention of vertical HIV transmission
1990s	Limited interventions. HIV counselling and testing for pregnant women were initiated.
2000	WHO recommended zidovudine (AZT) for HIV-positive pregnant women during labor to reduce transmission
2001	Introduction of single-dose nevirapine for both mother and newborn, as an alternative to zidovudine, to prevent transmission.
2006	Expansion of PMTCT interventions to include a more comprehensive antiretroviral regimen for pregnant women, including dual therapy (AZT + lamivudine)
2010	WHO recommended the option of Option A (ART during pregnancy and breastfeeding) and Option B (lifelong ART for all HIV-positive pregnant women), depending on local resources
2013	WHO recommended Option B+ (lifelong ART for all pregnant women, regardless of CD4 count)? This became the global standard for PMTCT.
2016	Recommendation for ART to be initiated for all people living with HIV, including pregnant women, as part of the universal "Test and Treat" strategy.
2021	Continued focus on eliminating mother-to-child transmission (EMTCT) through universal access to HIV testing, ART, and safe infant feeding practices.

With each change, Uganda has attempted to harmonize its guidelines with the global recommendations. Over time, this has resulted in implementation challenges. The current prevention of vertical transmission (option B+) program takes the form of a cascade or steps of interventions (14), designed to collectively reduce or virtually eliminate the risk of vertical transmission of HIV among mother-infant pairs, with primary focus for vertical transmission prevention programs on the 3rd and 4th prongs (33, 102). Ensuring that pregnant and breastfeeding women are on treatment and virally suppressed was our key goal in this study.

The overall implementation structure for most programs targeting prevention of vertical transmission includes the WHO four-pronged approach (103, 104) and is based on:

1) Prevention of new HIV infections among women of childbearing age (15-45 years)

2) Prevention of unintended pregnancies among women living with HIV (WLH)

3) Prevention of HIV transmission from women living with HIV (WLH) to their offspring

4) Providing appropriate treatment, care, and support to WLH, their children, and families.

2.4. Utilization of prevention of vertical transmission services

Access to prevention of vertical transmission of HIV services is critical to the elimination of vertical transmission of HIV (95). Several countries, including Uganda, have made remarkable progress towards the elimination of vertical transmission of HIV. However, some bottlenecks remain in ensuring wider access to and utilization of these services across the cascade (22, 105, 106). In many countries, the majority of identified adults with HIV are women, and many women of reproductive age are diagnosed with HIV infection during pregnancy through prevention of vertical transmission of HIV services in antenatal care (31, 107).

With universal eligibility for ART for all pregnant and postpartum women living with HIV (based on the WHO's 2013 `Option B+' policy, many women of reproductive age initiate ART do so

during pregnancy (108). Prevention of vertical transmission services extend through early infant diagnosis around 6±10 weeks postpartum until the cessation of breastfeeding and documentation of the infant's final HIV testing status, which may extend well beyond 1 year postpartum based on the recently updated infant feeding recommendations. To prevent postnatal HIV transmission, mothers must maintain strict ART adherence and viral suppression throughout breastfeeding. However, it is important to note that transmission can still occur via infected cells in breast milk, even when the mother's viral load is suppressed. (109, 110).

2.5. Antiretroviral Therapy (ART) Adherence, Retention in Care among pregnant women

Women living with HIV who become pregnant risk HIV transmission to their sexual partners as well as the fetus. HIV-1 RNA suppression reduces these risks (105, 111), and with updated WHO guidelines, increasing numbers of women are initiating antiretroviral therapy (ART), rather than antiretroviral (ARVs) as prophylaxis, to both reduce the risk of perinatal transmission and maintain the woman's health (108). In addition to extended treatment eligibility, ensuring knowledge of HIV status, early initiation and adherence to ART, and disclosure of HIV status have been associated with improved child and maternal outcomes (39). Despite these efforts, global targets to eliminate vertical transmission of HIV are not on track (30, 112). The effectiveness of ART depends on adherence to medication, and several studies identify pregnancy and postpartum as periods during which women are at risk for poor adherence to ART. However, in Uganda, ART adherence has declined to 73% in 2023 from 82% in 2016/17, while ART retention is at 74% which is short of the Health Sector Development plan (HSDP) target and suboptimal (8, 85, 113).

Women living with HIV must be retained in HIV care to maintain access to ART and undergo safety monitoring as well as benefit from treatment and prevention of comorbid conditions. Retention in HIV care is a strong predictor of clinical outcomes, including viral load (VL)

suppression and survival (114, 115). For patients with chronic HIV infection, the ability to remain retained in care plays a critical role in achieving good health outcomes. Despite tremendous advances in HIV treatment, many persons with HIV infection do not receive consistent antiretroviral therapy, often due to poor engagement in long-term clinical care (115, 116).

Among pregnant women, elevated viral loads in the plasma or genitourinary tract increase the risk of vertical HIV transmission. Without any intervention, high viral loads have been associated with a 20±25% risk of vertical HIV transmission (117, 118). Effective antiretroviral therapy (ART) reduces viral load in the plasma and cervico-vaginal fluid by blocking HIV replication in people living with HIV infection, including pregnant women living with HIV. As a result, ART has been very effective in reducing both vertical and horizontal HIV transmission to 2% vertical transmission risk among women with a plasma viral load (VL) <1000 copies/ml (76, 111). Although perinatal transmission risk increases at higher maternal VLs and declines at lower maternal VLS, vertical transmission may occur with low maternal viraemia (119, 120). With expanded ART access, women living with HIV are increasingly likely to conceive on ART (95, 121, 122). Maintaining viral suppression may be particularly challenging during pregnancy and post-partum with psychosocial, cultural, and economic obstacles to adherence and retention (123, 124).

HIV disclosure among pregnant and postpartum women has been reported to be low, ranging from 16% to 86% in developing countries (124, 125). Additionally, the decision to disclose is mainly informed by perceptions of HIV stigma and, most importantly, the anticipated responses from individuals in their family and social networks (97, 126, 127). While disclosure of HIV status has the potential to elicit negative reactions, positive experiences of disclosure can give individuals access to social support, which facilitates HIV care engagement both emotionally (through

encouragement and advice) and practically (through reminders and financial assistance) (127). These positive experiences and the other documented benefits of HIV status disclosure have been reflected in the guidelines encouraging all women with HIV to disclose their status (128-133). The benefits of ART adherence are well known; indeed, non-adherence to ART has been associated with poor maternal and child health outcomes (134, 135) and, ultimately, increased risk of vertical transmission of HIV (136, 137). Altogether, interventions to promote care engagement among pregnant and postpartum women are important in achieving the goal of zero infections among children born to women with HIV (138, 139).

A combination of counseling and text message reminders significantly improved drug adherence as well as the CD4+ cell counts among non-adherent HIV patients on HAART in a study conducted in Nigeria and advocated for integration of drug adherence assessment as part of routine HIV clinic consultations and adherence counseling and text messaging to address adherence challenges among PLHIV (140). In addition, women must be retained in care and on ART to prevent HIV transmission to the infant during breastfeeding, to ensure receipt of drugs, and to identify treatment failure early (119). Women who continue in care often receive social support and secondary prevention messages that help them cope with the need to be on ART for life and sustained viral suppression (141).

2.6. Importance of monitoring VL in pregnant and breastfeeding women.

Although the importance of routine VL monitoring for individuals living with HIV on ART is widely recognized (45), there has been minimal attention to VL monitoring in pregnancy and the postpartum period to ensure viral suppression carries unique potential benefits for maternal, child, and family health (142). HIV viral load (VL) is the principal determinant of vertical HIV transmission, and rapid lowering of VL is a principal goal of antiretroviral therapy (ART) for all

vertical transmission prevention programs. Suppressing plasma HIV RNA load below detectable limits is therefore the primary goal of effective treatment of women living with HIV during pregnancy/breastfeeding. A maternal viral load above 1000 copies/mL during the last few weeks before delivery is a reliable determinant of increased transmission risk (34, 69).

An estimated 44% of people living with HIV globally were virally suppressed in 2016. The new '95-95-95' UNAIDS target proposes that 95% of all people living with HIV will know their HIV status, 95% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 95% of all people receiving antiretroviral therapy will achieve viral suppression by 2025 (97). However, the global gap in achieving this target in 2015 was around 11.9 million people living with HIV who did not know their HIV status, 12.7 million people in need of antiretroviral treatment, and 13.0 million people living with HIV who were not virally suppressed. A key determinant of viral suppression among people living with HIV remains knowledge of HIV status, yet only 86% of all people living with HIV knew their HIV status in 2023 (1, 34, 69, 143).

Despite the importance of ART for VL suppression during pregnancy and breastfeeding, there is mounting evidence that ART adherence may be inadequate during these critical periods (93, 123, 144). Consequently, VL suppression may be suboptimal, leading to a higher risk of vertical transmission and maternal disease progression (145). The drivers of non-adherence are variable and may include ART side effects or pill burden in the context of pregnancy; increased psychosocial stressors related to pregnancy or caregiving; fragmented health systems that may require women to attend different clinics or transfer services after delivery; and inadequate patient counseling on the importance of VL suppression, particularly during breastfeeding (146, 147). To meet the UNAIDS 2016-2021 strategy and the second target of Zero infections among children and mothers alive, there is a need to close these gaps and ensure that all pregnant women receive

ART and become virally suppressed. Thus, optimization of viral suppression is an essential tool /intervention for the elimination of vertical transmission of HIV (97, 143).

2.7. Obstacles to HIV virologic suppression during pregnancy and postpartum periods.

Challenges to achieving viral suppression include a knowledge gap on new scientific evidence that viral suppression is the single most risk factor for vertical transmission, stigma and discrimination (including the denial of health services), high rates of gender-based violence (including in conflict and emergencies), and gender inequities. Approximately 50% of all people living with HIV in Eastern and Southern Africa had achieved the viral suppression necessary to prevent HIV transmission in 2016 (31, 81). It is generally believed that if adherence is addressed, clients receiving ART will achieve viral suppression, unless the ART regimen is failing. The World Health Organization (WHO), based on a systematic review that showed 70% of clients re-suppressed after adherence interventions, recommended adherence interventions for clients with high viral load (148, 149). The World Health Organization (WHO), based on a systematic review that showed 70% of clients re-suppressed after adherence interventions, recommended adherence interventions for clients with high viral load.

In the START ART study that used theory-based interventions, including a revised viral load counseling protocol targeting the health system, the probability of ART initiation 14 days after eligibility increased compared with the standard of care. The proportion of patients starting ART on the same day was also high, suggesting both increasing access and completeness of ART initiation. This was also associated with greater HIV RNA suppression 1 year after ART initiation (24, 150, 151). This study was designed and use theory-based interventions to address the nearly 50% reduction in achieving viral suppression.

CHAPTER 3.0: METHODS AND MATERIALS

3.1. Study Overview

This was an Implementation Science Research study conducted in two phases.

During phase one (before Implementation) of the cluster randomized trial (CRT) study, we determined the prevalence of viral suppression and identified factors/motivators and barriers to achieving viral load suppression among pregnant and post-partum women using retrospective data from the SEARCH trial (Objective 1). In addition, we obtained evidence on existing facility and community-specific barriers and facilitators of viral suppression among women of reproductive age; processes and procedures of viral load testing and counseling in all 14 HIV care clinics selected to participate in the study.

In **Figure 3** below, the "before" refers to the period before the implementation of the ENHANCED-SPS intervention. Based on the findings from objective one and the identified facility and community-specific barriers and facilitators of viral suppression among women of reproductive age, we used the PRECEDE model of health promotion to design and refine an intervention that included enhanced viral load counseling and standardized peer mother support (ENHANCED-SPS) to address the structural barriers and unique needs of the target population.

In the second phase (also known as "after" period /the implementation phase) of the study, we evaluated the effect of the intervention on the primary endpoint of viral suppression and selected secondary endpoints, including adherence to antiretroviral therapy (ART), and disclosure of HIV status among pregnant and postpartum women living with HIV in South Western Uganda. In addition, we assessed the effect of the intervention on infant HIV testing among children born to participants enrolled in the ENHANCED-SPS trial. A total of 14 public health facilities with the

highest seroprevalence of HIV in rural south western Uganda were randomized to either intervention or control arm at a ratio of 1:1. Within the intervention facilities, we evaluated the introduction of a multi component ENHANCED-SPS intervention while in the control arm we implemented the standard of care (SOC) as per national guidelines among pregnant and breastfeeding women living with HIV.

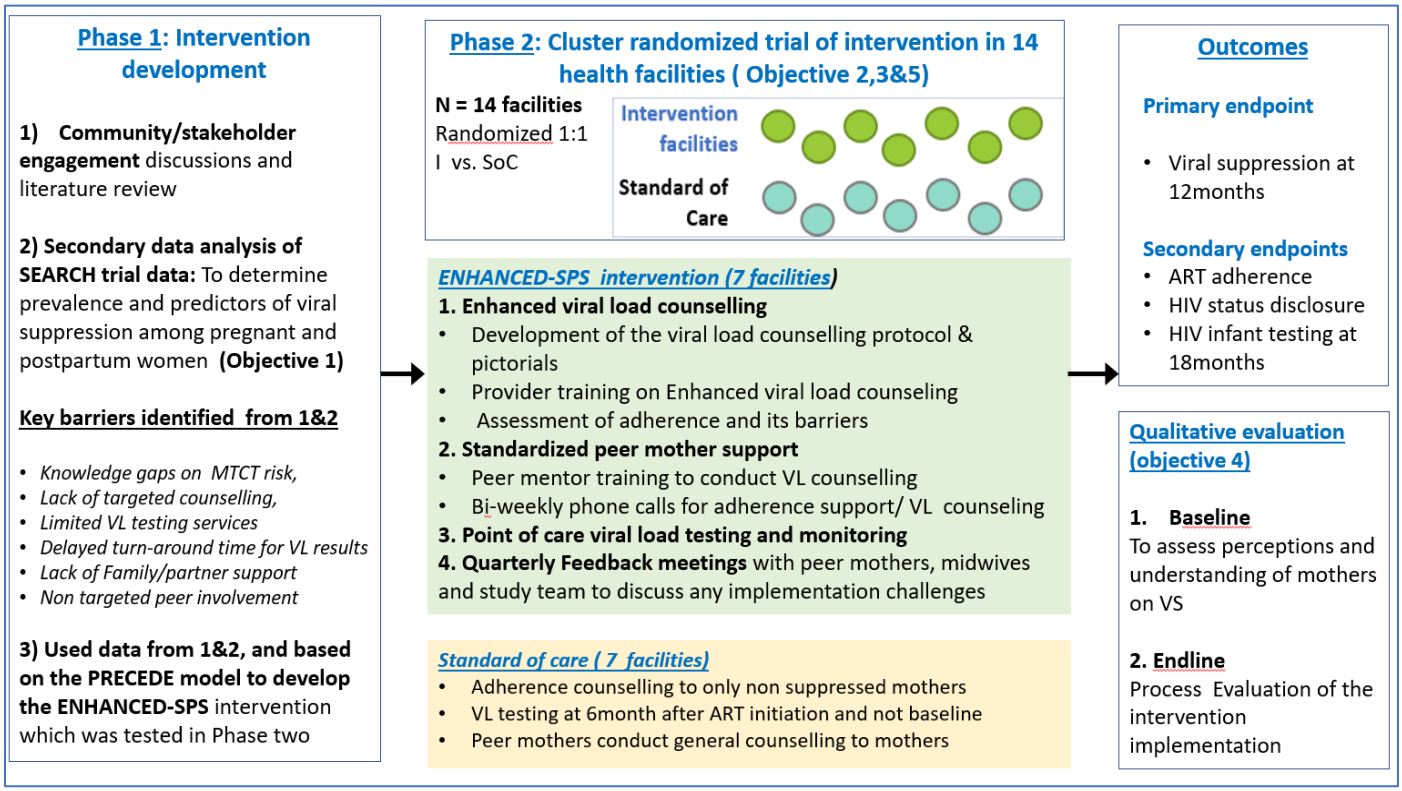


Figure 3: Enhanced-SPS study Schema.

3.2. Study design

This was an Implementation Science Research study to evaluate a multi-component of an Enhanced Viral load (VL) counselling and Standardized Peer-mother support (ENHANCED-SPS intervention) through a cluster randomized trial design (CRT). This CRT was designed to rigorously evaluate the effects of the ENHANCED-SPS intervention on viral suppression and other care outcomes (ART adherence and HIV status disclosure) among pregnant and

breastfeeding women with HIV in 14 public health clinics in South Western Uganda (Clinicaltrials.gov: NCT04122144). The 14 clinics were randomized to either intervention or control clinics at a ratio of 1:1.

This patient-centered intervention was developed using the PRECEDE model of behavioral change (152) and designed to address the structural barriers and unique needs of pregnant and postpartum women during phase one of the study. In addition, we determined the prevalence of viral suppression and identified factors/motivators and barriers to achieving viral load suppression among pregnant and postpartum women using retrospective data from the SEARCH trial and used the findings to refine the ENHANCED-SPS intervention. After phase one, Phase two of the study started with the implementation of enhanced viral load counseling and standardized peer mother support intervention.

3.3. PHASE ONE

Objective 1: To determine the prevalence and identify the predictors of viral suppression among pregnant and postpartum women living with HIV in 32 communities (comparing 16 intervention communities to 16 Control communities) of the SEARCH trial (NCT:01864603).

3.3.1. Overview and design

This was a retrospective study of the prevalence and predictors of viral suppression among pregnant and post-partum women living with HIV enrolled in the SEARCH trial (NCT:01864603). The SEARCH trial was a cluster-randomized trial that compared an intervention of baseline testing plus annual testing, eligibility for universal ART, and patient-centered care to an active control of baseline HIV and multi-disease testing and national guideline–restricted ART. It was conducted from 2013 to 2017 in 32 communities across three rural regions: 10 communities in Southwestern Uganda, 10 in Eastern Uganda, and 12 in western Kenya (15, 153, 154) (150, 151)**.**

In this secondary analysis, we sought to determine the prevalence and predictors of viral suppression among WLHIV of reproductive age who reported current pregnancy or live birth in the prior year at trial completion (year 3) in both intervention and control communities. We also compared population-level VS estimates among all women living with HIV aged 15-45 years (including in-migrants) in intervention and control communities. And lastly, we evaluated predictors of viral suppression among these women. Additionally, we also evaluated pregnant and non-pregnant women who remained non-suppressed to understand their barriers within the SEARCH communities. These barriers and motivators identified facilitated refinement of the ENHANCED-SPS intervention, which was then implemented in phase two.

3.3.2. Study setting

The SEARCH trial was conducted/implemented in 32 communities (16 intervention and 16 control communities) in Uganda & Kenya from 2013 to 2017 and enumerated 150,395 adults overall at baseline. The 32 communities were selected from 52 candidate communities that met initial eligibility criteria of a rural geopolitical community, with a population of 10,000, within the catchment area of a President's Emergency Plan for AIDS Relief (PEPFAR)-supported HIV clinic in southwestern Uganda, eastern Uganda, or western Kenya (Figure 4).

There were selected 16 matched pairs were selected based on region, population density, occupational mix, access to transport routes, and number of trading centers. They were supported by the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)—a PEPFAR-implementing partner that facilitated HIV care in government-run clinics in Uganda. These clinics provide a full array of HIV care services and women's health services, including antenatal care, ART for pregnant women, and prevention of vertical transmission of HIV services.

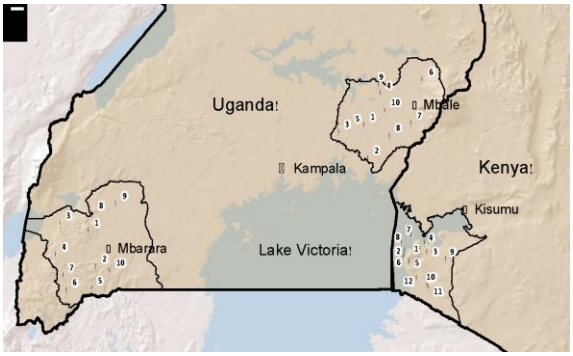


Figure 4:Map of SEARCH trial communities.

3.3.4. Study population

Data from all 16 intervention communities and 16 control communities on all women living with HIV of reproductive age were reviewed to determine the proportion of women who reported pregnancy and /or live birth over a period of 3 years of follow-up. We also looked at the pre-determined variables and viral load results of all the pregnant and non-pregnant women of reproductive age living with HIV to determine the rates and determinants of viral suppression. Out of 150,395 adult (≥15 years) residents enumerated in the SEARCH trial at baseline, 62,066 were women of reproductive age (15-45 years) and included in this secondary analysis. During year 3 of the trial, there were 77,862 women aged 15–45 years and enumerated in the 32 study communities, inclusive of in-migrants and young women (12–14 years old at baseline) who turned 15 years during follow-up and excluding women who had aged out, died, or out-migrated.

Inclusion criteria

The study population of interest was all women of reproductive age (15-45 years) and residents of the study communities.

Exclusion criteria

Women who had aged out, died, or out-migrated by FUY3, as well as those missing data on pregnancy and birth status in the previous year at FUY3, were excluded.

3.3.5. Sample size considerations

This was a secondary analysis of the SEARCH trial, whose sample size calculations were conducted to detect an effect on HIV incidence among all adults (15+ years) without HIV at baseline (153). Here, we retrospectively conducted power calculations to determine the prevalence of viral suppression among pregnant and postpartum women with HIV at year 3, as well as compare the prevalence between trial arms. Of the 77,862 women of reproductive age and residents of study communities at year 3, there were 41,598 from the 16 intervention communities and 36,264 from the 16 control communities. With 82% coverage of HIV testing, 10% HIV prevalence among those tested, and 15% known to have HIV reporting a current pregnancy or recent birth, we anticipated having ~480 pregnant/postpartum women with HIV at year 3 in each trial arm (~960 women total). This sample size would provide ~5% margin of error for determining the prevalence of viral suppression in each arm, accounting for clustering by community (coefficient of variation k=0.1). This sample size would also provide 80% power to detect a ~10% difference in the prevalence of viral suppression between arms, accounting for clustering (k=0.1). These calculations are conservative, given our use of targeted maximum likelihood estimation (TMLE), described below, in the primary analysis. Briefly, TMLE makes use of data from all women of reproductive age – including those with missing HIV status and missing viral suppression status – to improve precision and robustness.

3.3.6. Study Outcomes

The primary outcome was the population-level proportion of pregnant or postpartum women living with HIV who were virally suppressed (HIV RNA <500 copies/mL) at trial completion (year 3). In each community, we estimated the following HIV care cascade outcomes among female residents (inclusive of in-migrants) aged 15-45 years who reported a current pregnancy or live

birth in the last year: proportion of PLHIV who knew their status, proportion of PLHIV with known status who had initiated ART, proportion of PLHIV on ART who were virally suppressed (VS), and proportion of all PLHIV who were virally suppressed. We considered HIV RNA levels (viral loads) measured annually from baseline to follow-up year 3 among women of reproductive age enrolled in the SEARCH trial.

We also reviewed data on other variables collected annually during the community health campaigns (CHCs) or home base testing activities including demographic characteristics (age, sex, education, occupation, marital status, income, religion), viral load results, pregnancy status, wealth index, ART status/regimen, number of live children, time of pregnancy, and marital status.

3.3.7 Data management and Analysis

In each community, we estimated the following HIV care cascade outcomes among female residents (inclusive of in-migrants) aged 15-45 years who reported a current pregnancy or live birth in the last year: proportion of PLHIV who knew their status, proportion of PLHIV with known status who had initiated ART, proportion of PLHIV on ART who were virally suppressed, and proportion of all PLHIV who were virally suppressed. We considered HIV RNA levels (viral loads) measured annually from baseline to follow-up year 3 among women of reproductive age enrolled in the SEARCH trial. The primary outcome was the population-level proportion of pregnant or postpartum women living with HIV who were virally suppressed (HIV RNA <500 copies/mL) at trial completion (year 3).

Targeted maximum likelihood estimation (TMLE) was used to adjust for differences in the characteristics of women with known versus unknown HIV status, and known versus missing viral suppression status. In sensitivity analyses, we calculated unadjusted cascade estimates among women with known HIV status and measured viral load. We obtained estimates of cascade

outcomes and population-level suppression at baseline and year 3 in both arms, and at years 1 and 2 in the intervention arm. We compared year-3 estimates by arm with community-level TMLE, with adaptive selection of adjustment variables (candidates included baseline suppression and proportion of young women). Finally, we used TMLE to assess arm-specific predictors of VS among all women of reproductive age living with HIV at year 3.

In summary, during phase one of the study, we identified predictors of viral suppression among the pregnant and postpartum women living with HIV who were not virally suppressed by follow-up year three from the SEARCH trial. We used these findings together with pre-study discussions during community engagement with peer mothers at non-study facilities on the contribution of viral suppression to maternal and child health to refine the ENHANCED-SPS intervention based on the PRECEDE model.

After phase one, Phase two of the study started with the implementation of enhanced viral load counseling and standardized peer mother support (ENHANCED-SPS) intervention.

3.4. PHASE TWO

This phase describes the implementation of the ENHANCED-SPS intervention and evaluation of its effectiveness on viral suppression, ART adherence, HIV status disclosure, and EID. The study schema (Figure 3) summarizes the two phases together, including the process of intervention development under theoretical frameworks.

3.4.1. Study design

This was a cluster randomized trial designed to evaluate the effectiveness of an enhanced viral load (VL) counselling and standardized peer-mother support (ENHANCED-SPS intervention) on viral suppression and other care outcomes (ART adherence and HIV status disclosure) among

pregnant and breastfeeding women with HIV in 14 public health clinics in South Western Uganda. Clinics were randomized to either intervention or control clinics at a ratio of 1:1. All clinics/ health facilities provided HIV care, were government-run with support from PEPFAR-implementing partners, and had existing peer-mothers to provide health education for pregnant and postpartum women in HIV care.

All participants received standard-of-care services for pregnant and postpartum women: HIV testing, viral load testing, ART initiation, ART card documentation, general counseling, and adherence counseling every 3 months if not virally suppressing. The standard visit schedule for pregnant and postpartum women with HIV was monthly and followed in both arms. Women enrolled from intervention facilities also received the ENHANCED-SPS intervention, described next. There were no other interventions or changes in HIV care for pregnant or postpartum women during the study period.

Implementation of the intervention: This period is referred to as the implementation phase of the ENHANCED-SPS intervention. During this period, we evaluated the introduction of a multi-component ENHANCED-SPS intervention primarily designed to improve viral suppression among pregnant and breastfeeding women living with HIV. During this period, all pregnant/breastfeeding women living with HIV enrolled in the intervention study clinics received the ENHANCED-SPS intervention over a period of 12 months from enrollment, while those in the control clinics continued to receive standard of care (SOC) activities during routine HIV care visits at the health facilities as described in the study schema (Figure 3).

3.4.2. Study Setting

The ENHANCED-SPS Study took place at 14 public health facilities with some of the highest seroprevalence of HIV in rural Southwestern Uganda (155-157). The 14 facilities were pair-

matched based on distance, patient burden, and socioeconomic characteristics (Table 2). All facilities provided comprehensive HIV care, were supported by PEPFAR-implementing partners, and offered tailored services for pregnant and post-partum women: HIV testing, ART initiation, viral load testing, and general counseling. The facilities also had trained midwives, who provide standard antenatal and postnatal care, as well as peer-mothers, who are lay women with HIV and trained to support pregnant, post-partum, and other mothers with HIV. In addition to these routine services, we offered the ENHANCED-SPS intervention, which is described below.

Table 2: Study sites in the ENHANCED-SPS study.

Clinic	DISTRICT	Clinic Name	Clinic Level*
1	Sheema	Kigarama	HC III
2	Bushenyi	Kyeizoba	HCIII
3	Kiruhura	Sanga	HCIII
4	Ibanda	Bisheshe	HC III
5	Mbarara	Ruharo Mission	Hospital
6	Kiruhura	Rushere Mission	Hospital
7	Bushenyi	Kyamuhunga	HC III
8	Ibanda	Kikyenkye	HCIII
9	Lyantonde	Lyantonde	Hospital
10	Mbarara	Nyakayojo	HCIII
11	Mbarara	Mbarara regional referral	Regional referral
12	Masaka	Masaka Regional referral	Regional referral
13	Ibanda	Bufunda	HCIII
14	Kiruhura	Kashongi	HCIII

***HC: health center**

Clinic randomization: The 14 clinics described above were randomized to the intervention vs. control condition in a 1:1 ratio. A computer-generated blocked randomization design was used to assign each clinic to intervention or control. The randomization information was known to the research and health facility teams.

3.4.3. Study site preparation

Before study initiation and participant enrollment, the following activities were completed:

Study Initiation Meeting: A meeting was held with all facilities and their respective in-charges, where the protocol overview, randomization details and study design were discussed to ensure buy-in and involvement in the study.

Clinic Meetings: Meetings were conducted at each clinic, attended by the clinic in charge and staff (midwives) responsible for vertical transmission prevention programs. The following topics were covered:

- An overview of the study and its goals.
- A review of the randomized design, explaining the differences between intervention and control clinics and outlining the distinct activities for each group.
- A review of the study timeline, including schedules for intervention delivery and outcome measurements.
- Distribution of sensitization materials, which included instructions on how participants could contact study staff for questions or concerns (via telephone, in person, or email).
- An assessment of existing resources required for successful study implementation.

Evaluation of clinic enrollment capacity, physical resources, and the quality of medical records

3.4.4. Study population

The study population consisted of pregnant and postpartum women living with HIV, aged between 15-45years and accessed care from these public health facilities and were eligible for enrollment in the ENHANCED-SPS study. Enrollment occurred from September 1, 2019, to October 30, 2020. Eligible and consenting women were followed for 12 months.

Inclusion criteria

Women were eligible if they were (1) pregnant with a prior HIV diagnosis attending their first antenatal clinic (ANC) visit, (2) newly diagnosed with HIV during their first ANC visit, or (3) breastfeeding and newly diagnosed with HIV at their postnatal visit.

Exclusion criteria

Women who were critically ill.

3.4.5. ENHANCED-SPS Study Intervention development and components

The multi-component, peer-led ENHANCED-SPS intervention was systematically developed using the four phases of the PRECEDE framework for health promotion. This systematic application of the PRECEDE model allowed for a comprehensive understanding of the complex interplay between individual behaviors, environmental constraints, and system-level factors influencing viral suppression in women living with HIV. The resulting intervention was evidence-informed and contextually grounded and holds the promise for improving viral suppression, maternal and child health outcomes.

Below, we outline the application of the four assessment phases of the PRECEDE model that informed the design of a multicomponent intervention aimed at improving viral suppression among women of reproductive age, particularly pregnant and postpartum women living with HIV.

1) **Social and community Assessment**: In this phase, we focused on understanding the broader social, community, and contextual factors influencing adherence to ART and viral suppression among women of reproductive age, including pregnant and post-partum/breastfeeding women living with HIV. To inform this phase, we reviewed literature to identify known barriers to viral suppression. In addition, community engagement activities were undertaken, including meetings with women and peer mothers to discuss the concept of viral suppression, informal interviews with women living with HIV, peers, and community members. Key barriers identified included poor ART adherence,

largely attributed to stigma, fear of side effects, and challenges associated with disclosing HIV status. Many women reported not fully understanding the importance of viral suppression or its relationship to vertical transmission of HIV. Particularly among those recently diagnosed, there was a notable lack of information and support. These findings underscore the need for targeted interventions that address not only knowledge gaps but also the social determinants of health behavior.

2) Epidemiological, Behavioral, and Environmental Assessment:

In this phase, **epidemiological** data from the SEARCH trial were analyzed to determine the prevalence and predictors of viral suppression among women of reproductive age, pregnant and postpartum women in all communities (intervention and control). The findings were supplemented by data obtained from interviews, focus groups, and a comprehensive review of existing literature. Then, in behavioral and environmental assessments, factors associated with viral suppression were identified, and the most important and changeable behavioral and environmental factors associated with viral suppression were found.

Behavioral Assessment identified several factors linked to poor viral suppression, including:

- Inadequate knowledge and misconceptions about ART and viral suppression.
- Poor adherence to ART regimens.
- Non-disclosure of HIV status to family or partners, which impacted treatment continuity and social support.

Environmental Assessment revealed structural barriers affecting viral suppression outcomes:

- Delayed turnaround time for viral load results due to centralized laboratory systems.
- Infrequent viral load testing due to limited provider motivation and system inefficiencies.
- Inadequate infrastructure for point-of-care viral load monitoring.

These environmental factors affect timely adherence counseling and resulted in missed opportunities for intervention. Based on importance and changeability ratings, the most critical behavioral and environmental determinants were prioritized for intervention development. Target behaviors for change included enhancing provider-initiated viral load testing and improving adherence counseling practices using real-time viral load data. Other factors such as new HIV diagnosis, pregnancy and care status were also considered as factor that influence the ability to achieve and maintain viral suppression

3) Educational and Ecological Assessments: This 3rd step of assessment within the PRECEDE model identified the predisposing, enabling, and reinforcing factors that influence behavior change in the target population.

Predisposing factors are those that drive and motivate health-related. They included individual-level beliefs, attitudes, and knowledge deficits related to ART adherence and viral suppression. For example, some women believed ART was only necessary when symptomatic, leading to irregular adherence.

Enabling factors are those that facilitate performance of the health action, such as resources, skills, and supportive policies that are essential to conduct the behaviors (158). In this study, the key enabling factors were availability and accessibility to peer and provider counseling services, enhanced viral load counseling protocol, availability of point-of-care viral load testing, access to educational tools such as flip charts and other informational resources for the providers and the peers, ongoing mentorship and capacity building for both the providers and peer mothers.

Reinforcing factors were those that supported sustained behavior change, such as social support and encouragement from significant others. This included motivation from healthcare workers,

family members, and peer support groups. The influence of peer mothers was especially noted as a positive force in sustaining ART adherence and promoting understanding of viral suppression.

4) **Administrative and Policy Assessments**: The final assessment phase of the model focused on identifying organizational, administrative, and policy-related factors that would impact the implementation of the planned intervention (159).

***Key activities included**:*

- Assessments of the health facility infrastructure and staff capacity.
- Planning and budgeting for training activities targeting healthcare providers and peer mothers.
- Selection of personnel for implementation at various health facilities.
- Conducting site initiation meetings to identify barriers and facilitators at the organizational level.

These discussions highlighted critical issues such as unclear provider roles in peer-led support, limited training on current HIV guidelines, and inadequate coordination mechanisms. Health facility in-charges and peer coordinators contributed valuable insights into local policy challenges and helped outline logistical requirements for successful implementation.

Following this detailed assessment, key barriers were identified, prioritized, and targeted by the intervention to improve viral suppression. The barriers included: 1) Knowledge gaps on MTCT risk, 2) Lack of targeted counselling, 3) Limited VL testing services, 4) Delayed turnaround time for VL results, 5) Lack of Family/partner support, and 6) Non-targeted peer involvement. These identified barriers were discussed, and consensus was reached between the PhD student and

doctoral committee/supervisors about the priority barriers to be targeted by the different intervention components.

Specifically, the framework analysis guided the identification of "**predisposing" factors** that impact behaviour (such as, knowledge gaps, misconceptions, attitudes, or beliefs that influence adherence to ART), "**enabling" factors** to facilitate behaviour while making it easier (resources and support systems that facilitate adherence resulting in sustained viral suppression); and **"reinforcing" factors** that include motivation or consequences of following a behavior (i.e., that encourage continued adherence to treatment) (Figure 2) (83).

As a result, an appropriate educational and environmental-based intervention was subsequently designed to address these factors, emphasizing improved knowledge, access to supportive resources, and community-level reinforcement strategies to improve viral suppression. The multicomponent intervention was finalized, and three major intervention components were carefully selected to target the identified barriers to viral suppression, ensuring that the lived experiences and needs informed the intervention of the target population (Table 3).

The intervention aimed to optimize virologic outcomes among pregnant and breastfeeding women by enhancing their understanding of viral suppression and its role in vertical HIV transmission, promoting timely ART adherence, and strengthening the support systems (family and peers) surrounding them.

Table 3:Enhanced viral load (VL) counselling and Standardized Peer-mother Support (ENHANCED-SPS) intervention (Peer-led Model), Target audience and Purpose.

Intervention components	Target audience and frequency of delivery	Purpose
1. Enhanced VL counselling		
1. Development of the enhanced VL counselling protocol (Figure 5) 2. Midwives/ providers received the initial training on how to deliver the intervention 3. Assessment of adherence and its barriers 4. Education and case studies of VL and adherence counselling	1. Training to midwives and peer mentors on the enhanced VL counselling protocol i.e., how to deliver the intervention at the start of the study and continued mentorship throughout the study 2. Midwives provided the initial and ongoing viral load counselling at every clinic visit using flip charts 3. Assessment of individual barriers on adherence to ART by the midwives /peer mentors at every clinic visit and peer mothers every 2 weeks via a phone call	Predisposing
2. Standardized Peer mother Support (SPS)		
.6. Training on mandatory provision of enhanced VL counseling during routine counseling/health education activities 7. Bi-weekly phone calls by peer mother to provide VL counseling and 8. Flip charts with simplified messaging on role of VL in MTCT (Figure 5) 9. Client information cards (Figure 6) on importance of adherence and reminders of the next visit appointments.	1. All mothers attending ANC and enrolled in the intervention clinics were offered counselling based on their VL results by the peer mothers 2. Mothers also received bi-weekly phone calls to provide additional VL and adherence counselling 3. Peer mothers and midwives discussed adherence barriers based on the VL results (i.e., if VL is high, likely poor adherence and if VL is low likely good adherence) and assessment of barriers for personalized care and management 4. All intervention clinics received Flip charts with simplified messaging 5. All mothers received a participant /client information card with information on adherence in MTCT and reminders of the next appointment date	Predisposing and enabling
2. Feedback & motivation for viral load (VL) testing		
(11. Point of care Viral load testing to all participants at baseline and end line 12. Feedback meetings with providers and peer mothers	1. Mothers were provided with a phone contact of the peer mentor to consult and ask any questions 2. Peer mothers contacted all mothers to provide VL counselling and assess adherence barriers and any other concerns every 2weeks for 12 moths 3. Quarterly feedback meetings between peer mothers, study staff and midwives 4. POC VL testing & monitoring at baseline and 12 months	Reinforcing and Enabling

a) Enhanced viral load counselling and Standardized Peer mother support provided by trained midwives and peer-mothers in the intervention arm. At the start of the study, a standardized viral load counselling protocol was developed featuring simplified key messages and graphics about viral load to enhance understanding. This counselling protocol was reviewed and approved by the Makerere University School of Medicine Research and Ethics Committee (REC REF 2018-074). Following the approvals, a structured training session was conducted, involving at least two midwives and one peer-mother from each intervention facility. The training focused on using the counselling protocol effectively, interpreting viral load results, and guiding mothers on adherence strategies based on their results. Specifically, the counseling sessions utilized **a desk guide flip chart** which presented clear and concise messages about viral suppression and its critical role in preventing vertical HIV transmission (Figure 5).

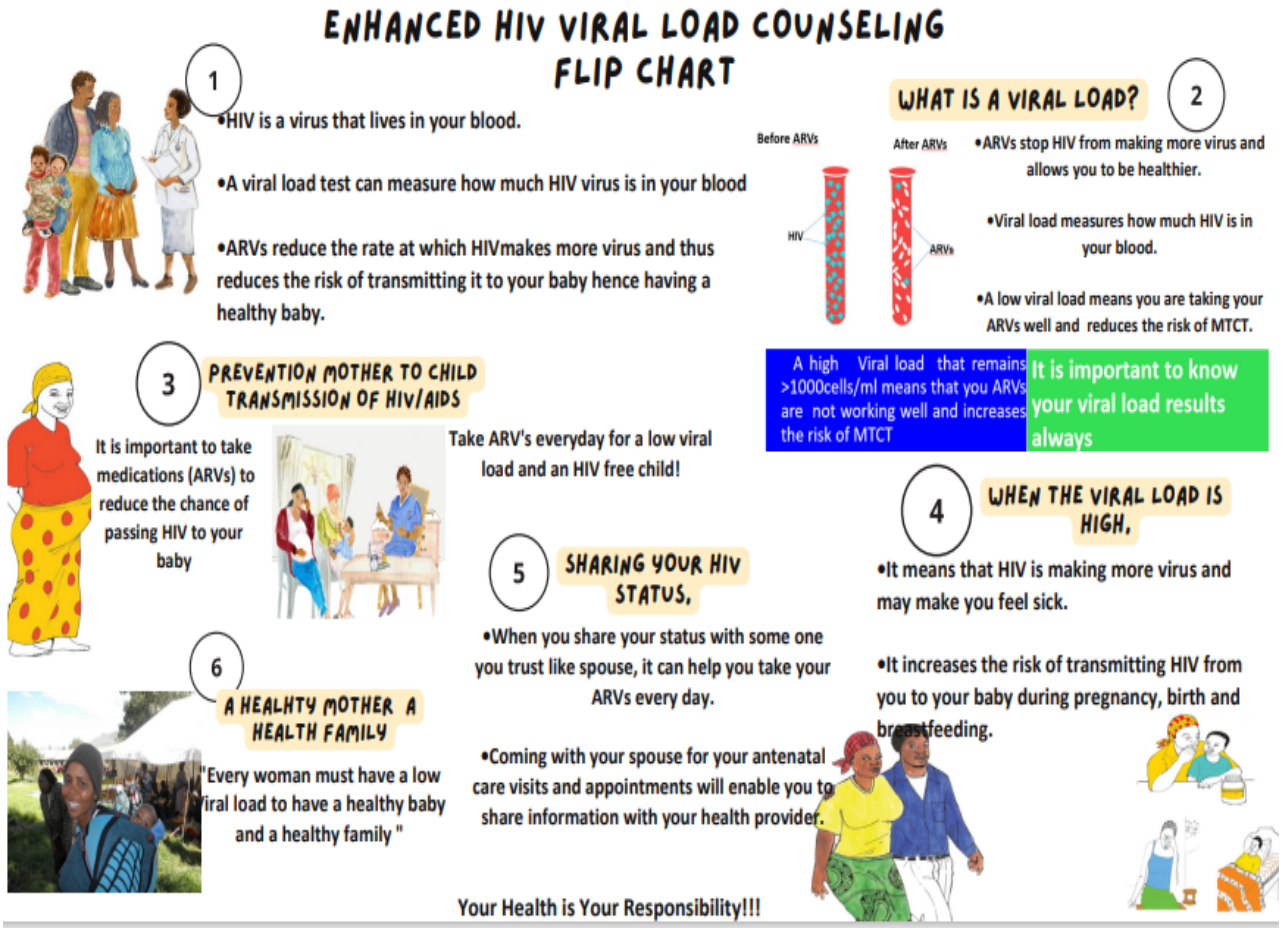


Figure 5: Enhanced counselling on viral load flip chart with key messages

In addition to in-person counseling, peer mothers conducted bi-weekly follow-up phone calls to all pregnant and breastfeeding women in the intervention arm, reinforcing viral load and adherence counseling (Table 3). These interactions reinforced messages about the risks of perinatal HIV transmission if viral suppression was not achieved. They also engaged in discussions about different adherence scenarios and their potential impact on viral suppression (Figure 5).

To further support adherence, each mother received a **participant card** containing motivational messages, reminders of clinic appointments, and reinforcement of the importance of consistent adherence to treatment (Figure 6).

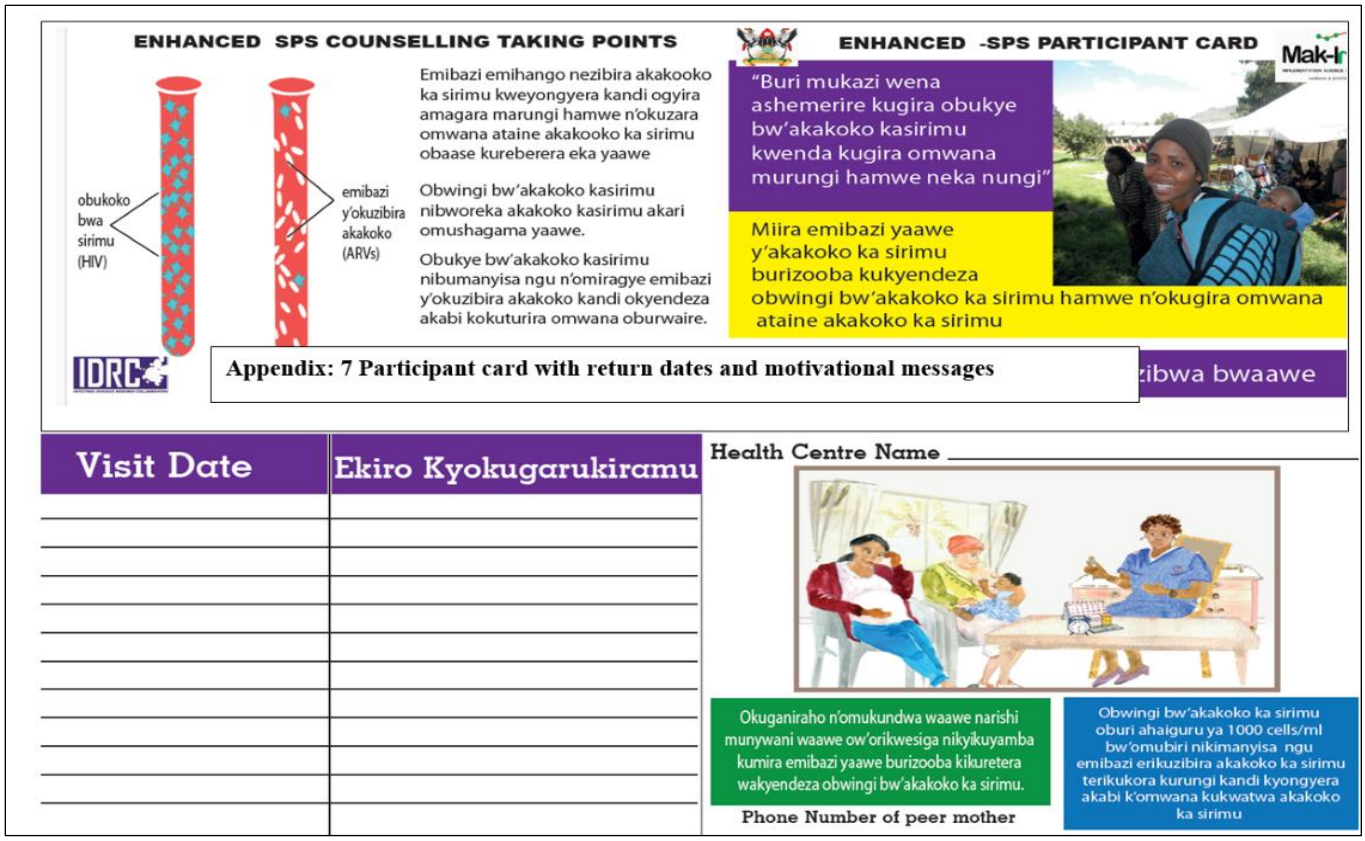


Figure 6:Participant card with motivational messages

b) Provision of point-of-care (POC) viral load testing using GeneXpert

Point-of-care (POC) viral load testing using GeneXpert was conducted at baseline and again at the 12-month follow-up. At baseline, viral load results were made available during the first antenatal care (ANC) visit and postnatal visit or within 3 days after enrollment visit via phone call for all participants in the intervention arm to inform targeted viral load counseling.

All pregnant and breastfeeding women enrolled in the intervention facilities, regardless of their baseline viral suppression status, received **enhanced viral load counselling** facilitated by midwives and peer-mothers. During routine clinic visits, mothers underwent **adherence assessments using the POC viral load results**, where potential barriers to adherence were

identified and discussed. Personalized strategies were then developed to help overcome these barriers, ensuring continued support for sustained viral suppression.

c) Quarterly Feedback Meetings and Discussions

To ensure the effectiveness of the intervention and address any challenges in achieving viral suppression, structured **quarterly feedback meetings** were conducted. These meetings brought together **peer-mothers, midwives, and study staff** to review progress, share experiences, and collaboratively identify solutions to emerging barriers.

During each session, peer-mothers provided firsthand insights into the experiences of pregnant and breastfeeding women receiving viral load counseling, highlighting common adherence challenges and facilitators. The midwives contributed their perspectives on clinical aspects, service delivery constraints, and patient engagement strategies. Study staff facilitated discussions, analyzed trends in viral suppression, and ensured that key implementation challenges were systematically addressed.

3.4.6. Standard of care (SOC)

In control clinics, HIV care for pregnant and postpartum women followed Uganda's national guidelines. This included HIV testing, ART initiation, documentation, general and adherence counseling (every three months if not virally suppressed), ART drug supply based on prescriptions, and viral load (VL) testing every six months post-ART initiation. VL samples were collected via phlebotomy or dried blood spots and sent to the Central Public Health Laboratory (CPHL) in Kampala for testing. Results were then transmitted back to clinics, with midwives informing mothers, usually at their next visit. Note that newly diagnosed pregnant women start ART immediately, with viral load tested after six months.

If viral load is detectable but <1000 copies/ml, adherence support is provided, and testing continues annually. If >1000 copies/ml, intensive adherence counseling is given, and ART is adjusted if resistance is found. For women already on ART, viral load is tested at the first antenatal visit (152).

3.4.7. Participant Enrolment and Study Procedures

a) Referral and Eligibility Screening

- Pregnant women at any gestational stage aged 15–45 years diagnosed with HIV at their first antenatal care (ANC) visit or during a follow-up ANC or postnatal care (PNC) visit were referred by Ministry of Health (MoH) midwives to a study peer-mother or midwife for eligibility screening, provided informed consent, and enrolled into the study.
- In addition, women living with HIV and already in care attending their first ANC visit were also referred for enrollment.
- Participants were recruited from multiple entry points, including mother-baby care points, ANC/PNC clinics, and other referral sources. Once enrolled, participants were followed through pregnancy, delivery, and breastfeeding.

a) Baseline Enrolment Procedures

- Upon consenting and enrollment, participants received a study participant card containing motivational messages on adherence and their scheduled return appointment dates (Figure 6).
- Point-of-care (POC) viral load (VL) testing was conducted for all enrolled mothers at baseline.
- All participants received viral load and adherence counselling during their baseline visit.
- Baseline data collection included socio-demographic information, ART initiation dates/regimens, and barriers to achieving viral suppression.

b) Study Follow-up Activities

1. **Monthly Follow-up Visits**

- Participants were assigned monthly appointment dates, which were recorded on their study participant cards.

2. **Adherence Counselling and Viral Load Monitoring**

- At each follow-up visit, peer-mothers and midwives assessed adherence barriers and discussed viral load results with participants:
- High VL indicated poor adherence, prompting tailored interventions.
- Low VL suggested good adherence, reinforcing positive adherence behaviors.
- Personalized adherence support was provided at every visit or point of contact.

3. **12-Month Endpoint Assessment**

At the 12-month follow-up visit, the study team measured key outcomes, including:

- Viral load levels
- Retention rates
- ART adherence
- HIV status disclosure
- Early infant diagnosis (EID) outcomes
- Vertical transmission rates

- Additionally, retrospective data were extracted from clinic registers and HIV blue cards of all enrolled participants to supplement follow-up data.

This structured process ensured comprehensive follow-up and evaluation of maternal and infant health outcomes throughout the study at monthly scheduled follow-up visits.

3.4.8. Sampling Procedure and Sample Size Estimation

3.4.8.1. Sampling Procedure

The primary sampling units were health facilities with high-volume HIV clinics within the same geographical area within the districts of Southwestern Uganda. The HIV clinics were purposively selected based on their geographical location, patient volume, and the absence of any ongoing related projects that could interfere with the intervention or study outcomes at these facilities.

Eligible participants were recruited and enrolled consecutively as they presented at the clinics, until the target sample size for each facility was reached. All eligible participants within a sampled clinic /health facility who gave consent (aged ≥18-45 years or emancipated minors aged 15-17 years) were enrolled into the study.

3.4.8.2. Sample Size estimation and statistical considerations

Sample size and power calculations were based on the standard formulas for cluster randomized trials with proportion endpoints (153). We expect these calculations to be conservative because of the precision gained through our pre-specified choice of a one-sided hypothesis test at the 5% significance level.

The ENHANCED-SPS trial was designed to compare viral suppression at 12 months between randomized arms, as described in the Statistical Analysis Plan (154). Briefly, accounting for the cluster randomized design (153), we estimated 14 health facilities (7 per arm) would provide 80% power to detect a difference of a least 15% in average viral suppression, assuming 70% suppression in the control, a harmonic means of 70 participants per cluster, and a coefficient of variation k=0.1 (150).

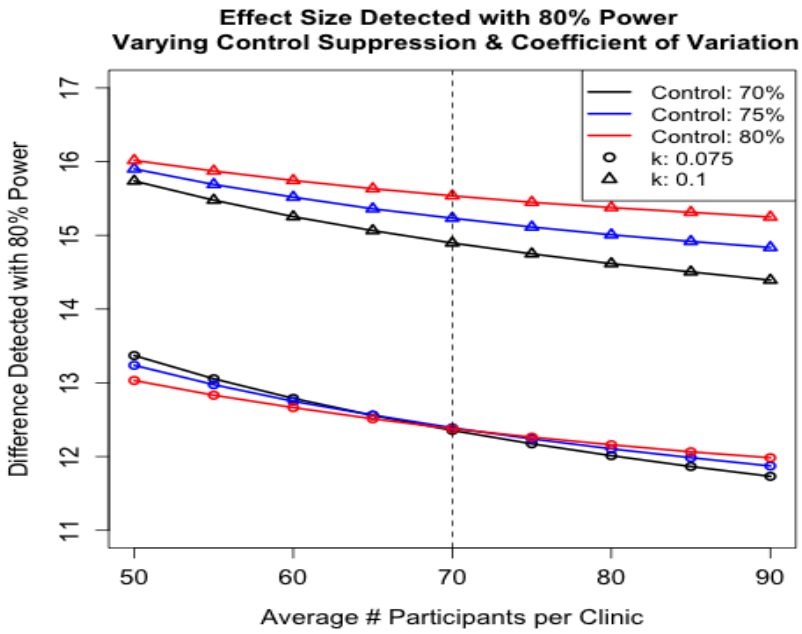


Figure 7: Power calculations

3.4.9. Data collection and data management

This includes the quantitative phase evaluating the effect of the intervention on viral suppression and retention among pregnant women. The intervention included implementation of a full range the Ministry of Health strategies for ensuring that viral suppression is achieved in all women living with HIV enrolled in mother-baby pair /HIV clinics. Routine data was collected from mothers at each of the follow-up visits using a follow-up case record form. Data was also collected from the Ministry of Health blue cards periodically for the enrolled participants to capture data for different follow-up visits. The other baseline variables measured at each clinic visit included;

Independent Variables:

Demographics and socio-economic characteristics

Age in years, religion, village of residence, tribe, marital status, education level, occupation, and monthly income, alcohol use, and mobility patterns. family support, distance/transport to facility, and family support.

Additionally, ART-related factors such as disclosure status, ART adherence, drug regimen, pregnancy status, and viral load status were also assessed through self-reports and documented in study case report forms and HIV blue cards.

ART initiation, adherence factors, and behavior

Disclosure status, ART adherence status, ART use/drug regimen, pregnancy status, VL measurements and socioeconomic status, diet/nutritional status, use of complementary medicine or herbs, alcohol use, smoking, and other clinical events during pregnancy. Data on adherence and documentation of counseling were also collected through self-reports and documented in case report forms and HIV blue cards. We abstracted data from EID registers and cards on EID testing, time, and type of testing.

Study outcomes

The primary outcome of this study was the proportion of mothers with optimal viral suppression (defined as HIV-RNA<1000 copies/ml) and predictors of suppression. Secondary outcomes included adherence to ART; HIV status disclosure at 12 months in the study.

Additionally, we evaluated the effect of the intervention on completion of infant HIV antibody testing and vertical transmission rate at 18 months after delivery, including the DNA/PCR results.

3.4.9. Statistical Analysis

Despite regular viral load monitoring, offered every 6 months or more frequently for pregnant and breastfeeding women, viral load data was subject to missingness at baseline and at endline. For some women, this missingness may reflect being out of care. For others, this missingness may reflect shortages of viral load assays. Yet, for others, this missingness may reflect gaps in the data system. Given our reliance on routinely collected viral loads and on the EMR system in the control

arm, we anticipated that missingness at baseline and end line would be greater in the control arm than in the intervention arm.

Our ability to adjust for differential measurement was attenuated by the magnitude of missing outcomes. As a result, we pre-specified the following approach in our SAP (160):

A. **If 50% or greater of control participants have an end-line viral load, we would compare end-line viral suppression by arm.**
B. **If fewer than 50% of control participants have an end-line viral load, we would compare the change in viral suppression from baseline to end line in the intervention arm only.**

Since more than 50% of the control participants lacked Viral load results, there were not sufficient data to support a by-arm comparison of end-line viral loads. We therefore used **approach B** of our pre-specified analysis plan for viral suppression, the primary endpoint, and this determined the approach taken for the secondary endpoints of ART adherence and disclosure. We conducted the following analysis within the intervention arm only.

Objective 2: Viral suppression Outcome

Among pregnant and breastfeeding women who received the ENHANCED-SPS intervention, we conducted a longitudinal analysis to evaluate changes in viral suppression, defined as HIV RNA <1000 c/mL, from baseline to end line. A threshold of suppression of 1000 c/mL was pre-specified to accommodate varying lower limits of detection across assays. This threshold is also the Ministry of Health standard.(161) For each participant, we defined baseline and end line as the viral load measure closest to and within 3.5 months of enrollment and 12 months of follow-up, respectively. Through review of routinely collected clinic data and study logs, we obtained additional information on participant demographics and their HIV care status. We classified women based on their characteristics at enrollment: age (15-24 years, 25-34 years, 35+ years), peripartum status

(pregnant or breastfeeding), care status (with "recent" as a diagnosis within 2 weeks of enrollment), ART use, and marital status.

In this pre-specified analysis among intervention participants, we used TMLE to compare the change in the proportion with viral suppression from baseline to 12 months of the ENHANCED-SPS intervention. We chose TMLE because it facilitates flexible adjustment for differences between participants with measured versus missing outcomes, is appropriate for repeated measures, and accounts for the correlation of participants within clinics (162, 163). Our adjustment set included age, peripartum status (pregnant or breastfeeding), and care group (recently vs. previously diagnosed). Our corresponding missing data assumption was that within all values of age, peripartum status, care group, and time, viral suppression among participants with a measured viral load was representative of viral suppression among participants with missing viral loads. Within TMLE, Super Learner was used for flexible adjustment and to combine predictions from stepwise regression, main terms regression, and the mean. Secondary analyses were unadjusted (i.e., contrasts of the raw proportion with viral suppression among those measured with viral load). Using the Student's *t*-distribution, we calculated two-sided 95% confidence intervals (CIs) and tested the null hypothesis that the ENHANCE-SPS intervention was not associated with improvements in viral suppression with a one-sided test at the 5% significance level. Subgroups included age group (15-24 years, 25-34 years, 35+ years), peripartum status, care group (recently diagnosed, previously diagnosed), ART status at enrolment (on ART, on ART for <6 months, or on ART for 6+ months), and marital status (never married, currently married, versus previously married or separated). We also examined viral suppression among participants who switched versus those who did not switch to a dolutegravir-based ART regimen during follow-up. All analyses were done in R, version 4.3.3.

Objective 3: ART Adherence and HIV Status Disclosure Outcome

In this pre-specified analysis among intervention participants, we used targeted minimum loss-based estimation (TMLE) to account for clustering, repeated measures, and missing data to robustly estimate the proportion of participants with ART adherence at baseline, 3, 6, 9, and 12 months of follow-up(162, 163). Through TMLE, we used Super Learner, a machine learning method, to flexibly adjust for age, peripartum status, and care group (recently vs. previously diagnosed) and, thus, account for differences between participants with and without adherence measures. Using the influence curve and the student's *t*-distribution, we calculated 95% confidence intervals (CIs) and evaluated the null hypothesis that the ENHANCE-SPS intervention was not associated with changes in ART adherence from baseline to 12 months of follow-up with a two-sided test at the 5% significance level.

Secondary analyses were unadjusted (i.e., differences in the empirical proportion of adherence measures who were classified as adherent). These analyses were repeated for the secondary endpoints of disclosure to anyone and disclosure to a partner or spouse by baseline, 3, 6, 9, and 12 months of follow-up. All analyses were repeated within baseline subgroups defined by age group, peripartum status, ART duration, and viral suppression status at enrollment. All analyses accounted for repeated measures and clustering by clinic. Analyses were done in *R*, version 4.4.0, using the *ltmle* package (164, 165).

Objective 4: EID and perinatal transmission outcomes

We conducted a retrospective evaluation of infant HIV testing during and after the implementation of the ENHANCED-SPS intervention. At each facility, we obtained data on infants born to ENHANCED-SPS participants during the one-year trial follow-up. Specifically, routinely collected data from clinic visits and documented through the electronic medical record or Uganda

EID care cards were manually reviewed and extracted. We collected data on each step of the Ugandan EID testing algorithm and recorded the testing results. As shown in Figure 8, Ugandan EID guidelines recommend the first PCR test at 4-6 weeks (or at earliest identification of exposure thereafter), a second PCR at 9-months (if breastfeeding within 6-weeks of the 1st PCR), a third PCR at 6-weeks after breastfeeding cessation (if breastfeeding within 6-weeks of the 2nd PCR), and a final HIV rapid antibody test at 18 months for all infants without a prior positive PCR (166). Additional variables captured from the health records included maternal characteristics at trial enrollment: age, pregnancy status, care status with recently diagnosed defined as within 2 weeks, and marital status.

The secondary outcome of this study was the completion of the EID testing algorithm, defined as having the final HIV antibody rapid test at 18 months of age or a prior positive PCR result. Secondary endpoints included completion of each of the tests recommended by national guidelines (Figure 8) (167). We calculated the completion of the second and third PCR assuming all infants had been recently breastfed. For each testing endpoint, infants who had previously died or whose mothers had transferred care to a different clinic were excluded, while infants who were lost to follow-up were assumed not to have completed the relevant test. An additional outcome was perinatal transmission of HIV.

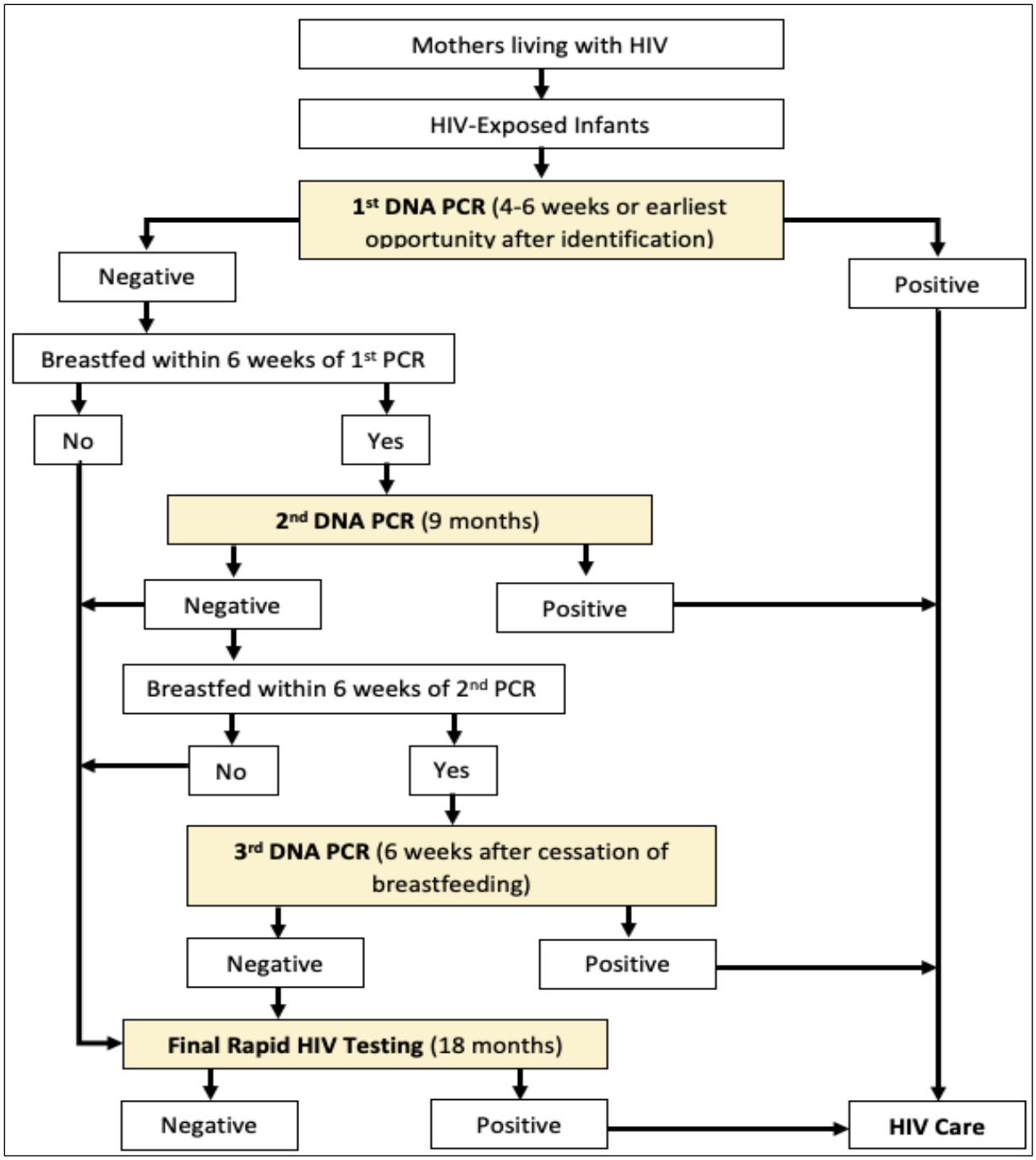


Figure 8: Schematic of the Ugandan testing algorithm for HIV-exposed infants*

**This schematic is adapted from the "Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda – 2022" (159)]. According to these guidelines, up to 3 HIV DNA PCR tests are conducted for HIV-exposed infants. The first test should be done at 4-6 weeks after birth or immediately thereafter when identifying the infant was HIV-exposed. Infants with a negative first test who have been breastfed within 6 weeks of the 1st PCR should be retested at 9-months. Those with a repeat negative PCR result who have been breastfed within 6 weeks of the 2nd PCR should be retested 6-weeks after the cessation of breastfeeding (recommended up to 12 months). All HIV-exposed children with negative PCR tests should receive a final rapid HIV antibody test at 18 months.*

3.5. Objective 5. Qualitative evaluation

3.5.1. Overview

A qualitative process evaluation was embedded within an intervention trial, using in-depth interviews to explore participant perceptions, contextual barriers and facilitators, and mechanisms influencing intervention outcomes. We conducted in-depth interviews with study participants to understand the perceptions of women on viral suppression, *mechanisms* through which the intervention succeeded/ failed, and the *characteristics* of women who did not get virally suppressed at the end of the study period. This was followed by key informant interviews for the health care providers (midwives) and peer mothers to understand the mechanisms through which the intervention succeeded or failed.

A sample of pregnant women, peer mothers, and health workers/midwives from each participating facility participated in in-depth interviews to explore their experiences and perceptions throughout the implementation period.

3.5.2. Study population and Sample size

We interviewed midwives and peer mentors from each of the 5 intervention clinics (comprehensive sample), and a total of 10 Healthcare providers were interviewed (n=10). In addition, we interviewed 20 participants across the 5 intervention clinics (n = 4 per site), purposively selecting one breastfeeding mother, one pregnant woman, one adolescent (pregnant or breastfeeding) and one non-suppressed woman of reproductive age from each facility. The interviews were conducted at baseline and end line.

Table 4:Summary qualitative methods

Study design	Qualitative study with narrative approach
Study population	Health providers on the implementation processes including observations Patients on understanding and perceptions of viral suppression; motivators to taking drugs, satisfaction and general experiences (barriers and facilitators)
Sampling and sample size	Purposive sampling and sample size were by data saturation Participants were stratified for selection according to their facility, enrollmen category and viral suppression status at baseline for maximum variation
Data collection	IDI: Moderator-fluent in Runyankole/ Rukiga and Used Pretested IDI guides Discussions were captured on an audio recorder 10 IDI (providers) & 20 IDIs (participants).
Measurements	We conducted interviews at baseline and 12 months of follow up.
Data analysis	IDIs were transcribed into English Dedoose software was used for coding and analysis. Used reflexive thematic analysi and mapped the key findings on the Theoretical Domains Framework (TDF)

3.5.3. Procedures for qualitative interviews

From the participants enrolled in the trial, we purposively sampled mothers living with HIV and healthcare providers. All participants interviewed for the in-depth interviews provided additional verbal and written informed consent to participate in the qualitative interviews. After consent, individual interviews were conducted using a comprehensive interview guide (given in Appendix: 5). To ensure accuracy and consistency, the interview guides were developed in English, translated

into Runyankole, the language spoken and understood by the participants, and then back-translated into English. Questions asked included knowledge and understanding of viral load, support received from providers during antenatal and postpartum periods as well general HIV care.

The interviewers were research assistants fluent in both English and Runyankole and were experienced in conducting qualitative interviews. The research assistants were trained in qualitative interviewing, and the interviews were conducted in a private location within the health facility. Interviews were audio-recorded, transcribed, and coded for analysis.

3.5.4. Domains of inquiry:

Aim 4 overall generated rich data on understanding and perceptions of women on viral suppression, the implementation process of the intervention, and qualitative data on facilitators and barriers to uptake of this intervention. This data also helped us understand what key enablers and barriers to achieving viral suppression, so our results can be translated with confidence to other settings, and if the intervention was not implemented properly, thus determining its scalability.

3.5.5. Trustworthiness

We employed several approaches to ensure the trustworthiness of the data. First, we followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines (168) and used the 32-item COREQ checklist to ensure consistency and transparency in the collection, management, and analysis of the study data. Second, reflexivity. Since the study involved only pregnant and breastfeeding women who are supported by peer mothers and midwives in their routine care, we ensured that qualitative interviews were conducted by an independent team of research assistants to minimize bias and ensure credibility and conformability of the research findings (169). Third, prolonged engagement, all RAs who participated in the qualitative studies had previous involvement in the implementation phases of the trial study, hence interacted with the study

participants, peer mothers and midwives for more than 3 weeks, and found it easy to establish rapport and conduct the in-depth interviews. Fourth, during analysis, the final codes and themes reported in the study were preceded first by an independent review of study team members, and discrepancies were resolved by group consensus following review of all the independent transcripts and reports (170).

3.5.6. Data management and analysis

In-depth Interviews were transcribed verbatim by the interviewers and then translated into English from the local language by independent research assistants. Transcripts were checked by the student (JK/PI) by the research assistants against the audio files for accuracy. The student (JK) read all the transcripts and the field notes to identify the meanings and patterns of the data relating to the research questions. Qualitative data were analyzed using two stages;

Stage 1: T**hematic analysis**, employing an **inductive approach** to identify patterns and generate themes emerging directly from the data without predefined categories.

Based on the six stages of thematic analysis (170), the transcripts were read and re-read by the researchers to gain a deeper understanding of the meanings of the data. Initial codes were generated by a team of four researchers by studying fragments of data, including words, lines, and segments, to understand their meaning (171).

The codebook was later presented with codes based on the lines of inquiry from the interview guide. Emerging themes were highlighted, and the final codebook was completed with all data, and the generated codes were imported into Dedoose software for coding and analysis. The results are presented in line with the emergent themes with verbatim and rich quotes extracted to support the narratives describing the findings of each of the thematic areas.

Stage 2: We then used the TDF framework (172)to link emerging themes into barriers and enablers of viral suppression within each theme to TDF domains (Table 5.). Coded transcripts were re-read and all the inductive themes were mapped deductively to the relevant TDF domain(s) if they were perceived to have an impact on the mothers' perceptions and understanding of viral suppression and its effect on vertical transmission.

Table 5:Theoretical domains framework definitions and associated questions.

TDF domain	Definition
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	The confidence that things will happen for the best or that desired goals will be attained
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Intentions	Conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention, and decision processes	Ability to retain information, focus selectively on aspects of the environment, and choose between 2 or more alternatives
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, an adaptive behavior
Social influences	Interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors
Emotions	Complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioral regulation	Anything aimed at managing or changing objectively observed measured actions

3.6. ETHICAL CONSIDERATIONS

3.6.1. Institutional Review Boards

Initial permission to conduct this study was obtained from the Clinical Epidemiology Unit. Ethical approval for this study was obtained from the Makerere University School of Medicine Research

and Ethics Committee (SOMREC-2018-074) and final approval was obtained from the Uganda National Council for Science and Technology (UNCST HS- 2468) before the study was implemented in the clinics. We also sought consent and administrative clearance from the District Health Officers of all participating districts and facility in-charges to allow implementation of study activities in their health facilities. A letter of support and clearance from the SEARCH trial Principal Investigators to use data from the SEARCH trial (Objective- one) was obtained at the inception of the study.

3.6.2. Confidentiality

The privacy of subjects and parents/mothers enrolled in the study was ensured, and data were protected to maintain confidentiality. Study participants were identified only by their unique identification number on study documents, except for those used for contact information. Participant study documents were kept in individual files in secure filing cabinets during the study and were accessed by study personnel.

Data extracted from patients/mothers' charts (e.g, ART care card ['blue card'], PMTCT register, ART register, and lab register) were entered via password-protected study-authorized laptops and kept in locked offices.

3.6.3. Informed Consent Procedures

All participants provided informed consent to participate in the study voluntarily. Written informed consent was sought from participants enrolled in intervention clinics. The informed consent forms contained all the information the participant needed to make an informed decision about whether or not to participate in the study. The consent forms were read aloud to participants/mothers by

trained staff. Forms used in the study were translated into the locally used language, which is Runyankole and Luganda, used at the study sites.

A waiver of consent was obtained from SOMREC for using data from the SEARCH study for AIM 1 and also for data abstraction activities of participants enrolled in the ENHANCED-SPS study from the Ministry of Health blue cards and ANC registers.

3.6.4. Potential Benefits and Risks to Participants

The participants received no direct benefits from the study, but those randomized to the intervention clinics received more educational messages concerning their health and ART adherence than those in the control facilities. The study also employed peer mothers to deliver some of the components of the intervention, which posed a potential risk of others learning the HIV status of the mothers enrolled in the study during the follow-up visits. These identified/ anticipated risks were discussed during the training of the peer mothers to ensure they maintained confidentiality regarding all the information received from the participants.

3.6.5. Study Monitoring

The study monitoring was done by the supervisors and the Doctoral Committee of Makerere University through regular meetings and update presentations. The Makerere University Implementation Science Training Advisory Committee provided oversight through regular progress updates and presentations.

3.6.6. Study Discontinuation and Stopping Rules

The ENHANCED-SPS trial followed the guidelines below for discontinuation and was monitored by both the doctoral committee and the Makerere University Implementation Science Training Advisory Committee to ensure participant safety and scientific integrity.

Participant Discontinuation

Participants were free to withdraw from active participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- The participant meets a previously unrecognized exclusion criterion
- Significant non-compliance with the study
- Any event or situation that occurs such that participation would not be in the best interest of the participant
- Finally, the trial may be halted if external shifts in National PMTCT guidelines or regional healthcare infrastructure render the ENHANCED-SPS strategy redundant or ethically non-viable i.e if the intervention components integrated in standard of care guidelines.

Study Discontinuation

The study may have been discontinued at any time by the IRB or other government (MoH) entities as part of their duties to ensure that research participants are protected.

CHAPTER 4.0: RESULTS

4.1. Phase 1: Objective 1: Prevalence and Predictors of Viral Suppression among Pregnant and Post-partum Women in the SEARCH Universal Test and Treat Trial.

4.1.1. Study Population

Demographic characteristics

Overall, a total of 62,066 women of reproductive age (15-45years) enrolled in the SEARCH trial at baseline were included in this analysis; 32,954 women in intervention with a median age of 25years [IQR: 19-34] and 29,112 women in control communities with a median age of 26 [IQR: 20-34]. During year 3 of the trial, there were 77,862 women age 15-45 years in the 32 study communities, inclusive of in-migrants and young women (12-14 years old at baseline) who turned 15 years during follow up and excluding women who had aged out, died, or out-migrated: 41,598 women in intervention (median age: 24[IQR: 19-33] and 36,264 women in control communities (median age:25[IQR:19-33]) **(Table 6).**

HIV Testing coverage, HIV prevalence, and pregnancy/live birth at baseline

At the time of baseline HIV testing, 93% (57,813/62,066) of all women of reproductive age and 99% (6,995/7,047) of HIV-positive women responded to the following pregnancy/live birth questions: “Are you pregnant now?” and “How many live births have you had in the past year?”. Among women living with HIV aged 15-45 years, 33% reported a current pregnancy or at least one live birth in the prior year at baseline.

Table 6: Demographic characteristics of 15-45-year-old women residents of SEARCH Communities in rural Uganda and Kenya, stratified by arm, at baseline and year 3 of the trial.

	Intervention Baseline, N (%)	**Year 3, N (%)**	**Control Baseline, N (%)**	**Year 3, N (%)**
	N = 32,954	**N = 41,598**	**N = 29,112**	**N = 36,264**
Age in years, median (IQR)	25 (19-34)	24 (19-33)	26 (20-34)	25 (19-33)
Region				
Kenya	11,568 (35.1)	13,529 (32.5)	10,352 (35.6)	11,934 (32.9)
Uganda-West	10,453 (31.7)	13,992 (33.6)	9,304 (32)	12,129 (33.4)
Uganda-East	10,933 (33.2)	14,077 (33.8)	9,456 (32.5)	12,201 (33.6)
Educational attainment[a]				
Less than primary	20,627 (62.6)	28,013 (67.3)	18,653 (64.1)	24,126 (66.5)
Primary	5,188 (15.7)	5,723 (13.8)	4,702 (16.2)	5,268 (14.5)
Secondary or higher	7,139 (21.7)	7,862 (18.9)	5,757 (19.8)	6,870 (18.9)
Occupation[b]				
Formal sector	8,493 (25.8)	7,260 (17.5)	6,612 (22.7)	6,446 (17.8)
High-risk informal	744 (2.3)	660 (1.6)	1,245 (4.3)	1,076 (3)
Low-risk informal	21,177 (64.3)	21,456 (51.6)	18,847 (64.7)	19,215 (53)
Other	1,035 (3.1)	1,259 (3.9)	913 (3.1)	1,160 (4)
No job or disabled	1,424 (4.3)	1,506 (4.7)	1,435 (4.9)	1,401 (4.8)
Marital status[c]				
Single	9,587 (29.2)	8,204 (25.5)	7,645 (26.3)	7,483 (25.5)
Married	20,399 (62)	21,531 (67)	18,757 (64.6)	19,477 (66.5)
Widowed, divorced, or separated	2,890 (8.8)	2,404 (7.5)	2,649 (9.1)	2,341 (8)
Alcohol use[e]	1,712 (6.1)	1,219 (3.6)	1,469 (5.9)	984 (3.2)
Mobile[f]	4,702 (14.3)	1,483 (3.6)	3,910 (13.4)	1,300 (3.6)
Pregnancy or live birth[g]				
Reported current pregnancy	2,776 (9.1)	2,496 (7.5)	2,528 (9.3)	2,506 (8.3)
Reported live birth in prior year	8,448 (27.6)	4,431 (13.3)	7,579 (27.7)	4,038 (13.3)

a-Education missing on 82 (0.1%) and 16,444 (21.1%) at baseline and year 3, respectively.
b-Occupation missing on 141 (0.2%) and 16,423 (21.1%) at baseline and year 3, respectively.
c-Marital status missing on 139 (0.2%) and 16,422 (21.1%) at baseline and year 3, respectively.
d-Household wealth index, defined from principal component analysis of household item survey, missing on 220 (0.4%) and 6,209 (8%) at baseline and year 3, respectively.
e-Alcohol use missing on 8,915 (14.4%) and 14,104 (18.1%) at baseline and year 3, respectively.
f-Mobile, defined as spending one or more month away from the community in the past year, missing on 13,896 (17.8%) at year 3
g-Pregnancy or live birth status missing on 4,253 (6.9%) and 14,449 (18.6%) at baseline and year 3, respectively.

Among the women of reproductive age, HIV testing coverage at baseline was 91% (30,074/32,954) and 92% (26,895/29,112) in intervention and control communities, respectively. Baseline HIV prevalence among women who tested varied by region: 23.8% in Western Kenya, 7.7% in Western Uganda, and 3.7% in Eastern Uganda.

Testing, HIV prevalence, and pregnancy/live birth at year 3 of the trial

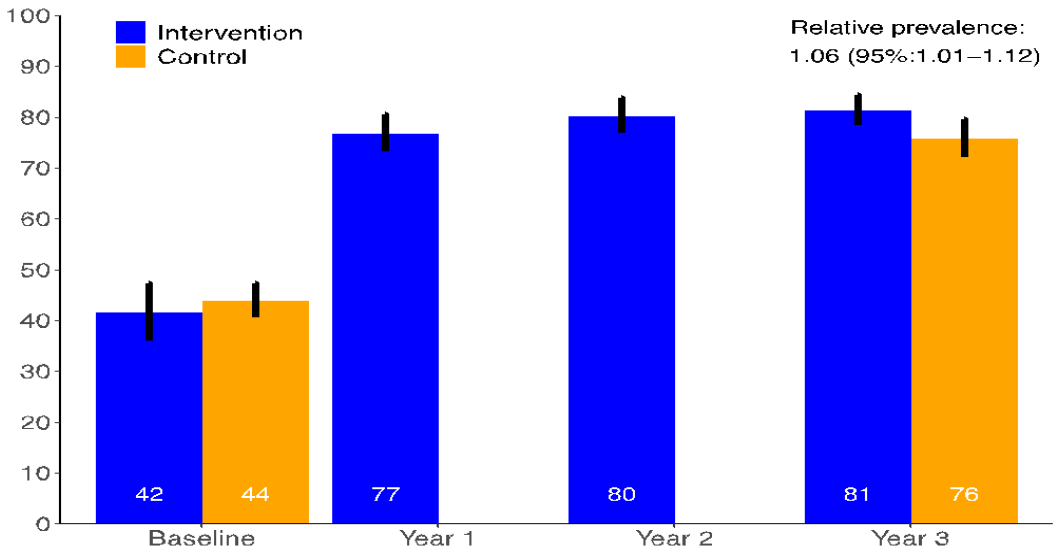
Among the 77,862 women aged 15-45 years enumerated in the 32 study communities at year 3, HIV testing coverage was 80% (33,326/41,598) and 84% (30,282/36,264) in intervention and control communities, respectively, at year 3 of the trial**.**

Year 3 HIV prevalence among women aged 15-45 years who tested was 10.6% (3,540/33,326) and 10.2% (3,086/30,282) in intervention and control communities, respectively. At the time of year 3 testing, 81% (63,413/77,862) of all women of reproductive age and 99% (6,557/6,626) of HIV-positive women responded to the pregnancy/live birth questions. Among women with HIV, 14% (481/3,505) reported a current pregnancy or a live birth in the prior year at year 3 of the trial in intervention communities, compared to 16% (487/3,052) in control communities **(Table 6).**

4.1.2. Prevalence and predictors of viral suppression

Prevalence of Viral Suppression among pregnant/post-partum women

Among 15-45-year-old women living with HIV who reported current pregnancy or live birth in the prior year at baseline, HIV viral suppression was 42% (95% confidence interval (CI): 36-47%) in intervention communities, and 44% (95% CI: 41-47%) in control communities, after adjusting for missingness in HIV status and viral load. During subsequent annual rounds of offering universal HIV testing in intervention communities only, VS estimates among pregnant and postpartum women were 77% (95% CI: 73-80%) and 80% (95% CI: 77-84%) in follow-up years 1 and 2 of the trial, respectively (Figure 9).



	Intervention		Control	
	Adjusted*	Unadjusted**	Adjusted*	Unadjusted**
Baseline	536/1290 (42%)	417/952 (44%)	489/1113 (44%)	357/718 (50%)
Year 1	590/765 (77%)	568/724 (78%)		
Year 2	497/621 (80%)	480/586 (82%)		
Year 3	393/483 (81%)	384/464 (83%)	373/491 (76%)	366/476 (77%)

*Adjusted for missing measures on HIV status and viral suppression with TMLE for community, age group and mobility
**Unadjusted: Number measured viral suppression divided by number known to be HIV-positive with HIV RNA level measured.

Figure 9: Estimates of population-level HIV viral suppression among women aged 15-45 years and reporting a current pregnancy or live birth over the prior year by study year in the SEARCH trial.

HIV Cascade at Baseline and follow-up Year 3

Among 15-45-year-old women living with HIV reporting a current pregnancy or live birth in the prior year during year 3 of the trial, 95% (95% CI: 92-98%) and 91% (95% CI: 89-93) knew their HIV status in intervention and control communities, respectively. Of those with a prior diagnosis of HIV, 98% (95% CI: 97-99%) and 95% (95% CI: 94-97) were on ART in intervention and control communities, respectively. Of those on ART, 88% (95% CI: 85-91) and 87% (95% CI: 84-91) were virally suppressed, respectively (Figure 10).

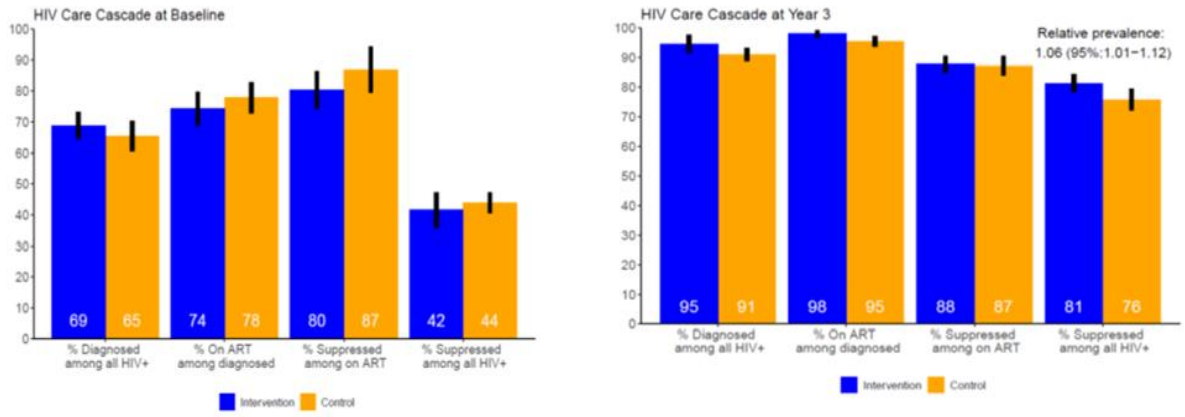


Figure 10: HIV Cascade at Baseline and follow-up Year3

At year 3, overall population-level prevalence of VS among 15-45-year-old women reporting a current pregnancy or live birth in the prior year had increased to 81% (95% CI: 78-84%) in intervention communities compared to 76% (95% CI: 72-80%) in control communities (Figure 11). At year 3, the population-level prevalence of VS among women reporting current pregnancy or live birth in the prior year was 6% higher in intervention versus control communities (adjusted relative prevalence: 1.06, 95% CI: 1.01-1.12; p=0.02).

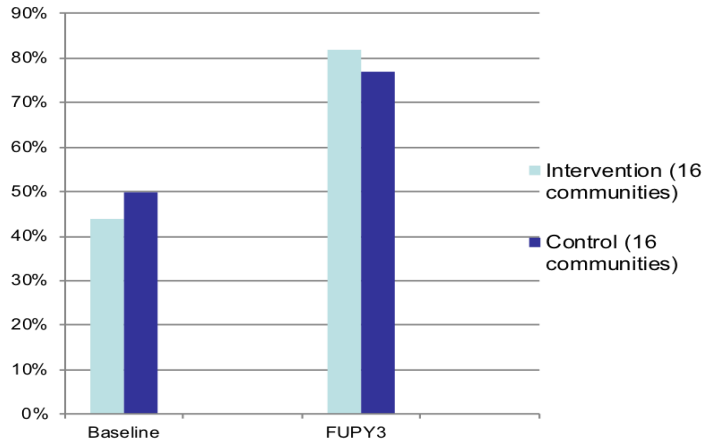


Figure 11: Viral Suppression among women reporting pregnancy-related event over time (baseline to follow-up year 3)

Prevalence of Viral Suppression among Women of Reproductive Age

In comparison, population-level VS estimates for all 15-45-year-old women living with HIV (regardless of reported pregnancy or life birth) at year 3 was 77% (95% CI: 74-80%) in intervention versus 68% (95% CI: 66-70%) in control communities (adjusted relative prevalence: 1.13, 95%CI:1.08-1.19; p<0.001). These improvements in viral suppression were also seen across the regions over the three years of follow-up (Figure 12).

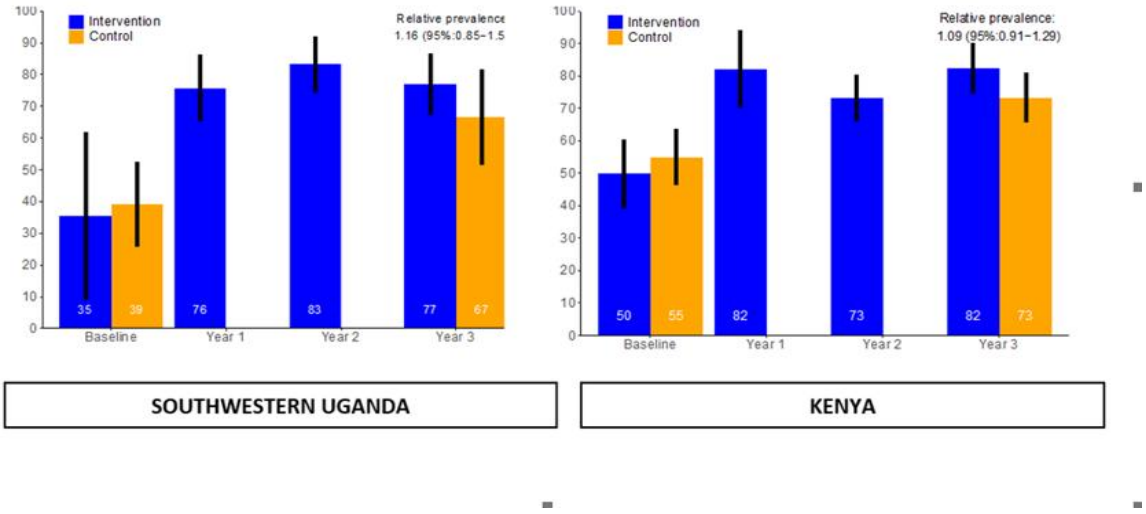


Figure 12: Viral Suppression rates by region

Predictors of Viral Suppression among pregnant/post-partum women by SEARCH trial arm

Age was the strongest predictor of viral suppression (VS) across all communities. Compared with young women aged 15–19 years, older age consistently predicted higher VS at year 3. In the intervention arm, VS increased progressively with age, from RR 1.05 (95% CI: 0.85–1.25) among women aged 20–24 years to RR 1.40 (95% CI: 1.10–1.70) among those aged 40–45 years. A similar but less pronounced trend was observed in the control arm, with RR 0.95 (95% CI: 0.80–1.20) for ages 20–24 and RR 1.35 (95% CI: 1.05–1.65) for ages 40–45. Marital status was not a significant predictor of VS. Being single (RR 0.95, 95% CI: 0.75–1.15) or

separated/divorced/widowed (RR 0.90, 95% CI: 0.75–1.10) was not associated with higher suppression compared to married women.

Pregnancy status showed mixed associations. In intervention communities, self-reported current pregnancy or live birth in the prior year was not associated with VS at year 3 (RR 1.01, 95% CI: 0.98–1.05, p=0.43). In contrast, in control communities, women with a current pregnancy or live birth in the prior year were more likely to be suppressed. Incident pregnancy did not affect maintenance of VS (96% vs. 97%; RR 1.00, 95% CI: 0.96–1.03) or achievement of VS (77% vs. 74%; RR 1.04, 95% CI: 0.95–1.13) at year 1 in intervention communities (*Figure 13).*

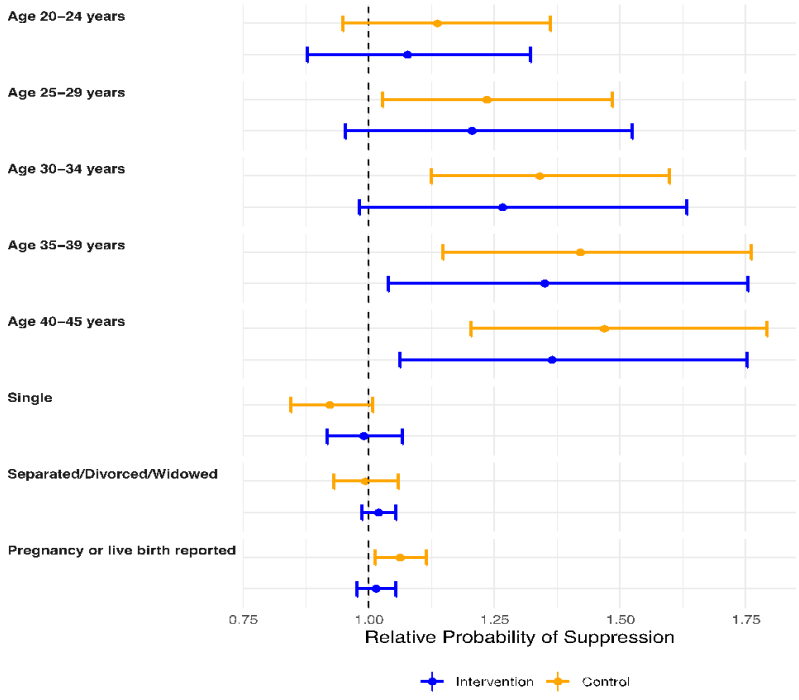


Figure 13:Adjusted predictors of HIV viral suppression (HIV RNA<500 copies/mL) among women living with HIV aged 15-45 years. ***As assessed during Year 3 of the SEARCH Study using targeted maximum likelihood estimation (TMLE), treating the community as the independent unit. Each relative probability is adjusted for the other predictors and region. Reference categories are age 15-24 years, marital status of married, and not reporting a pregnancy or live birth in the prior year.*

4.2. PHASE TWO: Effect of the ENHANCED-SPS intervention on viral suppression, HIV status disclosure, and adherence to ART (Objective 2&3).

This section summarizes the effects of the ENHANCED-SPS intervention. The primary outcome evaluated is viral suppression over time, while other outcomes include adherence to antiretroviral therapy (ART), and HIV status disclosure.

We present results from **the intervention arm only**, following more than 50% of our participants in the control arm missing data on routine viral load measurement within the MoH HIV blue card record, which prevented by arm comparison of the primary outcome as pre-specified in our methods and statistical analysis plan. Further details are available in the Statistical Analysis Plan (160), and a step-by-step description of TMLE for change over time analyses is given in Kabami et al(173). We also detail how the intervention influenced early infant HIV testing and perinatal transmission**.**

4.2.1. Objective 2. Effect of the intervention on Viral suppression over time among pregnant and breastfeeding women.

We present the change over time in viral suppression from Baseline to 12 months of Follow-up among participants in the intervention arm only.

4.2.1.1. Description of the study participants

This analysis included 505 pregnant and post-partum women receiving care at 7 health facilities with the ENHANCED-SPS intervention. Their median age was 28 years [IQR:24-32]; 96% were pregnant, and 69% were previously diagnosed with HIV **(Table 7).** At enrollment, 29% were not on ART; 8% had been on ART for <6 months, and 64% for 6 or more months. Among those on ART, the most common regimen was efavirenz-based (95%).

Table 7:Baseline characteristics for the ENHANCED-SPS study participants in N (%).

	Frequency n (%)
	N=505
Age in years	
- Aged 15-24 years	123 (30%)
- Aged 25-34 years	220 (54%)
- Aged 35+ years	64 (16%)
Enrollment group	
- Pregnant and a previous diagnosis of HIV	348 (69%)
- Pregnant and new diagnosis	135 (27%)
- Breastfeeding and a new diagnosis	22 (4%)
Marital status*	
- Never married	40 (11%)
- Married	276 (76%)
- Separated, divorced, or widowed	48 (13%)
Baseline ART regimen*	
- Efavirenz-based regimen	388 (95%)
- Other baseline ART regimen	20 (5%)

4.2.1.2. Change in viral suppression from Baseline to 12-months of Follow-up

Among the 505 participants, 455 (90.1%) had a baseline viral load measurement, and 354 (70.1%) had a follow-up viral load measurement. Accounting for possibly differential viral load ascertainment, the estimated proportion with viral suppression was 70.0% (95%CI: 65.9-74.1%) at baseline. After 12 months of implementing the ENHANCED-SPS intervention, the estimated proportion with viral suppression was 94.9% (95%CI: 92.5-97.4%), corresponding to an absolute increase of 24.9% (95%CI: 21.6-28.2%; $p<0.001$). In addition, 98% of the women who were

suppressed at baseline maintained viral suppression after 12 months of receiving the intervention. Furthermore, 88% of women without viral suppression at baseline achieved suppression at the end of follow-up.

The intervention also resulted in significant improvements over time within subgroups defined by age group, peripartum group, care status, ART status, and marital status (Figure 14). By age group, the greatest increase in viral suppression was among the youngest participants (15-24 years) from 55.5% at baseline to 95.1% at 12-months and corresponding to an absolute increase of 39.5% (95%CI: 25-54.1%; p<0.001). Improvements in viral suppression decreased with increasing age: 18.1% (95%CI: 13-23.3%; p<0.001) increase among participants aged 25-34 years and 15.7% (95%CI: 1.8-29.6%; p=0.017) increase among participants aged 35 years and above.

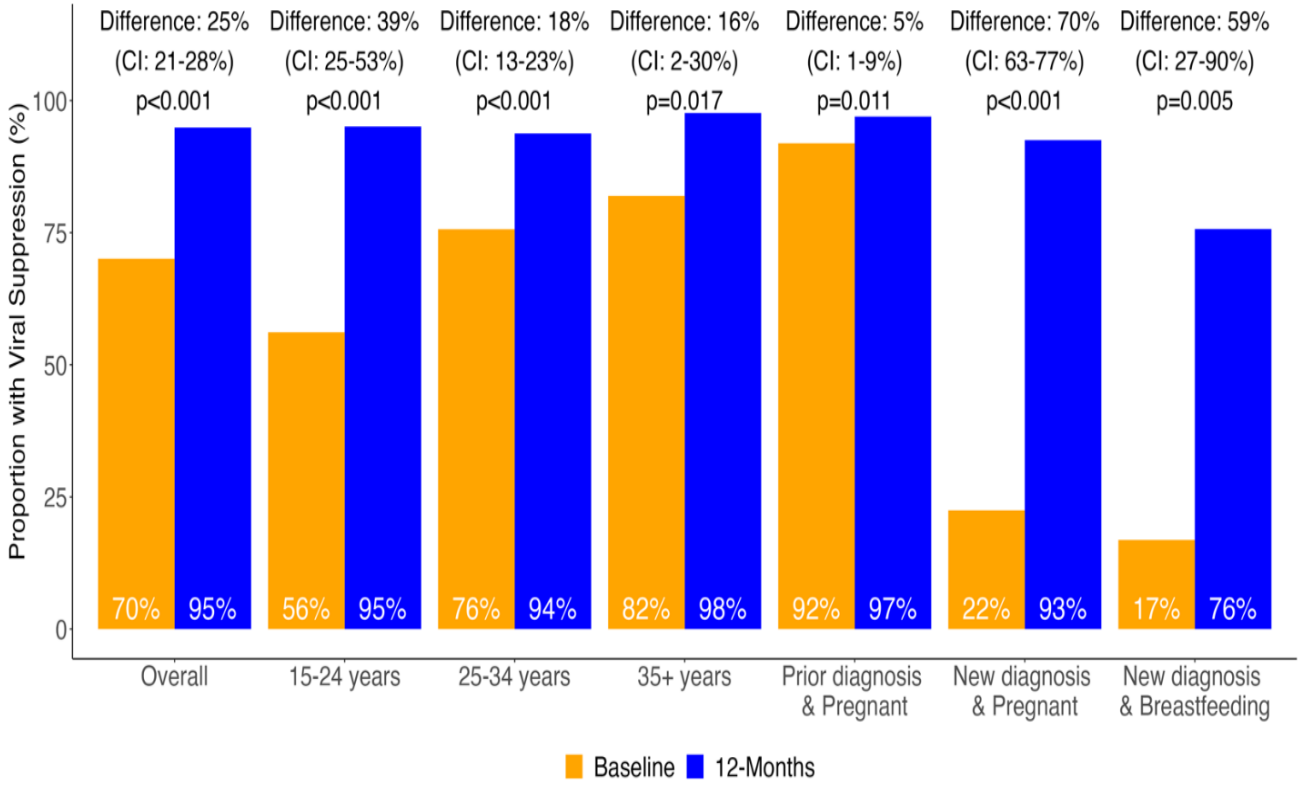


Figure 14: Estimated change in HIV viral suppression (<1000 c/mL) from baseline to 12 months of follow-up, overall and by key subgroups

Importantly, Viral suppression varied by peripartum and marital status. Suppression rates were lower among breastfeeding women, increasing from 16.8% at baseline to 75.7% at 12 months (58.9% increase; 95% CI: 27.4–90.3; p=0.005). In contrast, 72.4% of pregnant women had viral suppression at baseline, rising to 95.6% at 12 months (23.1% increase; 95% CI: 21.3–25.0; p<0.001). By marital status, improvements were 17.0% (95% CI: –4.8–38.9; p=0.051) among never-married women, 28.1% (95% CI: 26.0–30.1; p<0.001) among married women, and 11.3% (95% CI: 1.5–21.1; p=0.016) among those with other marital status.

Participants recently diagnosed with HIV showed the greatest improvement in viral suppression, rising from 21.7% at baseline to 91.0% at 12 months (69.3% increase, 95%CI: 61.0–77.6; p<0.001). Previously diagnosed participants improved more modestly, from 91.9% to 97.0% (5.0% increase, 95%CI: 1.0–9.0; p=0.011). During follow-up, 81 (23%) switched to a dolutegravir (DTG)-based regimen, but significant gains were observed regardless of switching Those who switched achieved 98.4% suppression at the end of the follow up period representing a slightly larger absolute increase of 23.9% from 74.6%; 95%CI: 14.0–33.7; p<0.001), while those who did not -switch reached 95.2% (an absolute increase of 27.2% from 67.9%; 95%CI: 19.2–35.3; p<0.001).

4.2.2. Objective 3: Effect of the intervention on ART adherence and HIV status disclosure over time among pregnant and breastfeeding women.

4.2.2.1. Description of the study population

A total of 505 pregnant and postpartum women with HIV were included in the analysis for the HIV status disclosure and ART adherence, and baseline characteristics already described in section 4.2.1.1 above (Table 7)

4.2.2.2. Change in ART adherence over time from Baseline to 12 months of Follow-up

As shown in Table 8 below, the estimated proportion of participants who were ART adherent was 68% (95%CI: 62,74%) at baseline and increased to 93% (95%CI: 85,100%) after 3 months of the ENHANCED-SPS intervention. After 12 months, an estimated 93% (95%CI: 81,100%) of participants were adherent, corresponding to an absolute increase of 25% (95%CI: 9,40%; p=0.009) from baseline. Baseline adherence varied by age group: 56% for 15–24-year-olds, 76% for 25–34-year-olds, and 81% for 35+ year-olds (Table 8).

Over the 12-month follow-up, the proportions with good adherence increased to 89%, 94%, and 100%, respectively; therefore, the largest changes in adherence were among the youngest women. Adherence among the pregnant women was 71% at baseline, and this proportion increased to 93% at 3 months and was largely sustained throughout the follow-up period. Only 5% of the breastfeeding women were adherent at baseline, but this proportion reached 100% by end line.

Participants on ART for 6+ months sustained high levels of adherence (≥92%) throughout the study. Adherence among participants on ART for less than 6 months was low at baseline at 22% and increased to 86% after 3 months and reached 95% at 12 months.

Importantly, the majority of the participants who were virally suppressed at enrollment were adherent throughout; specifically, among this subgroup, the estimated proportion with adherence increased from 88% at baseline to 96% by 3 months and was sustained. Equally important, the proportion of participants without viral suppression at enrollment with poor adherence was reduced from 80% at baseline to 15% at 12 months. Similar results were observed in unadjusted analyses, which excluded participants without adherence measures.

Table 8: Estimated proportion adherent to antiretroviral therapy (ART) over time.

	Baseline (95%CI)	3-months (95%CI)	6-months (95%CI)	9-months (95%CI)	12-months (95%CI)
Overall	68% (62,74)	93% (85,100)	93% (87,100)	93% (86,100)	93% (81,100)
Age group					
Aged 15-24 years	56% (40,72)	92% (84,100)	90% (83,97)	90% (78,100)	89% (72,100)
Aged 25-34 years	76% (70,81)	95% (88,100)	98% (94,100)	94% (87,100)	94% (84,100)
Aged 35+ years	81% (75,87)	98% (92,100)	95% (88,100)	100% (100,100)	100% (100,100)
Peripartum status					
Pregnant	71% (68,74)	93% (85,100)	95% (88,100)	93% (86,100)	92% (80,100)
Breastfeeding	5% (0,24)	87% (68,100)	70% (25,100)	100% (100,100)	100% (100,100)
ART status					
On ART <6 months	22% (10,34)	86% (67,100)	86% (72,100)	89% (79,99)	95% (87,100)
On ART 6+ months	95% (92,98)	97% (94,100)	98% (94,100)	97% (90,100)	92% (79,100)
Suppression status					
Suppressed	88% (83,94)	96% (90,100)	97% (92,100)	98% (93,100)	97% (88,100)
Non-suppressed	20% (16,23)	83% (64,100)	83% (63,100)	81% (63,99)	85% (68,100)

[1]*Estimates are from TMLE accounting for differences between participants with and without adherence measurements.*

4.2.2.3. Change in HIV status Disclosure to anyone over time from Baseline to 12-months of follow-up among pregnant and breastfeeding women.

As shown in Table 9 below, the estimated proportion of participants who had disclosed their HIV status to anyone (e.g., family or friend) was 80% (95%CI: 69,90%) at baseline and increased to 90% (95%CI: 84,97%) by 3-months of the ENHANCED-SPS intervention. After 12-months, an

estimated 94% (95%CI: 89,99%) of participants had disclosed their status, corresponding to an absolute increase of 14% (95%CI: 8,21%; p=0.003.

Changes in disclosure varied by baseline subgroup (Table 9). The largest improvements were for the youngest participants (15-24 years); specifically, the proportion who had disclosed increased from 73% at baseline to 92% by 12-months. Disclosure among women who were breastfeeding at enrollment consistently lagged behind disclosure among women who were pregnant at enrollment; after 12-months, the estimated proportions who had disclosed to anyone were 81% and 94%, respectively.

Similar trends were seen for participants who were on ART for less than 6 months at enrollment and participants without viral suppression at enrollment; their disclosure rates increased to ~85% by 12-months from ~50% at baseline. Among participants on ART for 6+ months and those with viral suppression at enrollment, disclosure was >90% at baseline and exceeded 95% by the close of the follow-up period. Again, similar results were seen in unadjusted analyses, excluding participants without disclosure measures.

Table 9: Estimated proportion of enrolled participants disclosing their HIV status to anyone over time.

	Baseline (95%CI)	3-months (95%CI)	6-months (95%CI)	9-months (95%CI)	12-months (95%CI)
Overall	80% (69,90)	90% (84,97)	91% (86,97)	94% (89,98)	94% (89,99)
Age group					
Aged 15-24 years	73% (57,88)	89% (81,97)	90% (83,97)	92% (85,98)	92% (85,98)
Aged 25-34 years	83% (73,94)	93% (88,98)	94% (89,99)	96% (92,100)	97% (94,100)
Aged 35+ years	87% (83,90)	94% (90,98)	95% (91,100)	97% (93,100)	97% (93,100)
Peripartum status					
Pregnant	81% (72,91)	92% (86,97)	93% (88,98)	94% (90,99)	94% (90,99)
Breastfeeding	45% (09,81)	67% (39,94)	67% (39,94)	76% (52,100)	81% (60,100)
ART status					
On ART <6 months	51% (28,73)	78% (66,89)	80% (70,91)	85% (75,95)	86% (76,96)
On ART 6+ months	97% (92,100)	98% (94,100)	98% (94,100)	98% (95,100)	99% (96,100)
Viral suppression status					
Suppressed	93% (86,100)	97% (94,100)	97% (94,100)	98% (95,100)	98% (96,100)
Non-suppressed	50% (31,70)	78% (64,91)	80% (67,93)	84% (73,95)	85% (74,96)

[1]*Estimates are from TMLE accounting for differences between participants with and without adherence measurements.*

4.2.2.4. Change in HIV status disclosure to partner or spouse over time from baseline to 12-months follow-up among pregnant and breastfeeding women

Similar trends were observed for disclosure specifically to a spouse or partner over time. At baseline, spouse/partner disclosure was 79% (95%CI: 68,91%) and increased to 89% (95%CI: 84,94%) after 3-months of receiving the ENHANCED-SPS intervention. After 12-months, an estimated 93% (95%CI: 89,98%) of the participants had disclosed to their spouse or partner,

corresponding to an absolute increase of 14% (95%CI: 3,25%; p=0.019). As before, changes in spouse/partner disclosure varied by subgroups. Large improvements were observed among the youngest women (aged 15-24 years) whose disclosure rates increased from 72% to 93%; breastfeeding women whose disclosure rates increased from 45% to 87%, and virally non-suppressed women whose disclosure rates increased from 50% to 91%.

4.2.3. Objective 4. Effect of the ENHANCED SPS intervention on EID and Perinatal transmission of HIV among infants born to participants enrolled in the ENHANCED-SPS study.

4.2.3.1. Study Accrual and Characteristics

A total of 464 infants born to participants of the ENHANCED-SPS study were included in this analysis, with 234 in the intervention arm and 230 in the control arm (Figure 15**).** At trial enrolment, their mothers had a median age of 29 years with slightly over 50% aged between 25-34 years; 90% were pregnant; 28% were recently diagnosed with HIV, and 77% were married (Table 11). Additional characteristics, such as duration on ART and viral suppression status, were only available in the intervention arm and excluded.

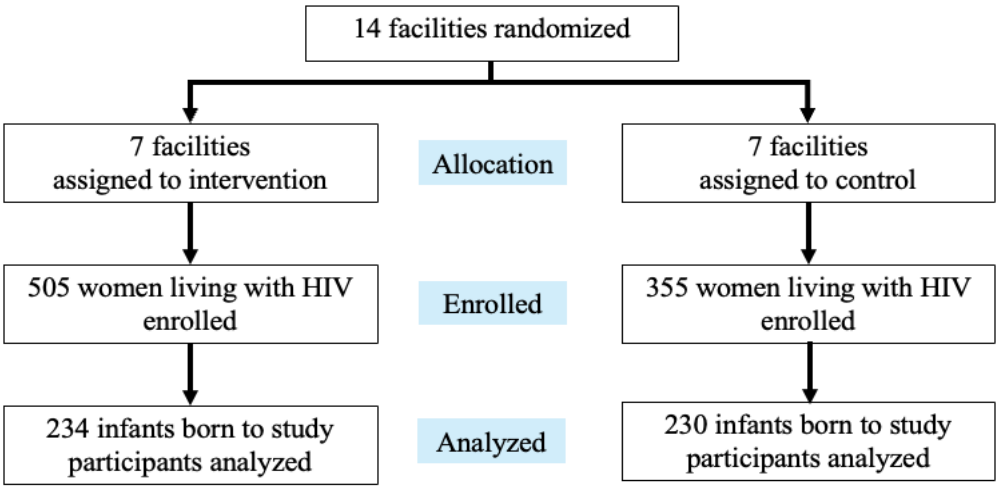


Figure 15: Early: Early Infant Diagnosis CONSORT Diagram

Table 10: Demographic characteristics of the ENHANCED-SPS participants who gave birth to the 464 infants included in this analysis

	Intervention (N=234)	Control (N=230)
Age		
-Age 15-24 years	64/212 (30%)	46/226 (20%)
-Age 25-34 years	119/212 (56%)	114/226 (50%)
-Age 35+ years	29/212 (14%)	66/226 (29%)
Peripartum status		
Pregnant	226/232 (97%)	223/227 (98%)
Breastfeeding	6/232 (3%)	4/227 (2%)
Care status		
Recently diagnosed[1]	54/232 (23%)	74/227 (33%)
Previously diagnosed	178/232 (77%)	153/227 (67%)
Marital status		
Never married	22/198 (11%)	21/217 (10%)
Married	153/198 (77%)	167/217 (77%)
Previously married or separated	23/198 (12%)	28/217 (13%)

[1]*Diagnosed within 2 weeks of study enrollment.*

4.2.3.2. Effectiveness of the intervention on completion of final antibody rapid HIV Testing at 18months among exposed infants

After 18-months of follow-up, 13 infants had transferred care and 9 had died. Of the remaining 442 infants (220 intervention and 222 control), none had a prior positive PCR test and the final antibody rapid HIV testing coverage (primary outcome) was significantly higher in the intervention arm at 94.5% (95%CI: 91.6-97.5%) compared to 83.3% (95%CI: 78.4-88.3%) in the control arm. Therefore, the intervention increased completion by 11.2% (95% CI: 5.4-17.0%; p< 0.001).

Intervention effectiveness on the final antibody rapid HIV testing varied by subgroups. Testing coverage rates among infants born to the youngest women (aged 15-24 years) did not differ between arms and were 90.0% (95%CI: 82.3-97.7%) in the intervention and 93.0% (95%CI: 85.4-

100%) in the control. However, a significantly higher proportion of infants born to intervention participants aged 25-34years completed rapid antibody testing: 96.4% (95% CI: 93.0-99.8%) in the intervention versus 76.4% (95% CI: 68.4-84.3%) in the control arm corresponding to a difference of 20.1% (95%CI: 11.4-28.7%; p<0.001). Among infants born to participants aged 35years and above, 100% completed rapid antibody testing in the intervention arm compared to 87.7% (95%CI: 79.6-95.8%) in the control arm: an increase of 12.3% (95%CI: 4.2-20.4%; p=0.003).

Testing coverage also varied by maternal time since HIV diagnosis. Specifically, completion rates among infants born to mothers with a recent HIV diagnosis were 85.7% (95%CI: 78.0-97.0%) in the intervention arm compared to 68.1% (95% CI: 57.1-79.2%) in the control arm: an increase of 19.4% (95%CI: 4.8-33.9%; p=0.009). Completion among infants born to previously diagnosed mothers was notably higher in both arms but still significantly higher in the intervention than the control: 96.5% (95%CI: 93.7-99.2%) versus 90.0% (95%CI: 85.2-94.8%), respectively, for a difference of 6.5% (95%CI: 0.9-12.0%; p=0.02). Finally, testing completion varied by marital status; infants born to women who were never married had the lowest coverage in both arms but larger intervention effects (20.9% improvement), as compared to infants of women who were married (11.0% improvement) and infants of woman who were previously married or separated (10.7% improvement).

4.2.3.3. Completion of Prior Steps of the EID Testing Algorithm

Coverage of the first PCR test was high in both arms: 98.7% (95%CI: 97.3-100%) in the intervention and 99.1% (95%CI: 97.9-100%) in the control (Figure 16). The proportion of infants completing their second PCR test in the intervention arm was slightly, but not significantly, higher than in the control arm: 91.3% (95%CI: 87.6-95.0%) versus 89.0% (95%CI: 85.0-93.1%), respectively. However, the proportion of infants completing the third PCR test was significantly higher in the intervention arm compared to the control arm: 89.7% (95%CI: 85.8-93.7%) versus 74.9% (95%CI: 69.1-80.6%), respectively, and corresponding to a difference of 14.8% (95% CI: 7.9-21.8%; p<0.001). The median age at third PCR completion (among those testing) was 13.8 months and similar by arm: 13.9 months in intervention and 13.7 months in control.

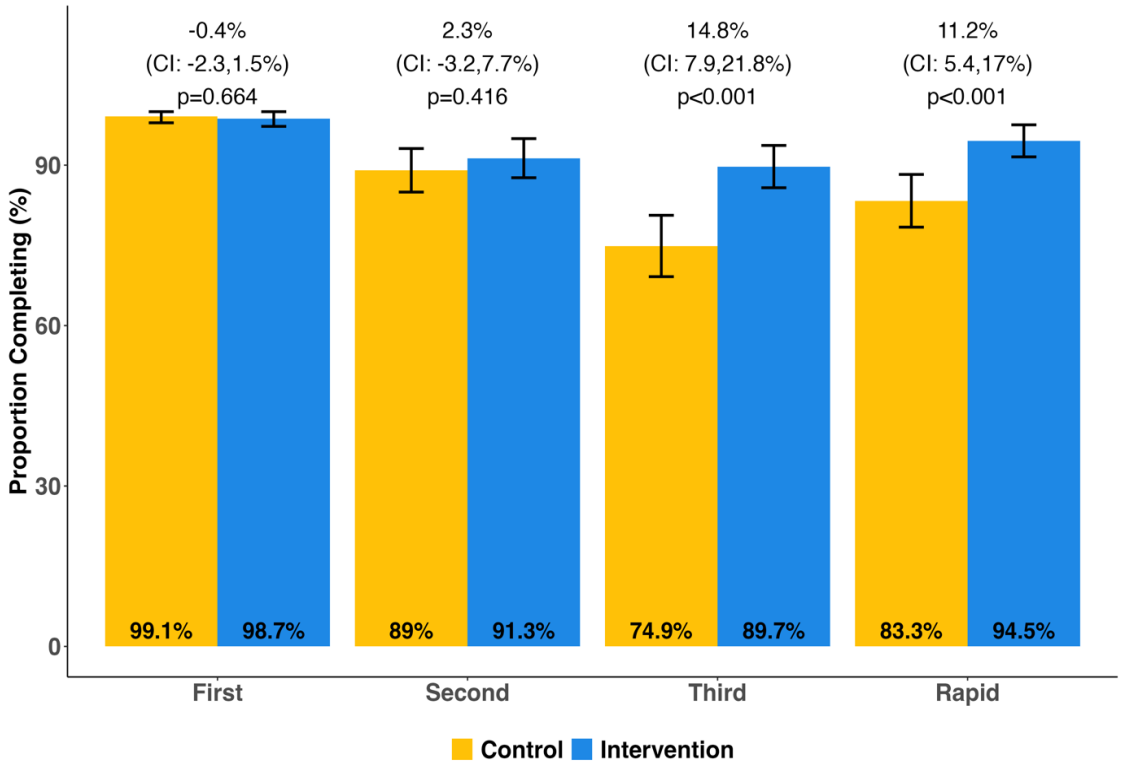


Figure 16: Effectiveness of the ENHANCED-SPS intervention as compared to the standard-of-care (control) on completion of each step in the early infant diagnosis testing algorithm

The intervention significantly improved third PCR completion among infants born to women who were ages 25-34 years (18.2% improvement), ages 35+ years (18.1% improvement), previously diagnosed (14.8% improvement), married (13.7% improvement), and previously married or separated (20.7% improvement; see Table, Supplemental Digital Content 3). There were no significant differences for infants born to women who were the youngest (5.7% improvement), recently diagnosed (13.2% improvement), or never married (15.9% improvement).

4.2.3.4. Perinatal transmission of HIV

The perinatal transmission outcome was evaluated in 442 out of 464 (94%) infants who completed the final HIV rapid antibody testing at 18 months. All infants were negative for HIV and, thus, there were no transmissions during follow-up in either arm. It is worth noting, however, that two infants (1 control and 1 intervention) tested positive at the time their mothers enrolled (baseline) in the ENHANCED-SPS trial.

4.3. Objective 5: Qualitative Evaluations

We conducted qualitative evaluations to understand perceptions of viral load testing and suppression in HIV care among pregnant and breastfeeding women. We specifically explored the understanding and interpretation of viral suppression and its role in vertical transmission. In addition, we evaluated the implementation processes to explore mechanisms through which the intervention succeeded/ failed and the *characteristics* of women who did not get virally suppressed at the end of the study period.

This was followed by key informant interviews for the health care providers (midwives) and peer mothers to understand the mechanisms through which the intervention succeeded or failed.

4.3.1. Perceptions and understanding of women on viral suppression

4.3.1.1. Description of the study population

Thirty-two (32) pregnant and breastfeeding women were interviewed. The median age was 29 years; 46.9% aged between 18-24years and 40.6% aged between 25-34years. Majority of the participants were married at 90.6% while single and divorced/separated comprised only 9.4%. Of the participants interviewed, 25 % were known to have HIV, in care and virally suppressed at first antenatal care (ANC) visit, 37.5% were known to have HIV and were in care but non-suppressed at their first ANC visit, while 37.5% were newly diagnosed with HIV at first ANC visit. (Table 11)

Table 11: Demographic characteristics of the study participants for the qualitative interviews

Characteristic	Number (%) of participants
Age	
18-24	15 (46.9)
25-34	13 (40.6)
35-44	04 (12.5)
Facility level for care	
HCIII	13 (40.6)
HCIV/Hospital	19 (59.4)
Marital status	
Married	29 (90.6)
Single	2 (6.3)
Divorced/separated	1 (3.1)
Viral Suppression status	
Suppressed	8 (25)
Not Suppressed	12 (37.5)
Newly diagnosed	12 (37.5)

4.3.1.2. Stage 1: Thematic analysis

From the thematic analysis stage, three broad themes emerged. Within each theme, several barriers and enablers were identified and subsequently mapped on the domains of the TDF framework, reported as follows;

Theme 1: Women's understanding and motivations for attaining and maintaining viral suppression

Women described viral load in lay terms as *the number of viruses in the blood.* For example, *"a high viral load means an increase in the number of viruses in the blood and thus implies a weak body."* Pregnant women expressed their understanding of a "high and low" viral load and its implications for vertical transmission of HIV. They described viral suppression as a state of having a very low amount of the virus in their blood and an important aspect for good health overall. They explained that if the viral load is high, it increases the chances of HIV transmission to the baby. They also understood that viral suppression serves as an indicator of whether one is taking their ARVs as prescribed or not.

… "If someone doesn't take his or her medication well, the amount of HIV increases in the blood, the immunity decreases down and the person gets other opportunistic infections. But if someone adheres well to HIV medication, the amount of HIV reduces, the immunity is boosted, and other diseases are limited, and chances of giving birth to a baby without HIV are high (19-year-old pregnant woman-already in care-not suppressed)

The desire to have an HIV free baby was a major motivation for WLHIV to work towards attaining viral suppression. Women explained their strategies for attaining suppression. They ensured to take their medication at the stipulated time, others set alarms at specific times, ensuring that they

have their meals ready on time. For some, it was just a reflex action because of the strong desire to live and look after their families.

"It (viral load testing) has helped me to keep track of the time that I am supposed to take my medicine and not to exceed that specific time. It has helped me to make sure that before I take my medicine, I should not be stressed and that I should first eat well before I take my medicine and I think this will give me a better life (42-year-old pregnant woman-already in care-not suppressed).

Other women explained that they were aware that if they stopped their medication, the virus would increase in their blood and would infect their unborn babies.

"I know that if I stop taking it (ART) then the HIV in my blood will increase and eventually I can infect my unborn baby…" (25-year-old pregnant woman-already in care-suppressed)."

Women also reported that they were motivated to take their medications as prescribed because they were able to fulfil their fertility desires, moreover, free of HIV.

"… I wanted a child, so I knew that if I start HIV care and treatment even if I get pregnant, I will give birth to a baby who is not infected and God made it for me and I gave birth to a child without HIV (19-year-old pregnant woman-already in care-not suppressed)."

Additionally, some participants shared experiences of mothers in their surroundings who were living with HIV and adhered to their medicines as prescribed, who were virally suppressed, and had babies without HIV. This gave hope of delivering HIV-free babies to the mothers and acted as a form of reassurance to the participants that if they adhered well to their medication, they would also have HIV free babies.

"… I have been seeing my colleagues who also have HIV and also get pregnant but because they take their medicines well and take advice from the nurses, they are able to produce babies without HIV. When they told me that I have HIV, I said to myself, ''I am going to listen to the nurses and I will do whatever they ask me to do so that I live a good life and also have a healthy partner (42-year-old pregnant woman-already in care -not suppressed).''

Theme 2: Viral load testing experiences and provider support

Women perceived VL testing as part of routine care for WLHIV attending the health facility, and there was less anxiety when testing for viral load compared to the HIV test.

"Everything went well because they got the blood sample the same way they had when testing for HIV, except this time the anxiety was less … because this time, I was aware of my HIV status and I just wanted to know whether the amount of HIV had increased or reduced (23-year-old pregnant woman already in care-suppressed)".

Mothers described the processes of viral load testing at the health facility. They explained that their blood samples were taken, and they received the results on a given return date. On that day, they received information on whether their viral load was high or low. They had concerns about the amount of blood taken for viral load testing, the turnaround time of the results, and questions about why viral load tests should be done routinely even when one is suppressed.

"… they teach us about viral load testing as a group after which each person goes to the doctor alone, they take blood sample for viral load testing and they tell us when to come back for viral load results…and they counsel us basing on whether the viral is high or low (27-year-old pregnant woman, already in care- suppressed)".

The providers provided WLHIV with information about their viral loads and viral suppression; in group sessions at the triage using illustrations such as the emoji, and individually counseled them after they received their results.

"…the provider pulled out two files with; one picture of a smiling face while another one had a picture of an annoyed face…who…didn't take their medication on schedule while one with smiling face took their medication on schedule and without missing. That demonstration made me happy (27-year-old pregnant woman, already in care-suppressed)".

Interactions with providers after receiving viral load test results included encouraging clients to adhere to their medication as prescribed or else their viral loads would surge. They explained to mothers with suppressed viral loads about the consequences of having an increased viral load.

"If viral load is low, they encourage us to continue adhering because when it is low, it means that the virus is just dormant /suppressed and if someone doesn't adhere, it multiplies again. And if viral load is high, it means that someone has been taking drugs poorly, they encourage him or her to start taking drugs on schedule without missing (27-year-old pregnant woman-already in care-suppressed)".

Not all women fully benefited from the support from the providers. Some reported lack of clear information on viral loads from the providers. One participant revealed that she was not informed why her blood sample was taken and does not recall receiving her test results.

"Yes, the providers said they wanted to know the amount of the virus in my blood, but they did not tell me the results (19-year-old pregnant woman already in care-not suppressed)".

Awareness of the viral load test results determined the refill time for the pregnant woman to return to the clinic. The turnaround time for receiving viral load results varied depending on the time each woman had until the next refill, and on whether they were suppressed or not.

"…I did not get my results right away, I waited for about 2 months to get them…on my return date, that's when the providers find the viral load results in your file. When you are suppressed…you are given 3 months' refill because you will have impressed the provider with your good adherence…those not suppressed and not adhering well are given 1-month refill, and they are also sent to a counsellor…" (32-year-old pregnant woman already in care-suppressed).

Mothers reported their experiences with providers in addressing issues surrounding unsuppressed viral load and strategies for attaining suppression. They acknowledged that counselling was important during this time to support the mothers to achieve viral suppression as a primary goal of ART.

"You know I had tested for viral load, and I was not suppressing, when I went back after the counselling that I got, I was told that my viral load had lowered, and so that's why I was appraised and urged to continue adhering well (28-year-old pregnant woman-already in care-not suppressed).

One mother explained being advised by the provider that an unsuppressed viral load could accelerate illness which would result in stigma. This information was very helpful and encouraged mothers to strive to adhere in order to achieve good health.

"they say that when you do not adhere well on your medication, your viral load will go up and HIV symptoms will spring up too. Eventually you will develop stigma and start hiding from people (35-yearl-old pregnant woman-already in care- not suppressed)."

The providers helped the women to understand and address issues such as the scheduling of time for taking pills that may lead to a decrease in the viral load. A mother also explained that the health worker advised her to avoid stress and to maintain proper nutrition in order to keep her viral load down and remain suppressed. The providers also helped clients get rid of the fear related to having a high viral load.

"I asked the nurse if it was possible to regain my immunity and lower my viral load when I adhere to HIV medication? ''as long as you take your medicine on time and try to avoid stress, you will regain your health'' she answered me…if I get angry and stressed, I will fail to eat and the medicine may not work for me." (42-year-old pregnant woman already in care- not suppressed).

Theme 3: Challenges to achieving viral suppression.

Despite the described benefits of viral suppression, women reported challenges to achieving viral suppression, which included non-disclosure of HIV status, anticipated stigma, and distance to clinics, resulting in missed appointments. In addition, some women reported distress arising from being both pregnant and having HIV, which created anxiety about the possibility of having a baby with HIV. Other Challenges were related to the healthcare system, such as variations in the relay of viral load test results. For instance, women expressed concerns about delays in the return of viral load test results and the lack of general HIV counseling and education within the maternal and child health section of the health facility. All these challenges were reported to affect women negatively and hinder them from achieving viral suppression

Fear of HIV- related stigma at the clinic visits was reported to hinder achieving viral suppression especially for women who had not yet disclosed to anyone. This was very common when the initial diagnosis of HIV was made at antenatal clinics. Stigma was reported as one of the key reasons for missed appointments and non-disclosure resulting in viral non-suppression. The fear to be seen by

friends or other acquaintances resulted in several adjustments to clinic visits and resulted in delays or eventually missing of clinic visits.

"...some people fear to meet each other at the health center and they try their best to make sure that they do not reach there at the same time (unknown age, pregnant woman-newly diagnosed with HIV-not suppressed)."

In other instances, some pregnant women were skeptical about disclosing their HIV status for fear of being denied financial support from their partners during the pregnancy. Much as the women appreciated the importance of viral suppression, the fear of unknown consequences resulting from disclosure to their partners limited their ability to achieve viral suppression,

"I think that since I am already pregnant for him, once I disclose that I have HIV he may not give me any assistance like paying for my rent. Secondly, I fear that once he knows about it, he will tell all his sisters and the mother. Something that may not make them happy (27-year-old pregnant woman-already in care- suppressed)."

Distance to the health facility, coupled with transport challenges, hindered timely refills and adherence to clinic appointments. Participants reported transport challenges, which were further complicated by pregnancy, since they could not walk for long distances. Most times this resulted in missing their clinic appointments, which eventually contributed to poor adherence and subsequent viral non-suppression.

"Yes, I sometimes miss coming to collect my medicine because the transport is too high around shillings 20,000 and do not have energy to travel by foot (27-year-old pregnant woman-already in care - not suppressed)."

Participants expressed concerns about the possibility of vertical transmission during breastfeeding. A client explained that after learning that she had a high viral load, her main concern was about the possibility of infecting her breastfeeding baby.

"I feared because I had given birth and I was breastfeeding my child, so I feared that my child might contract HIV from me (23-year-old pregnant woman-already in care- suppressed)."

Some clients expressed a preference for receiving same-day results after viral load testing with near point-of-care viral load testing.

"Of course, I would prefer to know the results on that same day of testing because I am always anxious to know whether the HIV in my body has increased or reduced and whether I am taking my medicine well or not (20-year-old pregnant woman-already in care-unknown viral load status)."

However, there were variations in how clients received their viral load test results. A participant revealed that her blood sample was taken two months ago but has not received her test results. Some clients expressed concern about not being informed about the reason for taking their blood samples and not being able to receive test results in a timely manner. Participants also express anxiety as far as the delay to convey viral load test results is concerned as well as the lack of general HIV counselling and education within the maternal and child health section.

"The last time I was pregnant they did not tell me the results, may be some time back, they had tested me, and I was told that I had suppressed (32-year-old pregnant woman-already in care-suppressed)."

"…what I remember, I did not get my results right away, I waited for about 2 months to get them. So, on your return date, that's when the providers find your viral load results in your file (32-year-old pregnant woman-already in care- suppressed)."

"They didn't tell me what it (the viral load test) was for and up to now I have not yet known the results. They told me that I will know what came out of the test when I come back (25-year-old pregnant woman-already in care-suppressed)."

Long waiting hours with no provision of lunch for clients in the public health facilities was another barrier to accessing HIV care. Women reported that the average waiting time of 5-7 hours when they visited the clinic at times hindered their return for subsequent clinic visits. ..*"There's when we reach at the clinic at 8 am and leave at 6 pm, those are 10 hours of waiting, we even fear to be looted along the way while going back home. The clients are always very many, and also the providers delay to start working (29-year-old pregnant woman-already in care- unknown viral load status).*

Table 12: Barriers to and enablers of viral suppression within each recognized theme mapped to the relevant Theoretical Domains Framework domains with illustrative quotes.

TDF Domain	Key findings	Key enablers	Key barriers	Supporting Quotes
Knowledge	Women demonstrated understanding of viral load concepts, viral suppression, and implications for vertical HIV transmission	•Accurate lay comprehension of "viral load" and "suppression" •Understanding link between adherence and mother-to-child transmission	•Gaps and delays in receiving test results and explanation	*"A high viral load means an increase in the number of viruses in the blood and thus implies a weak body"* *"If someone adheres well to HIV medication, the amount of HIV virus reduces… chances of giving birth to a baby without HIV are high."* "*They said they wanted to know the amount of the virus…but did not tell me the results." (19-year-old)*
Skills	Strategies used by women to ensure adherence and viral suppression included timely medication intake, meal preparation, and alarm setting.	• Self-management routines (alarms, meal prep) •Stress-management before dosing	• Some women lack structured reminder systems	*"It has helped me to keep track of the time… and to make sure I should first eat well before I take my medicine."* *"I knew that if I start HIV care and treatment, take my drugs… I will give birth to a baby who is not infected."* *"I set alarms…make sure I have meals ready on time." (42-year-old)*
Social professional role and identity	Providers' role included offering regular counseling, education, and reassurance to clients about viral	•Embracing maternal role to protect baby •Viewing oneself as	• Fear that disclosure may threaten partner support	*"…the provider pulled out two files with one picture of a smiling face… that demonstration made me happy."* *"Providers encourage us to continue adhering because when it is low, it means that the virus is just dormant."* *"I fear if I disclose…he may not give me assistance…he will tell his family." (27-year-old)*

	suppression and ART adherence.	"responsible patient/mother"		
Beliefs about Capabilities	Women had confidence that, with good adherence, VL can be controlled and viral suppression achieved.	•Confidence from peer success stories • Belief that adherence "works" to suppress virus	• Doubt if faced with side-effects or stress	"I've seen colleagues…they take medicines well…and produce babies without HIV." (42-year-old)
Beliefs about consequences	Women strongly believed that adherence to ART prevents viral rebound and reduces transmission risk, providing motivation for consistent medication use.	• Fear of transmitting HIV to the baby • Recognition that suppression equals health	•Anticipated HIV-related stigma at clinic	*"If I stop taking it then the HIV in my blood will increase and eventually, I can infect my unborn baby."* *"I have been seeing my colleagues… because they take their medicines well… they produce babies without HIV."* *"Some fear to meet each other at the health center…and try not to reach there at the same time." (Newly diagnosed)*
Reinforcement	Positive outcomes (HIV-free child) and peer success stories reinforced behavior and ART adherence of the mothers	• Longer ARV refills as positive feedback • Provider praise when suppressed	• Inconsistent feedback for unsuppressed women	*"Suppressed…you get 3-months' refill…not suppressed…1-month and counselor referral." (32-year-old*)
Intentions	Women clearly expressed the intention to maintain	• Strong desire for HIV-free baby	•Competing priorities (transport	*"I wanted a child… I knew if I start HIV care I will give birth to a baby who is not infected."*

	adherence to ART primarily motivated by the desire to have HIV-free babies and preserve health.	• Commitment to family well-being	cost, hunger) may weaken intention	"*My desire to live and look after my family…makes medication a reflex action." (42-year-old)*
Goals	Primary goals included achieving and maintaining viral suppression to prevent vertical transmission and improving overall personal health outcomes.	• Clear health goal: "better life" through suppression	• Vague timeline for achieving suppression	*"…my viral load had lowered, and so that's why I was appraised and urged to continue adhering well."* *"Viral load testing…helped me…give me a better life." (42-year-old)*
Memory, Attention & Decision Processes	Women appreciated reminder systems (alarms and phone reminders) and ensuring specific times of taking their medicines improved adherence and consistency.	• Use of alarms and routines	• Stress or hunger can disrupt routines	*"Before I take my medicine, I should not be stressed…and first eat well." (42-year-old)*
Environmental contexts and resources	Reported challenges included long waiting times, distance to health facilities, transport	• Group education sessions at triage	•Transport costs, long distance • Long clinic wait	*"Transport is too high around shillings 20,000 and do not have energy to travel by foot."* *"…we reach at the clinic at 8 am and leave at 6 pm; those are 10 hours of waiting…"*

	costs, and limited HIV counseling at health facilities, negatively influencing adherence and clinic attendance.		times, no food	*"Transport is too high…do not have energy to travel by foot." (27-year-old)* *"Wait 10 hrs…fear being looted…no lunch." (29-year-old)*
Social influences	Observing positive outcomes in peers (HIV-free babies due to adherence) provided reassurance and motivated adherence behaviors among women.	• Group counselling and modelling • Provider/Nurse encouragement one-on-one	• Lack of partner/family support • Non-disclosure due to fear	*"I have been seeing my colleagues… they are able to produce babies without HIV."* *"I am going to listen to the nurses and do whatever they ask."* *"They teach us in group…then counsel based on high or low viral load." (27-year-old)*
Emotion	Women experienced anxiety around viral load results, especially related to vertical transmission risks and stigma associated with unsuppressed viral loads.	• Reduced anxiety when familiar with process	• Anxiety about infecting baby • Fear of stigma	*"I feared because I had given birth and I was breastfeeding… my child might contract HIV from me."* *"I am always anxious to know whether the HIV in my body has increased or reduced."* "*Anxiety was less…I just wanted to know if HIV has increased or reduced." (23-year-old)* *"I feared…breastfeeding…my child might contract HIV." (23-year-old)*
Behavioral Regulation	Need for more proximal (point-of-care) results to sustain motivation.	• Counselling after unsuppressed result	Some women do not receive post-test	*"After counselling…I was told my viral load had lowered…urged to continue." (28-year-old)* *"I prefer same-day results… I'm anxious to know whether HIV… has increased or reduced."*

		• Tailored adherence plans	counselling due to delayed results	
Optimism	Positive personal and peer experiences fostered optimism about achieving viral suppression and delivering HIV-free babies, encouraging continued adherence.	• Hope from peer examples • Belief in medication efficacy	Despair if results delayed or unclear	*"…I knew if I start HIV care… I will give birth to a baby who is not infected and God made it for me."* *"I have been seeing my colleagues who also have HIV… they are able to produce babies without HIV."* *"Seeing colleagues…have babies without HIV…gave me reassurance." (42-year-old)*

4.3.2. Implementation process evaluation

This section provides results from the qualitative evaluation of the ENHANCED-SPS intervention. Mechanisms and processes of success. We present results based on the ENHANCED-SPS intervention components comprising; provider training, peer support, enhanced viral load (VL) counselling, use of pictorial aids, phone call reminders, and point-of-care VL testing—aimed to improve viral suppression among pregnant women living with HIV. The qualitative evaluation is structured around the PRECEDE-PROCEED model's constructs: predisposing, enabling, and reinforcing factors, with cross-cutting themes including the implementation process, participant experiences, intervention outcomes, barriers, and sustainability.

Description of the study population

Twenty 21 participants (11 participants who received the intervention and 10 providers who delivered the intervention: 05 peer mothers and 05 midwives) were interviewed to understand the mechanisms of implementation, participant experiences, intervention outcomes and the enablers and barriers to the implementation of the intervention. The median age for the participants was 27 years (range was 19-42years); 27.3% aged between 18-24years and 63.6% aged between 25-34years. Of the 11 participants interviewed, 05 participants were suppressed at baseline and end line; 05participants were virally non-suppressed at baseline and suppressed by end line, and 01 was unsuppressed at end line.

Theme 1. Implementation process

The ENHANCED-SPS intervention was successfully rolled out and implemented across participating health facilities through multi-component strategies including provider training, standardized peer mother support, viral load counselling, phone call reminders, pictorial tools (flipcharts and patient

cards), and point-of-care viral load testing. Below we describe each of the components and the mechanism of implementation, benefits and any challenges (Table 13).

Table 13: Intervention Outcomes Mapped to PRECEDE Model Constructs

PRECEDE Construct	Intervention Component	Observed Outcome	Illustrative Quote
Predisposing Factors	Provider Training	Improved provider knowledge, confidence, and motivation to deliver VL-focused counseling.	"Now I can confidently explain viral load and suppression. The training changed how I talk to patients."
Enabling Factors	Flipcharts & Pictorial Aids	Increased client understanding of VL and ART adherence. Enhanced health literacy.	"When I saw the pictures, I understood why I need to take my pills every day."
	Point-of-Care Viral Load Testing	Immediate VL results led to real-time counseling, better engagement, and quicker clinical action.	"Getting the result immediately made me want to do better. I knew where I stood."
	Patient Cards	Improved patient tracking and adherence support; fostered continuity of care.	"I kept my card and checked it after every visit. I could see my progress."
	Integrated VL Counseling into Routine Care	Streamlined counseling led to more consistent patient-provider interactions and reduced missed opportunities.	"I didn't have to wait long or go to another clinic—it was all done together."
Reinforcing Factors	Peer Support (Peer Mothers)	Strengthened motivation and adherence through shared experiences and trust-building.	"She [peer mentor] was like me… I believed her when she said I can suppress the virus."
	Consistent Messaging Across	Reinforced behavior changes through repeated, aligned messages from providers and peers.	"They all told me the same thing—it stuck with me, and I started taking my pills better."

Provider Training

Peer mothers and midwives reported that the training addressed a significant knowledge gap in viral load monitoring and patient management prior to the intervention. The training significantly enabled improved service delivery by deepening providers' understanding of viral load testing and counseling. This enhanced knowledge empowered them to go beyond standard of care guidelines /government protocols, ensuring timely care for newly diagnosed mothers. The training also fostered a crucial culture of continuous learning and information sharing at the clinics. Peer mothers and healthcare providers actively shared their newfound knowledge with colleagues and patients, creating a positive "ripple effect" throughout the health facilities.

"Before the Enhanced SPS Program, we had not received any training...we were equipped with knowledge...which we passed onto patients." ***(IDI_Peer_Bisheshe HC III)***

"In government...we wait six months for VL...but during Enhanced SPS, even newly identified had their VL tested." ***(IDI_Provider_Lyantonde*)**

This training led to notable shifts in clinical practice, including earlier viral load testing for newly diagnosed mothers and improved interpersonal skills emphasizing respectful, patient-centered care and reshaping how providers approached adherence support.

"We learned how we should be handling patients... sometimes we handle patients in a wrong way, but the training helped us understand the need to handle every patient as an individual." ***(IDI_ENHANCED-SPS_Peer_Lyantonde Hospital)***

This training resulted in improved patient-provider interactions and enhanced care and acted as reinforcing factor to improve adherence and viral suppression. Providers felt more competent and effective in their roles, leading to greater job satisfaction.

"*The ability to handle patients for them to have good health was a direct benefit of the training, contributing to a more positive and productive work environment. "* ***(IDI_ENHANCED-SPS_Peer_BISHESHE HC III_ 18.05.2023_BA*.**

Some of the things I didn't know was how to handle patients because sometimes I would handle patients poorly and it makes them feel bad but when I went for the training, they taught me how I should be handling patients in order for them to have good health, something I didn't know. ***(IDI_ENHANCED-SPS_Peer_BISHESHE HC III)***

Feedback Meetings and discussions

Peer and midwives' trainings were further supported by regular feedback meetings between peer mothers, mid-wives and study staff to discuss lessons, challenges and best practices. These feedback meetings facilitated reflection on the key implementation barriers and shared learnings and possible solutions to address them.

During the meetings, "providers could discuss challenges and collaboratively find solutions, gaining "additional information which also I could pass to the patients and they feel helped"

***(IDI_ENHANCED-SPS_Peer_BISHESHE HC III_ 18.05.2023_BA*).**

These feedback meetings helped us to identify the gaps so that we can put more effort and improve in areas which needed improvement.

(IDI_ENHANCED-SPS_Provider_01_KIKYENKYE)

*Feedback meetings helped us in a such way that anything we could see in the study not working out well, we used that opportunity to report it so that we can discuss about it and look for the way forward**. (IDI_ENHANCED-SPS_Peer_BISHESHE HC III**)*

Use of Pictorials and Patient Cards

The consistent messaging from healthcare providers and peer mothers using flip charts solidified the understanding of mothers that proper adherence to medication was critical for their own health and for preventing HIV transmission to their babies. For example, health providers. Flipcharts and patient cards were integrated and used extensively during counselling to explain complex concepts such as viral load suppression and ART adherence.

"Would explain to them and show them using the pictures on the flipchart and cards how the HIV viruses increases when one doesn't take their medicine well and how the HIV virus reduces when they take their medication well"

(IDI_ENHANCEDSPS_Provider_02_KIKYENKYE_18.05.2023_MA.docx).

The pictorials/visual tools were culturally and linguistically appropriate i.e translated into local languages and made it easier for both providers and patients to communicate and understand HIV treatment pathways.

"Actually, another thing that really worked well for us was these cards (shows the cards) because they would clearly show the two sides, a suppressed mother and an unsuppressed mother and they also read this in their local languages which enabled them to read and interpret well the message that was written on the cards" ***(IDI_ENHANCED-SPS_Provider_01_KIKYENKYE).***

The flipcharts and patient cards played a crucial role in shaping the knowledge and beliefs of pregnant women living with HIV regarding their treatment and its benefits. Healthcare providers used the cards to visually explain the concept of viral load suppression and the importance of adherence. For example, the cards featured

"The card also had two pictures one was showing someone who is taking the drugs well and another one who is not taking drugs well. So, we could tell them that if you don't take your drugs well you will be like this picture and if you adhere well, you will be like this picture. After looking at different picture, they would want to be like that picture which showed someone who was adhering to ARVs medication and because of that they were encouraged not miss their appointment dates." ***(IDI-_ENHANCED-SPS_Peer_BISHESHE HC III)***

This visual education aimed to instill fear of negative outcomes from non-adherence and a desire for the positive health status depicted.

*"We also used the cards which helped us to elaborate to them well and when they saw the picture of the suppressed mother and the unsuppressed mother, they would also fear and endeavour to be like the good-looking woman who is suppressed." (**IDI_ENHANCED-SPS_Provider_01_RUSHERE_)***

"'They showed two examples of clients where one picture shows one with low HIV in the body and another showing too much HIV in the blood, the nurse taught us that when one takes their medicine well, then the levels of HIV reduce to extent that HIV will be 'sleeping' (suppressed) but when one is not taking their HIV medicine well then it will increase and also infect the unborn child. There is also a nice picture of a lady carrying a healthy child and this motivated me to keep taking my medicine well so that I be like her.'

IDI_ENHANCED_SPS_162223_1147_BISHESHE_18.05.2023_MA

The patient cards significantly enabled adherence by serving as practical tools for both patients and healthcare providers. For patients, the cards acted as a direct reminder for critical appointments and medication schedules

*"Returning dates were always indicated on the card, so the card would also act as a reminder so that the patients could come back on the exact date indicted on the card for refill" (**IDI-_ENHANCED-SPS_Peer_Bufunda HC III**).*

“The cards also helped us in educating these mothers about viral load and also because we wrote their appointment dates there, they would hardly miss an appointment date.” ***(IDI_ENHANCED-SPS_Provider_02_RUSHERE)***

While for providers, the cards were instrumental in streamlining patient management and follow-up. The cards also served as a tracking mechanism, helping providers to keep track of their patients, allowing for targeted interventions like phone calls to those who missed appointments.

*"recorded details like patient identification numbers, clinic return dates, the services provided to the mothers, and the upcoming services to be offered "****(IDI_ENHANCED-SPS_HC PROVIDER_Lyantonde).***

Phone Calls

Implementation of phone-based support and counselling was seamless and well-received. Providers used phone calls to deliver viral load counselling and adherence reminders and follow up on missed appointments. This bridged the gap between clinic visits and ensured continued patient engagement.

"They would call me and remind me of my return dates... even when I had forgotten." ***(IDI_ENHANCED-SPS_Clinic ID_1251)***

Participants' existing knowledge and beliefs about HIV management and the benefits of ART were reinforced and solidified by the intervention. The consistent messaging from providers through phone calls and counselling sessions helped to cement the understanding that proper adherence to medication was critical for their own health and for preventing HIV transmission to their babies. For instance, participants repeatedly noted that:

"*health workers would tell me to take my drugs in time and if it I get any health challenges because of the drug, I should go back and they change for me"* ***(IDI_ENHANCED-SPS_142113_ Clinic ID_1251).***

Similarly, another participant stated,

"They used to remind me to take my medicine well so that I reduce the amount of HIV in my body; they also used to remind us not to forget to come to the clinic for the next drug refill" ***(IDI_ENHANCED_SPS_122119_6395_RUSHERE).***

There was a clear described explicit connection between adherence and an HIV-negative baby was a powerful motivator throughout the process.

*"They were counselling and assuring me that if I take my drugs as directed, I will give birth to a baby who is not HIV positive. Each time they would give such kind of information, I would feel happy and encouraged to adhere to my drugs" (h12) (****IDI_ENHANCED-SPS_152226_Clinic ID_1186).***

The phone call intervention directly enabled participants to overcome barriers to adherence by providing practical support and reminders. A common challenge identified by participants was forgetting appointment dates and medication times. The proactive nature of the phone calls addressed this directly.

*"Mothers used to miss their appointments but because of calling to remind them of their refill dates, they were no longer missing" (****IDI_ENHANCED-SPS_Peer_Lyantonde Hospital*****).**

The consistent and caring communication from the peer mothers served as significant reinforcing factor. Participants expressed feeling valued and supported by the calls.

*Statements like "Calls would remind me when I have already forgotten and I would go and pick my drugs. It also showed me that these people they love and care for me" (**IDI_ENHANCED-SPS_142113_ Clinic ID_1251).***

Participants demonstrated the emotional and psychological reinforcement received. The feeling of being *"encouraged"* was a recurring theme

"I would feel encouraged because sometimes they would call me when I have already forgotten about my return dates" and *"I would feel encouraged to come and pick my drugs and take it as instructed" **(IDI_ENHANCED-SPS_112256_ Clinic ID_1033).***

Furthermore, the positive outcome of giving birth to an HIV-negative baby was the ultimate reinforcement of adherence, directly linked to the intervention's support. Participants explicitly stated,

*"The phone calls I were receiving, they helped me as a person because I gave birth to an HIV negative baby" (IDI**_ENHANCED-SPS_152226_Clinic ID_1186)***.

The positive feedback on viral load suppression provided during phone calls also served as powerful reinforcement:

*"What I benefited from phone calls is; my health was improved because each time I would come here for viral load testing, they would tell me that I am suppressed" **(IDI_ENHANCED-SPS_152226_Clinic ID_1186).***

Point-of-Care viral load testing

Rapid turnaround times for VL results was highly beneficial and enabled timely viral load counselling, prompt assessment of adherence and targeted support:

'It helped them to take well their medication because before they would take taking drugs as something that is not so important but after seeing their viral load results, they were encouraged to adhere for those who had not suppressed in order to suppress next time they are tested and also for their babies not to be infected and for those who had suppressed adhered to maintain viral load suppressed.' ***(IDI_ENHANCED-SPS_Peer_Lyantonde Hospital).***

"Receiving viral load in a short time helped mothers especially those mothers that had stigma from back home because of high viral load were able to suppress and become healthier, finding out how high or Low their viral load was helped these women to act accordingly and take necessary measures.' ***IDI_ENHANCED SPS_Provider_02_KIKYENKYE).***

Enhanced viral load counselling

During viral load counselling, peer mothers and e providers consistently emphasized that adherence leads to HIV-free infants, reinforcing the value of VL suppression:

'What made me happy in the journey of my pregnancy was counselling and guidance I was always receiving of which I followed until I gave birth to my health child and after giving birth to an HIV negative child, that is when I realised that whatever they were telling me was very important.' ***(IDI_ENHANCED-SPS_152226_Clinic ID_1186).***

*'In our EID section we didn't have any mother who had not suppressed and this proves that counselling was good and also calling to remind them and during that time, there was no any mother who was in the study and had a child who was HIV positive.'(IDI_****ENHANCED-SPS_Provider_02_RUSHERE).***

"Of course, they were informed because when you counsel someone you give the basic information so even if this mother is at home, she will know that Sister. G told me that every time I have to take

my ARVs so that I can suppress the virus. Remember most of these mothers were pregnant so, we brought in the element of telling them that if they take well their ARVs chances are high that they will give birth to HIV negative baby. And also, it doesn't make sense for you to have HIV negative baby and in the short run the mother you are going to leave the baby behind. So after taking the first PCR and babies were negative, the mothers appreciated and this gave them courage to adhere more on ARVs.' ***(IDI_ENHANCED-SPS_HC PROVIDER_Lyantonde).***

Theme 2. Participant Experiences

Participants described the intervention as empowering, emotionally supportive, and practical. The information delivered through training and pictorials significantly enhanced understanding of ART adherence and its link to viral suppression and HIV-free births

Improved Knowledge and Behavior

Participants repeatedly highlighted how phone calls and VL counseling reinforced the importance of adherence. This reinforcement was especially potent when linked to the tangible outcome of giving birth to an HIV-negative child.

"They would tell me... if I take my drugs as directed, I will give birth to a baby who is not HIV positive." ***(IDI_ENHANCED-SPS_152226_Clinic ID_1186).***

Psychosocial, Emotional Support and Motivation

Phone calls and peer support offered not just information, but emotional comfort and encouragement. Participants felt cared for and motivated to adhere to treatment.

"When i would be discouraged and thinking of even stopping taking the drugs when someone would call me asking whether I am still taking my drugs well, I would feel encouraged to continue taking my drugs and also remembering to go for my refills" ***(ENHANCED-SPS_142113_ Clinic ID_1251).***

Participants reported that phone call reminders played a critical role in reinforcing adherence behaviors and clinic attendance. Calls served as practical reminders and provided emotional support. *"They used to remind me to take my medicine well... and to come to the clinic for drug refills, when discouraged, calls made me feel cared for and encouraged to continue treatment."* ***(IDI_ENHANCED-SPS_142113).***

Peer Support as a Safe and acceptable approach

Using peer mothers to deliver the intervention provided a **supportive environment** and allowed mothers to connect with peers, which enhanced patient engagement and adherence. Participants described feeling understood and supported by peers who had lived experience of HIV. Peer support created a sense of shared understanding and comfort, as mothers connected over their common experiences: Peer support reduced isolation and stigma:

"Mothers going through the same situation would comfort each other*."****(IDI_ENHANCED SPS_Provider_01_RUSHERE).***

Enhanced Counselling and use of pictorials motivated participants:

Participants reported a deeper understanding of adherence, HIV transmission, and the role of ARVs due to repeated and consistent messaging from counselling, phone calls, and visual aids/ pictorials.

"Each time they gave such information, I would feel happy and encouraged to adhere to my drugs." *(IDI****_ENHANCED-SPS_152226_Clinic ID_1186).***

Flipcharts and pictorial cards helped demystify viral load concepts using culturally resonant illustrations.

"The cards were in the local language, easy for them to understand." ***(IDI_Participant Lyantonde).***

"When we taught them all about viral load using the pictures on the cards, in the local language and this helped them to understand well and for those mothers that had a high viral load were advised to take their medicine well so that they too can reduce the amount of HIV in their bodies" ***(IDI_ENHANCED-SPS_Provider_01_KIKYENKYE).***

Theme 3. Intervention Outcomes

Our intervention led to several significant outcomes, particularly in improved patient adherence and increased viral suppression. Participants directly attributed these outcomes to the combination of viral load counselling, pictorial aids, and phone calls:

"The phone calls helped me… I did all they told me to do and I suppressed and because of that I was able to give birth to an HIV-negative baby." ***(IDI_ENHANCED-SPS_152226_Clinic ID_1186).***

Healthcare providers also reported seeing changes in clinical practice and outcomes attributed to the intervention. We also observed an increase in provider competencies and improved patient-provider relationships as they used the patient-centered approach during the delivery of the intervention:

"We had some clients that never suppressed, but when we started testing their viral load and showing them the results, they suppressed." ***(Provider_RUSHERE).***

"After seeing their viral load results, mothers were encouraged to adhere so they could suppress the virus and give birth to HIV-negative babies." ***(IDI_ENHANCED-SPS_Peer_Lyantonde Hospital).***

*"It helped us to learn how to handle patients better... sometimes we handle patients in a wrong way instead of focusing on who they are and their specific challenges" (**Peer_Lyantonde Hospital).***

"*Some of the things I didn't know, how to handle patients because sometimes I would handle patients poorly and it makes them feel bad, but when I went for the training, they taught me how I should be handling patients for them to have good health, something I didn't know." (**IDI_ENHANCED-SPS_Peer_BISHESHE HC III).***

Pictorials/ visual tools, such as flipcharts and patient cards, enhanced understanding by illustrating the consequences of adherence and non-adherence in culturally relevant ways:

*"The pictures showed how HIV increases if medicine is not taken well, and how it reduces when adherence is good. This motivated me to take my medicine."**(IDI_ENHANCED-SPS_Provider_02_KIKYENKYE).***

Improved Adherence and Viral Suppression

Participants attributed their improved ART adherence and VL suppression to the intervention components. POC VL testing enabled prompt feedback, enhancing motivation. Phone calls played a direct role in improved adherence. There were some clients that never suppressed, but when they started testing and seeing their VL results, they suppressed. Participants echoed this:

*"Phone calls helped... I suppressed and gave birth to an HIV-negative baby." **(IDI_ENHANCED-SPS_152226__Clinic ID_1186).***

Earlier and More Frequent VL Monitoring:

Point-of-care testing enabled timely clinical decisions, promoting prompt adherence interventions.

"Before we didn't check VL for pregnant women, but now we make sure to know how our clients are doing." ***(IDI_ENHANCED-SPS_Provider_01_RUSHERE).***

HIV-Free Birth Outcomes

The ultimate indicator of intervention success was achieving and maintaining viral suppression and subsequently having —HIV-free births. This was commonly cited by majority of the mothers as the great motivation behind good adherence.

"I followed everything the health workers told me and... delivered an HIV-free baby." ***(IDI_ENHANCED_SPS_152105_2724_BUFUNDA).***

Theme 4. Barriers to viral suppression

Despite the intervention's overall success, some mothers continued to face barriers to viral suppression. Stigma and domestic challenges, such as partner misunderstandings, hindered adherence for a few participants. In addition, forgetfulness and transportation difficulties were initially common, though phone call reminders and simplified clinic schedules helped to reduce these obstacles.

*"I used to forget my appointment dates… but calls would remind me.***" (IDI_ENHANCED-SPS_152231_Clinic ID_1336**

Theme 5. Sustainability and Scalability

The intervention's success was reportedly grounded on the integration of simple scalable components like pictorial tools, peer-led education, and low-cost follow-up methods (phone calls). Participants and providers consistently emphasized the need for continuation and expansion of the program. The perceived value of the intervention components (especially phone calls and pictorials) was high. Providers expressed willingness to integrate these practices into routine care.

Sustainability:

The integration of peer mothers and continuous provider training fostered a culture of ongoing learning and information sharing within facilities, supporting sustainability.

"After training, I passed the information to patients and colleagues, which helped them a lot." ***(IDI_ENHANCED-SPS_Peer_BISHESHE HC III)***

The use of phone calls was noted as particularly sustainable given the relatively low cost and practicality, with healthcare workers extending this approach beyond study participants to other mothers:

"We used airtime to follow up mothers in the program and others to achieve positive results." ***(IDI_ENHANCED-SPS_HC PROVIDER_Lyantonde)***

Pictorial tools, being culturally and linguistically tailored, facilitated. Comprehension and understanding. The detailed patient cards supported systematic follow-up and data tracking.

There was a ripple effect of training and continuous learning mechanisms—such as clinic feedback meetings. Peer mothers and health providers reported sharing information with others:

"After coming from the training... I passed the same information I learnt to patients, which helped them a lot." ***(IDI_ENHANCED-SPS_Peer_BISHESHE HC III).***

"Even after the study, we continued applying what we learned."

Scalability:

The availability of airtime and structured feedback meetings improved follow-up and accountability of the implementation process. The intervention's components—training, pictorials, peer support, phone reminders were low-cost, culturally adaptable, and feasible to replicate. Providers noted using airtime to call both study and non-study patients: "*We used the same airtime to follow up mothers not in the program—we wanted positive results for all."*

CHAPTER 5.0: DISCUSSION

5.1. Summary of key findings

In phase one of the study, we found a significantly higher prevalence of HIV viral suppression among pregnant and recently post-partum women living with HIV in intervention communities that offered repeat out-of-facility testing with rapid linkage to streamlined HIV care compared to standard clinical care in control communities, following baseline universal HIV testing in all communities.

Among all 15–45-year women living with HIV, year 3 population level VS was higher in intervention (77%) Vs in control (68%). Though the absolute difference in prevalence of VS in the intervention versus control communities was relatively modest (6%), these gains occurred at a population level, in a group of pregnant/post-partum women living with HIV, who were ART-eligible throughout the trial, and in all communities that achieved prevalence of VS in pregnant/post-partum women beyond the "73%" threshold of the UNAIDS "90-90-90" targets for 2020 (165). In all communities, older age consistently predicted viral suppression at year 3 compared with age 15–19 years among women who reported pregnancy and live birth in the prior year. Viral suppression at year 3 was not associated with self-reported pregnancy or live birth in the prior year in intervention communities, while in control communities, women with a pregnancy or live birth in the prior year were more likely to have viral suppression at year 3.

Following the implementation of the intervention in phase two of this study, we found that the novel peer mother-led ENHANCED-SPS intervention that included enhanced viral load counselling, standardized peer mother support, and point-of-care viral load monitoring was associated with significant improvements in HIV viral suppression from 70% at baseline to 95% at 12-month (change= 24.9% (95%CI: 21.6-28.2%); p<0.0001) (174) . The improvements were particularly large

in the adolescent girls and young women (aged 15-24 years), among breastfeeding participants, and among recently diagnosed participants –suggesting benefits of peer-led intervention targeting these groups.

Furthermore, the ENHANCED-SPS intervention resulted in significant improvements in HIV status disclosure to anyone and, specifically, to a spouse or partner from ~79% at baseline to ~93% at 12-months of follow-up. The intervention was also beneficial in improving ART adherence over time from 65% at baseline to 93% at 12-month of follow-up (173). The improvements in disclosure and adherence were observed in different subgroups of age and enrollment status, with greatest among adolescent girls and young women (aged 15-24years) and recently diagnosed pregnant and breastfeeding women. These findings further highlight the effectiveness of an intervention at improving health outcomes among pregnant and breastfeeding women including EID in a resource-limited settings. Our findings demonstrate a significant increase in the proportion of children completing the recommended HIV rapid antibody testing in the intervention arm compared to the control arm at 94.1% and 81.9%, respectively; corresponding to 12.3% difference and this indicates sustained engagement with prevention of vertical transmission services over time.

The qualitative insights revealed that women's interpretation and understanding of viral suppression influenced their HIV care decisions including adherence to ART, disclosure of HIV status to their loved ones which subsequently resulted in improvements in viral suppression. We found that the intervention was implemented with high fidelity and was well-received by both providers and participants suggesting that the intervention is both sustainable and scalable across similar settings.

5.2. Discussion of key results

5.2.1. Improved Viral Suppression among Pregnant and Post-partum Women within SEARCH communities

We observed significantly high levels of viral suppression rates among pregnant/ postpartum women within communities where the SEARCH intervention was implemented compared to a control of baseline universal testing with ART eligibility for pregnant/postpartum women. Our results provide one of the first estimates of population-level prevalence of VS among pregnant and post-partum women, independent of ANC access, in Kenya and Uganda. These findings add to the evidence demonstrating population-level health benefits conferred by recent UTT interventions, which have included reductions in HIV-associated mortality, tuberculosis, and incidence. (175-177) .There are several potential explanations for the observed higher prevalence of VS among peripartum women in the communities where the SEARCH intervention was implemented than in control communities. First, annual, out-of-facility, population-wide HIV testing in intervention communities provided a platform to diagnose new infections that had occurred over the prior year, to identify new in-migrants to the community who had not been diagnosed previously, and to re-engage women living with HIV who had stopped ART.

Community-based testing can also reach women who do not access ANC, deliver at home, or do not engage in HIV testing during pregnancy, at delivery or during breastfeeding. Thus, in the communities where the SEARCH intervention was implemented, the proportion of pregnant or recently post-partum women in the final year of the trial who knew their HIV status was higher in intervention (95%) than control (91%) communities – even though in both arms, knowledge of HIV status exceeded 90%.

Second, referrals to HIV care following annual testing fairs prioritized pregnant and breastfeeding women by making appointments and starting ART within 48 hours of testing positive (including same-day ART starts), introducing women to clinic staff at testing sites, and closely following up and reaching out to women who missed their initial appointments. As a result, the proportion of pregnant/post-partum women on ART was higher in intervention than control, even though in both arms this proportion was very high (98% and 95%, respectively) and well above the UNAIDS 90% target.

Third, the streamlined model of care in the SEARCH intervention sought to reduce barriers to care, by reducing the frequency of clinic visits and waiting time at clinics, providing a welcoming environment with flexible appointment scheduling and mobile phone access to clinicians, and actively tracking those lost to follow-up. For pregnant and recently post-partum women, particularly those caring for a young infant, reducing these barriers to care access and easing transitions between ANC and HIV clinics may explain the higher proportion of women on ART and suppressed in intervention vs. control communities. Finally, universal ART eligibility in intervention communities resulted in a higher prevalence of suppression among women of reproductive age, providing an opportunity for VS pre-conception, which also likely contributed to the higher prevalence of VS in pregnant and post-partum women compared to the control.

The higher knowledge of HIV status and higher levels of VS achieved in pregnant and post-partum women may be potential benefits to implementing intermittent, large-scale HIV testing initiatives in medium to high-prevalence settings such as rural Uganda and Western Kenya. Although viral suppression among pregnant and breastfeeding women in the communities without the SEARCH intervention (control) exceeded the UNAIDS 90-90-90 target (73%) at 76%, the communities where

the SEARCH intervention was implemented achieved an even significantly higher level of suppression of 81%.

It remains unclear whether efforts to push levels of suppression further among the remaining 20-25% of unsuppressed WLHIV in communities that have surpassed "90-90-90" in SSA will require targeted outreach versus intermittent, non-targeted, population testing, or a combination of the two. The higher levels of suppression achieved among pregnant/post-partum women in intervention communities suggests that non-targeted, population testing can "move the needle" in knowledge of HIV status and ART access, even among a group of WLHIV that was eligible for ART and targeted for HIV testing at antenatal clinics.

Our results provide a population-level prevalence of VS among pregnant and post-partum women, and all women of reproductive age, including measures of each step of the HIV care cascade at year three of the SEARCH trial. One advantage of such population measures, as opposed to clinic-based measures, is that they are not conditional on accessing antenatal or post-partum HIV care. Published data on the prevalence of VS in pregnant and post-partum women in SSA are relatively sparse, and largely limited to clinic-based cohorts, with a large range of suppression estimates (30-98%) reported in these cohorts (177).

Our findings highlight ongoing challenges in adherence, even after exceeding the first two "90s", with 88% of pregnant/post-partum women on ART achieving VS in intervention communities. In a recent study from South Africa, the vast majority (over 90%) of instances of non-suppression during pregnancy among women on ART were attributable to non-adherence rather than pre-treatment drug resistance (178) demonstrating the need for adherence support interventions in pregnant/post-partum women.

Our findings further highlight that age was the strongest predictor of viral suppression, with older women achieving significantly higher rates than younger women. This age group also has the highest incidence of HIV and the lowest levels of viral suppression among persons with HIV in Uganda overall (179). This finding of lower prevalence of VS in younger women is consistent with prior literature (180, 181). In addition, it aligns with prior studies in sub-Saharan Africa, which have demonstrated that younger women living with HIV are less likely to maintain adherence, often due to stigma, limited partner support, competing childcare responsibilities, and socioeconomic vulnerability (182). In contrast, older women may benefit from greater treatment experience and stability in family and social structures (183, 184).

Additionally, marital status and pregnancy were not significant predictors of suppression and did not independently influence outcomes in this target population. This likely reflects on the impact of standardized ART access and integrated antenatal services that minimize disparities across these groups. This suggests that other behavioral and psychosocial factors, may play a greater role in determining adherence and treatment outcomes. (64, 185). These findings highlight the importance of age-sensitive and friendly approaches to HIV care, with a focus on addressing adherence challenges among younger women through integrated interventions such as peer-led initiatives, including online and digital adherence tools to support both HIV and reproductive health.(186, 187).

5.2.2. Peer-led viral load counselling improves viral suppression

Our multi-component, peer-led intervention significantly increased virologic suppression within 1 year of implementation from 70% at baseline to 95% at end line an absolute effect (RD**):** 25% (95%CI: 22-28); p< 0.0001. The greatest increase was among newly diagnosed: 70% increase (95%CI:63-77%) among pregnant women and 59% increase (95%CI:27-90%) among breastfeeding

women. Routine viral load counseling is an effective approach for identifying and responding to some of the barriers to ART adherence and is currently recommended for clients in care with a detectable viral load (188, 189). At least 50% of non-suppressors achieve viral suppression after viral load counselling (63, 189). This approach also allows for the prioritization of resources for viral resistance testing and second-line regimens to only those who need them, particularly in low resource settings (68). Our findings suggest that using peers to enhance this approach could improve and sustain viral suppression among pregnant and post-partum women. Specifically, 88% of participants who were not suppressed at baseline achieved viral suppression after 12 months of the ENHANCE-SPS intervention, and 98% of participants with viral suppression at baseline sustained it over follow-up.

In our study, we observed the largest increase in viral suppression among adolescent girls and young women aged 15-24 years, a group with the highest incidence of HIV, and lowest viral suppression rates in Uganda. Peer-based interventions have been shown to improve adherence to treatment (189-191), although prior findings on their effect on viral suppression are mixed (192, 193). Interventions to improve outcomes among adolescent girls and young women with HIV in sub-Saharan African have been limited, but some new strategies and approaches are now showing success. Increasing evidence including from studies done in Southwestern Uganda shows that rapid viral load feedback and viral load counseling improves viral suppression and retention in care for the youth (50). For example, the SEARCH-Youth study, a cluster randomized trial in Uganda and Kenya, found that point-of-care viral load testing coupled with viral load counselling and life stage assessments led to 88% viral suppression among women 15-24 years as compared to 83% in the standard-of-care (relative effect=1.06; p=0.026) (192). After one year of the ENHANCED-SPS intervention, viral suppression among women of the same age group was 95.1% and was higher than the previously reported rates, suggesting the additional contributions of peer-based interventions.

Our intervention was tailored to the unique needs of pregnant and post-partum women with HIV and was associated with significant improvements in viral suppression for these vulnerable groups. Specifically, after 12-months, 95.6% of participants who were pregnant at enrollment and 75.7% of participants who were breastfeeding achieved viral suppression. The lower rate of suppression among post-partum women highlights ongoing challenges in ART adherence for this group and the need for continued engagement with this category of women. Indeed, despite major advances in ART, low rates of HIV viral suppression among postnatal/breastfeeding women have been reported in other studies (194).

Our intervention was also associated with a 6.4% increase in viral suppression among pregnant and breastfeeding women on ART. This increase is comparable to the effect of SEARCH's universal HIV test-and-treat intervention, which resulted in 6% higher prevalence of viral suppression among women reporting current pregnancy or live birth in the prior year, as compared to the standard-of-care (63, 195). Notably, pregnant and post-partum women on ART in ENHANCED-SPS achieved higher levels of viral suppression than in SEARCH (97% vs. 88%, respectively), suggesting the added value the ENHANCED-SPS intervention components on ART adherence.

Within the ENHANCED-SPS study, improvements in viral suppression were larger for participants on ART for <6 months than participants on ART for longer: 24.6% vs. 4.1%. This result may not be surprising; however, point-of-care viral load testing with enhanced counselling at baseline could have provided a cue to action to participants more recently started on ART, leading to improved adherence and subsequent viral suppression. Furthermore, providing viral load counseling to all participants, irrespective of their baseline viral suppression status, may have contributed to sustained viral suppression among women with more ART experience and is a strong contrast with the standard-of-

care to only provide counseling to those failing on treatment (174). Finally, we observed the largest gains in viral suppression among recently diagnosed participants (69.3%), suggesting that the intervention could have facilitated ART initiation and care engagement among this group.

Our findings suggest that interventions including peer support and viral load counselling can have a positive impact on HIV viral suppression, and interventions tailored to pregnant and post-partum women with HIV can improve and sustain their viral suppression. Overall, evidence from this study can be used to improve maternal outcomes for women in HIV care and contribute to strengthening programs to prevent vertical transmission in Uganda and Sub-Saharan Africa. While previous studies have documented improvements in viral suppression in similar settings (50, 63), our rates are consistently higher than the expected under the standard-of-care, where estimates range from 70% among youth (age 15-24 years) to 76% among the women of reproductive age (192, 195-197).

Importantly, significant improvements were observed across age groups, for recently and previously diagnosed women, for women on ART for <6 months and 6+ months, and among women who did and did not switch to dolutegravir during follow-up. For the recently diagnosed group, it is challenging to disentangle the impact of the ENHANCED-SPS intervention from ART initiation; however, it is also possible that the intervention facilitated initiation and adherence to ART among these participants. Finally, the impact of the ENHANCED-SPS on hypothesized mediators (e.g., disclosure of HIV status and adherence to ART) as well as related outcomes (e.g., vertical transmission) remains to be understood.

5.2.3. Improvements in ART Adherence and HIV status disclosure

The ENHANCED-SPS intervention was associated with meaningful improvements in ART adherence from 65% at baseline to 93% at 12-months of follow-up. The ENHANCED-SPS

intervention was grounded in the PRECEDE framework and built on the existing peer mother program in public health facilities. We involved peer mothers in the design and delivery of this intervention. Peer mother programs, through which women with HIV who have generally high levels of ART adherence provide peer support, have been increasingly incorporated into programs to prevent vertical HIV transmission in many low- and middle-income countries.

Qualitative studies have found that peer mothers can foster engagement in HIV care, and they are a trusted source of information within the HIV clinics and community (70, 197). Although quantitative studies evaluating this approach have been relatively limited, recent data have demonstrated improved retention in care of 78% (79, 84) among pregnant women enrolled in the prevention of vertical transmission program in Tanzania (196, 197). A recent review of the Uganda national HIV/AIDS Strategic Plan indicated that the rates of viral suppression, disclosure and adherence among adults living with HIV are still below the set targets at 94%, 88%, 73% respectively and significantly lower than the results in this study further highlighting the benefits of our peer led model (8, 176). Our findings add to the evidence base for the effectiveness of peer-led programs for pregnant and postpartum women with HIV.

The ENHANCED-SPS intervention was also associated with improvements in HIV status disclosure to anyone and to a spouse or partner from ~79% at baseline to ~93% after 12-months of follow-up. Our intervention incorporated innovations of peer mother support and viral load testing and counselling to foster HIV status disclosure and ART adherence (198).

Prior studies of point-of-care viral load testing allowed for rapid feedback on viral load results to incorporate that data into counseling. Because of delays of weeks to months in turnaround time for viral load results in many settings, the salience of viral load counseling may be limited when applied

to prior behavior. Point-of-care viral load testing with rapid return of results has previously been shown to improve viral suppression in adult populations (197, 199). Our study adds to the evidence base on use of point-of-care viral loads during the critical time periods of pregnancy and breastfeeding. With ongoing scale-up of viral load testing, there are opportunities to engage peer mothers in providing counseling to foster ART adherence in programs to prevent vertical HIV transmission.

The ENHANCED-SPS intervention provided peer mentors with tools to provide structured counseling to mothers on their viral load results. Our ENHANCED-SPS counseling was through a study-designed flip-chart with the big catch phrase– "A healthy mother, a Healthy Family" which provided an opportunity to engage with the mothers in the prevention of vertical transmission and keeping them healthy (176). This motivational messaging may have created a desire in pregnant and breastfeeding women to stay healthy and have a healthy baby, thereby promoting adherence and disclosure. Our intervention extends prior work by our group demonstrating that interventions with structured viral load counseling (i.e., counseling describing viral load results and empowering patients with information on how ART adherence impacts viral load) increase viral suppression (192, 195, 200). The viral load counseling flip chart is a tool with clear and simple messaging reinforced counseling at routine visits and via phone calls and could be incorporated into standard peer mother programs.

Our study examined adherence among key subgroups, including younger women ages 15-24 for whom ART adherence and outcomes have been suboptimal across many contexts. Participants who were virally non-suppressed at baseline reported high rates of non-adherence compared to those who were suppressed, highlighting the importance of good adherence in achieving viral suppression. In

our study, switching ART regimens did not negatively affect adherence, potentially because most participants switched from efavirenz to dolutegravir as part of a change in first-line regimens rather than due to treatment failure or side effects.

Our results also provide preliminary evidence for the effectiveness of the ENHANCED-SPS intervention in the postpartum period. Multiple studies have demonstrated that retention in care and viral suppression drop in the postpartum period, threatening both maternal health and the risk of perinatal transmission during breastfeeding (95, 201, 202). Additional barriers and different motivations may impact ART adherence in the first year postpartum. Although only 4% of this study population was postpartum (breastfeeding), our results suggest that this intervention may be a promising approach to improve ART adherence in this group.

Our intervention also improved disclosure of HIV status in this population, both to anyone and to a spouse or partner. The disclosure levels achieved by young women (15-24 years) in the ENHANCED-SPS study far exceeded the disclosure levels among other counterparts in the SEARCH-Youth study, also occurring in rural Southwestern Uganda over the same time (192, 196, 203). Disclosure of HIV status lays a strong foundation for treatment support, reduces self-stigmatization, and improves treatment outcomes through facilitating adherence to ART (204). The relationship between disclosure of HIV status and adherence to ART is well documented, with disclosure improving adherence to ART (205), and early ART initiation improving disclosure (206); implementation strategies exist to support either disclosure or adherence but rarely both. The improvements in disclosure may have improved adherence to ART in this study. In a recently published study in Nigeria, fear of disclosure of HIV status was cited as a potential deterrent to adherence; measured adherence was only 62.5% (113, 207).

In a more recent exploratory qualitative study in Zambia, women agreed that disclosure and partner support were necessary preconditions to ART initiation and their subsequent adherence to ART (198, 208, 209). Our study builds on this literature, suggesting that interventions that address both disclosure and adherence rather than adherence in isolation are associated with improvements in both disclosure and adherence to ART in this population. However, disclosure may also increase the risk of intimate partner violence (IPV), stigma, or abandonment, particularly in settings with limited gender equity and social support (210).

5.2.4. Early Infant Diagnosis and Perinatal Transmission

The ENHANCED-SPS intervention prevented drop-offs at the 3rd and final test of the EID cascade. The findings of this study highlight the effectiveness of an intervention aimed at improving health outcomes among pregnant and breastfeeding women including EID in a resource-limited setting. Our findings demonstrate a significant increase in the proportion of children completing the recommended HIV rapid antibody testing in the intervention arm compared to the control arm at 94.1% and 81.9%, respectively. The 12.3% higher completion rate indicates sustained engagement with prevention of vertical transmission services over time.

These findings underscore the importance of targeted interventions in improving access to and uptake of prevention of vertical transmission services (70, 199, 211, 212). They also align with previous research highlighting the effectiveness of multifaceted interventions in enhancing maternal and infant outcomes, particularly in settings where access to healthcare services may be limited (127, 155, 176, 212). By addressing identified barriers to HIV care, such as maternal engagement and knowledge, the intervention demonstrated tangible benefits in improving testing rates among HIV-exposed infants (155, 213-216). Mothers' engagement and participation in programs relating to the improvement of infant outcomes results in great motivation and an obligation to adhere to the testing

algorithm due to their desire to have healthy babies. Therefore, the peer-led interventions are very critical in helping the mothers feel connected to the process throughout the Prevention of vertical transmission cascade (126, 217).

Furthermore, the significant increase in testing completion rates observed across most subgroups suggests that the intervention was effective in reaching and engaging a diverse range of mothers and infants within the study population. However, final infant HIV testing coverage was lowest among women recently diagnosed: 85.7% in the intervention and 64.4% in the control. Likewise, coverage among the youngest mothers (15-24 years) was lower than the other age groups in the intervention arm (90.0%), but higher than the other age groups in the control arm (90.9%). These findings underscore the importance of tailoring interventions to address specific barriers and preferences within subpopulations, thereby maximizing the reach and impact of programs to prevent perinatal transmission (218).

Related studies provide growing evidence that mHealth interventions can have a positive impact on health outcomes, including improved antenatal attendance, 1st DNA PCR testing coverage at 6weeks, and birthweight (219-221). Phone counseling has shown to offer practical approaches to reach and improve health outcomes of pregnant women with HIV and postpartum mothers in care. In a randomized trial conducted in Kenya, one-on-one counseling delivered via cell phone was very effective in retaining mothers with HIV in care and in promoting infant HIV testing and antenatal and postnatal care attendance (222, 223).

Furthermore, our findings support the use of peer mothers in improving timely testing and diagnosis of HIV-exposed infants, which approach that has previously been shown to improve early presentation for EID among HIV-exposed infants in other similar resource-limited setting in Sub-

Saharan Africa (71, 224). EID remains a key entry point into the pediatric HIV care cascade by ensuring timely identification and treatment of infants with HIV in the earliest stages of life and resulting in improved health outcomes (225, 226).

Importantly, there was lack of significant differences in vertical transmission rates across the intervention and control arms, which indicates huge successes with the current prevention of vertical transmission programs in both arms. Despite the effectiveness of Prevention programs in reducing vertical HIV transmission to below 5% when women are fully enrolled and adherent to antiretroviral therapy (ART), a significant proportion of new pediatric infections occur among women who are either not reached by these services or who disengage during the continuum of care (39, 75, 89). While our intervention successfully improved testing rates, it lacked a significant effect on long-term improvements in clinical outcomes, including perinatal transmission rates (227). Therefore, future research should focus on evaluating the long-term impact of interventions on clinical outcomes beyond the 18-month follow-up period.

5.2.5. Perceptions and understanding of viral load testing and suppression

In our qualitative evaluation, we explored pregnant and postpartum WLHIV perceptions of viral suppression and its implications during the perinatal period and found that women's interpretation and understanding of viral suppression influenced their HIV care decisions, including adherence and retention in care. These findings are presented within a context where attainment of fertility goals is deeply entrenched in traditional gender and socio-cultural norms that dictate women's fertility choices irrespective of the circumstances, including HIV infection (65, 228). Evidence indicates an increase in fertility intention rates among women living with HIV, hence the need for interventions

to optimize viral suppression as the single most important predictor of vertical HIV transmission (229-231).

The advent of multidisciplinary strategies within prevention of vertical transmission programs, including ART for all pregnant and breastfeeding mothers, averted concerns around the possibility of vertical transmission (232). This motivated mothers with HIV that, with a suppressed viral load, they could have HIV free babies and attain positive health outcomes. However, our findings indicate the fear and anxiety among mothers to continue breastfeeding despite at achieving viral suppression. This anxiety is exacerbated by the knowledge of HIV's transmission routes and the historical context of high transmission rates before the widespread availability of antiretroviral therapy (ART) (233). It is crucial to address these fears through continued counseling and reassurance from healthcare providers, emphasizing the effectiveness of ART and viral suppression in preventing vertical transmission, especially during breastfeeding.

Nonetheless, barriers to retention within vertical transmission prevention programs in low-resource settings persist (64, 65). In this study, access to the health facility, non-disclosure, and anticipated stigma were key hindrances to attaining viral suppression among pregnant and breastfeeding women. Non-disclosure of HIV status is proven to affect adherence to ART. Particularly, disclosure to sexual partners was revealed to be an important facilitator of viral load suppression (234). The study was conducted in a setting where men overrule decision-making in the household as well as resources. This may highlight that indirect male partner support influences retention in care among women living with HIV, more specifically in the perinatal period (121, 235). There is also a need to test interventions aimed at leveraging male partner support for HIV care, specifically in the perinatal period (235).

The turnaround time for receiving test results was another concern. Delays in obtaining results can cause anxiety and uncertainty, potentially affecting adherence to treatment and follow-up appointments (236). Health facilities should strive to streamline the testing process to reduce waiting times. This could involve improving laboratory efficiency, leveraging faster diagnostic technologies, and optimizing logistical aspects of sample transportation and processing (41, 236). Mothers questioned the necessity of routine viral load tests, particularly when their viral loads are suppressed. This points to a potential gap in understanding the rationale behind regular monitoring. Healthcare providers should emphasize the importance of consistent monitoring, even when viral loads are low, to maintain optimal health outcomes. Enhanced communication strategies, including educational sessions and informational materials, and peer support, could help address these misconceptions (237).

The physical distance to health facilities was another significant barrier reported by women. For women in remote or underserved areas, the travel burden can be particularly challenging, exacerbating the difficulties in maintaining regular healthcare visits, especially for the recently/ newly diagnosed and not suppressed. Addressing this barrier requires a multifaceted approach, the implementation of targeted outreaches, and leveraging peer support mechanisms to improve access to services at the community level. There is also a need to advocate and modify the current DSD models to accommodate the needs of clients who are newly diagnosed and not virally suppressed.

The finding that participants acknowledged the role of viral suppression in preventing vertical transmission of HIV highlights a significant understanding within the study population. This recognition indicates that participants are aware of the importance of maintaining low viral loads to minimize the risk of transmitting the virus to their children.

Previous evidence from the evaluation of prevention of vertical transmission programs in Namibia highlighted knowledge as a key determinant to adherence (238). This awareness among participants suggests that public health interventions and educational programs have successfully conveyed the critical link between viral suppression and prevention of vertical transmission. It reflects the effectiveness of ongoing efforts to educate people living with HIV, particularly expectant mothers, about the importance of adhering to antiretroviral therapy (ART) to achieve and maintain viral suppression.

Healthcare providers play a crucial role in ensuring that patients understand their treatment regimens and the significance of viral suppression in protecting their unborn or breastfeeding children. Continued support, counseling, and access to ART are essential to sustain viral suppression and, by extension, prevent vertical transmission. However, due to overstretching of the healthcare workforce, peer mothers can be supported. Health education and routine counselling from the providers encouraged women to continue taking ART as prescribed. Previous studies have shown that poor interpersonal interaction between HIV clients and care providers can lead to poor engagement in care (121). This arises from poor attitudes of providers coupled with clinic-level challenges that interfere with the quality of care (238, 239). On the contrary, women in this study attested to the positive attitude of the providers, revealing support with counseling and information on adherence and its importance to achieving viral suppression. They further reported achieving suppression after prior non-suppression through providers' active engagement in identifying and addressing barriers. The advent of client-centered care has also enabled HIV clients to efficiently navigate the structural barriers to viral suppression (195, 240). Training for the physicians and clinic workers in this area could further improve women's achievement of viral suppression.

With the scaling up of the ‘treat all policy’, women with HIV who are stable in care are most likely to attain or maintain viral suppression easily compared to those newly diagnosed with HIV (145). Anti-retroviral therapy and other support services to enhance engagement in care through best practices such as streamlined HIV care (241), option B+(64) and other differentiated care models, have led to subsequent improvement in viral load outcomes of HIV clients (242)

This also justifies the confidence displayed by mothers in this study that having a suppressed viral load could enable them to have HIV free babies and attain positive health outcomes. However, women diagnosed during the perinatal period are likely to face challenges while negotiating the HIV care system, and may face challenges of attaining suppression during pregnancy (135, 145). There is still a need for multidimensional interventions to optimize viral suppression for this subpopulation.

Our findings further reveal that viral load suppression is attainable within the context of the general HIV care setting. Strategies such as general counselling and group education, sharing of positive previous experiences about successful pregnancies and subsequent HIV free babies, ensuring sufficient drug stocks and deliveries, which form part of the routine HIV care setting, among others, contribute to viral load suppression(121). However, there is no deliberate effort targeted to mothers in the perinatal period, which leads to missed opportunities for attaining viral suppression, and as a result, HIV infections are persistent among children (19, 243, 244).

5.2.6. The ENHANCED-SPS intervention was successfully implemented

The qualitative findings from the process evaluation highlight the effectiveness of a multi-component, theory-driven strategy rooted in the PRECEDE model to improve viral suppression among pregnant women living with HIV. Our intervention successfully addressed behavioral determinants at the individual, interpersonal, and health system levels. Provider training improved

knowledge, confidence, and proactivity in viral load (VL) counselling, directly influencing care quality. Similarly, personalized counselling and locally tailored pictorial aids enhanced women's understanding of ART adherence and VL suppression, leading to increased engagement and self-efficacy in HIV care.

Peer support emerged as a critical reinforcing factor, with peer mothers offering both emotional and informational support. Their involvement fostered trust, reduced stigma, and created a community where women felt understood and motivated. In parallel, phone call reminders helped maintain adherence and served as emotional touchpoints between clinic visits, reinforcing health messages and improving provider accessibility. These components collectively supported sustained behavioral change by addressing enabling and reinforcing factors within the PRECEDE framework.

While the intervention showed strong promise, challenges such as stigma, unsupportive home environments, and initial knowledge gaps persisted, highlighting the need for continued education, partner engagement, and social support strategies. The simplicity and scalability of intervention components, including the pictorial aids and phone reminders, alongside institutional support structures, suggest the intervention is well-positioned for broader implementation and scale-up. Overall, ENHANCED-SPS presents a practical and replicable model for improving maternal and infant HIV outcomes, especially in resource-limited settings.

CHAPTER 6.0: STUDY STRENGTHS AND LIMITATIONS

6.1. Strengths

Strengths of this study include engagement of peer mothers throughout the study, from intervention development through delivery. This is among the first studies to rigorously evaluate an intervention combining point-of-care viral load testing and viral load counseling among pregnant and breastfeeding women with HIV. Our study was implemented with other concurrent routine care efforts provided by peer mothers and midwives to strengthen prevention of vertical transmission and ART services and may have improved other maternal and child health outcomes overall.

The routine care and public health setting of our study setting is a major strength representing real-world context and is easily transferable and scalable to other settings with a similar context in Sub-Saharan Africa.

The development and implementation of a flip-chart for the peer mothers remains a great tool and job aid that the other peer mothers within these facilities can be trained on to guide their counselling and interaction with mothers routinely. This is another strength of our study since this flip chart can be adapted and adopted by the ministries and implementing partners as a job aid to guide enhanced viral load and adherence counselling by the peer mothers.

These key findings contribute to the evidence that integration of peer-mother services in routine vertical transmission prevention programs improves ART retention and viral suppression among pregnant women and overall maternal and child health outcomes (174, 245).

6.2. Limitations

6.2.1. Selection Bias

The analysis in phase two of the study largely focused on the intervention arm for the primary outcomes due to lack of sufficient data on viral loads from the control clinics for by-arm comparisons, which limits our ability to draw contemporaneous causal inferences and may affect the representativeness of the findings. Moreover, the small sample sizes in certain subgroups—particularly the postpartum/breastfeeding category may have reduced the power to detect associations, thereby potentially introducing selection bias in these subgroup analyses. However, consecutive enrolment across all categories helped minimize this bias by ensuring an unbiased representation of participants. This approach likely reflects the true population distribution, given that most women are tested and diagnosed during pregnancy, with relatively few being diagnosed during the postpartum period.

The inability to measure EID testing outcomes and perinatal transmission among infants who were lost to follow-up or transferred out may introduce bias, as these missing data could influence the study's conclusions. However, we assumed that the characteristics of participants lost to follow-up were similar to those retained in the analysis, suggesting that the overall findings remain robust despite this potential bias.

6.2.2. Information Bias

This thesis utilizes data that was collected from the SEARCH trial in phase one and also relies on work that was conducted by the health workers/midwives in the prevention of vertical transmission clinics for Phase two of the study. Classification of current pregnancy and live birth over the prior year during phase one was based on self-report. This may have resulted in some misclassification, though it seems unlikely that self-report would be inaccurate for events such as pregnancy

(particularly in the second and third trimester) or the birth of a child, or that misclassification would have differed by trial arm. Additionally, incomplete viral load measures among WLHIV may have resulted in overestimates of population VS. However, both HIV testing coverage and viral load measures among WLHIV were high (>80%), and we adjusted for differences between persons with and without viral load measures.

In phase two, we analyzed data collected from participants during follow-up and also used data from the HIV care cards field at each routine visit, which is prone to information bias due to erroneous measurements and entries by health workers and irregular clinic visits by some clients. We noted that there was so much missing data in the control clinics, and we pre-specified that if data on the primary outcome were missing in 50% of the control facilities, we would only consider analysis on the primary outcome in the intervention arm only where data on the primary outcome was collected prospectively from the participants, rather than using secondary collected data. The missingness of the data on the primary outcome of viral suppression from control clinics prevented the by-arm comparison of the effect of the intervention on viral suppression.

In the intervention clinics, point-of-care (POC) viral load measurements were conducted to facilitate immediate viral load counselling. In control facilities, we relied on viral load data collected via dried blood spots (DBS) by the Ministry of Health, which were then sent to central laboratories for analysis. This difference in methodology may have resulted in incomplete viral load data for some women living with HIV (WLHIV). Additionally, by applying the same viral load cut-off to all participants—categorizing them simply as either suppressed or not suppressed—we may have inadvertently overestimated the true rate of population viral suppression.

While previous studies have documented improvements in viral suppression in similar settings in the absence of any additional interventions, our rates are consistently higher than the expected under the standard-of-care, where estimates range from 70% among youth (age 15-24 years) to 76% among the women of reproductive age (43, 63, 192, 196). Importantly, significant improvements were observed across age groups, for recently and previously diagnosed women, for women on ART for <6 months and 6+ months, and among women who did and did not switch to dolutegravir during follow-up. For the recently diagnosed group, it is challenging to disentangle the impact of the ENHANCED-SPS intervention from ART initiation; however, it is also possible that the intervention facilitated initiation and adherence to ART among these participants. Altogether, given the lack of a temporaneous control arm, we limit our interpretations to associational.

Reliance on routinely collected data—such as ART adherence information from HIV care/EID cards and registers—introduces risks of missingness and variability in data quality (246). Additionally, ART adherence and HIV status disclosure were self-reported rather than derived from controlled study logs, which could compromise the accuracy of these outcomes. While high levels of missingness on ART adherence precluded associational analyses, our approach prioritizes the use of routinely collected data, which provides a more realistic reflection of medication-taking behaviors compared to data collected through contrived study logs designed solely for research purposes.

Nonetheless, we employed robust Targeted Maximum Likelihood Estimation (TMLE) in our analysis to mitigate the impact of missing data.

6.2.3. Confounding Bias

Confounding arises when a variable is correlated with both the outcome and one or more exposures. Since this thesis primarily relied on secondary data in phases one and to some extent in phase two—

with a limited set of available variables—it is possible that some confounders affecting the primary outcome, such as adherence and disclosure in phase one, were not fully accounted for.

In phase two, the study intervention was multi-component, making it difficult to isolate the specific effects of individual components and to identify which elements had the greatest impact and benefit to the participants. This complexity highlights the need for targeting specific barriers with tailored intervention elements, as no single component may adequately address all the challenges to achieving viral suppression. Ongoing qualitative evaluations with participants and providers will yield some insights into mechanisms.

Additionally, in the recently diagnosed group, it was challenging to disentangle the direct impact of the intervention from the effects of ART initiation itself, potentially confounding the observed outcomes.

6.2.4. Random error

Random error refers to chance differences between observed values and the true value that arise purely by chance (234). In our study, we assumed that the target population and study sites were comparable. Furthermore, study facilities were assigned to either the intervention or control arm, and standardized flip charts and participant information cards were used to harmonize intervention delivery. These measures helped to minimize random error and reduce overall bias.

CHAPTER 7.0: CONCLUSIONS AND RECOMMENDATIONS

7.1. Conclusions

We found high levels of population-level viral suppression among pregnant and postpartum women within the SEARCH communities. The implementation of the SEARCH test and treat intervention resulted in significant gains in viral suppression among pregnant and post-partum women in the intervention communities compared to an active control that offered one-time, near-universal testing and ART eligibility. Additionally, we observed overall improvements in viral suppression across all women of reproductive age, demonstrating the benefits of ART scale up to enhance maternal health and reduce new pediatric HIV infections, hence providing insights into how to achieve the vertical elimination goal.

ENHANCED-SPS interventions significantly improved viral suppression.

The Peer-led ENHANCED-SPS interventions led to marked improvements in viral suppression over time among pregnant and postpartum women, highlighting the effectiveness of multi-component, community-based strategies in rural, resource-limited settings. Within one year of implementation, the multi-component, peer-led ENHANCED-SPS intervention was associated with substantial improvements in viral suppression among pregnant and post-partum women with HIV in rural Uganda.

Postpartum viral suppression remains suboptimal

Despite gains, viral suppression among breastfeeding women remains below UNAIDS targets. This underscores the need for targeted postpartum interventions and further research to address barriers and optimize care during this critical period.

Peer-led counseling enhances HIV disclosure and ART adherence

Enhanced viral load counseling by peers was strongly linked to better HIV status disclosure and improved ART adherence, especially among newly diagnosed women—highlighting the value of peer support models.

Early Infant Diagnosis (EID) is improved through targeted maternal engagement

Our findings contribute to the growing evidence supporting targeted interventions to improve early infant diagnosis (EID) rates among HIV-exposed infants. Interventions that engage mothers and address individual barriers to testing showed promising results in improving EID rates and demonstrated tangible benefits in preventing perinatal HIV transmission, particularly among hard-to-reach subgroups.

Education and stigma reduction are essential for long-term success

Clear, non-judgmental, culturally appropriate education on viral suppression, ART adherence, and stigma is vital for positive living during both pregnancy and post-partum periods. Health workers play a key role in delivering supportive counseling that promotes maternal well-being and success in the prevention of vertical transmission.

Peer support should be central to HIV maternal-child health programs

Tailored peer support interventions offer a scalable, sustainable strategy to strengthen maternal HIV care and accelerate progress toward eliminating vertical transmission across Uganda and Sub-Saharan Africa.

7.2. Recommendations

Based on the study findings, we propose and make recommendations that provide a strategic framework that utilizes and scales up components of the ENHANCED-SPS intervention to further improve maternal and infant outcomes through a concerted effort of the Ministry of Health, prevention of vertical transmission programs, local governments, implementing partners, Hospitals, lower-level health facilities and communities working together to improve maternal and child health outcomes in south western Uganda.

7.2.1. To the Ministry of Health

1. ***Integrate Peer-Led Support into Routine Services***

   Government health programs should prioritize the adoption and scale up peer-led interventions like ENHANCED-SPS in antenatal and postnatal clinics. This includes recruiting and training mentor mothers, formalizing their roles within health systems, and ensuring consistent funding for peer support programs.

2. ***Prioritize Postpartum Viral Suppression***

   Develop and implement targeted postpartum care protocols, including scheduled viral load monitoring, adherence counselling, and intensified follow-up for breastfeeding women. Allocate resources for operational research to identify specific barriers to suppression in this period.

3. ***Strengthen Early and Infant Diagnosis EID programs***

   Expand EID access by increasing point-of-care testing availability and streamlining lab result turnaround. Implement mother-centered counselling approaches to identify individual barriers and develop personalized plans to improve EID uptake.

4. ***Standardize Counselling and Education Materials***

Design and disseminate standardized, culturally appropriate materials that emphasize the importance of viral suppression, the role of ART, and prevention of vertical transmission. Train healthcare providers in effective communication and adherence counselling techniques.

5. ***Implement Disclosure and Stigma-Reduction Initiatives***

   Incorporate structured HIV disclosure counselling into maternal care guidelines. Develop stigma-reduction campaigns targeting both communities and health workers to create supportive environments for women to disclose their status safely.

6. ***Institutionalize Supportive Care Models***

   Mandate the integration of peer support and psychosocial care into national HIV and maternal health programs. Train health workers on creating respectful, client-centered care environments, and monitor adherence to supportive care standards through facility audits and client feedback.

7.2.2. Health facilities and care providers

i. Health workers should deliver clear and culturally appropriate education on the importance of viral load testing and achieving viral suppression in the prevention of vertical transmission.

ii. Health workers should encourage the creation of supportive, non-judgmental environments within health facilities. Peer support has been instrumental in enhancing adherence and disclosure, and should be an integral part of service delivery in government clinics and other care settings.

iii. Given that viral suppression among breastfeeding women remained suboptimal below the UNAIDS targets, it is essential to refine and intensify interventions during the breastfeeding /post-partum period and ensure that no mother is left behind.

iv. Institute clear systems that support the work of peer mothers in the health care delivery system to support other women to achieve good health for both the mother and the baby

v. Prevention of vertical transmission services should continue to prioritize interventions aimed at improving EID testing uptake, especially among recently diagnosed mothers, while also recognizing the need for sustained engagement to achieve meaningful improvements in clinical outcomes over the long term.

7.2.3. Community including pregnant and postpartum women

Women and community members to adopt behaviors that prevent vertical transmission, such as disclosing their HIV status to trusted family and friends for adherence support, and support one another in ensuring a healthy mother and a healthy baby.

7.2.4. Recommendations for future research

i. Vertical transmission prevention programs should design and implement interventions aimed at improving EID testing uptake, especially among recently diagnosed mothers living with HIV.

ii. Further research with a larger trial to inform the effectiveness of the ENHANCED-SPS Intervention on both maternal and infant outcomes and its scalability.

iii. Researchers need to design and optimize interventions that reduce missed opportunities during the post-partum period and explore the mechanisms for improvement.

iv. To develop appropriate job aids to support targeted and standardized support for the peer mother in the provision of quality maternal and child care in our setting.

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APPENDICES

Appendix 1: Publication for Objective One

Population-level viral suppression among pregnant and postpartum women in a universal test and treat trial

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Objective(s): We sought to determine whether universal 'test and treat' (UTT) can achieve gains in viral suppression beyond universal antiretroviral treatment (ART) eligibility during pregnancy and postpartum, among women living with HIV.

Design: A community cluster randomized trial.

Methods: The SEARCH UTT trial compared an intervention of annual population testing and universal ART with a control of baseline population testing with ART by country standard, including ART eligibility for all pregnant/postpartum women, in 32 communities in Kenya and Uganda. When testing, women were asked about current pregnancy and live births over the prior year and, if HIV-infected, had their viral load measured. Between arms, we compared population-level viral suppression (HIV RNA <500 copies/ml) among all pregnant/postpartum HIV-infected women at study close (year 3). We also compared year-3 population-level viral suppression and predictors of viral suppression among all 15 to 45-year-old women by arm.

Results: At baseline, 92 and 93% of 15 to 45-year-old women tested for HIV: HIV prevalence was 12.6 and 12.3%, in intervention and control communities, respectively. Among HIV-infected women self-reporting pregnancy/live birth, prevalence of viral suppression was 42 and 44% at baseline, and 81 and 76% ($P = 0.02$) at year 3, respectively. Among all 15 to 45-year-old HIV-infected women, year-3 population-level viral suppression was higher in intervention (77%) versus control (68%; $P < 0.001$). Pregnancy/live birth was a predictor of year-3 viral suppression in control ($P = 0.016$) but not intervention ($P = 0.43$). Younger age was a risk factor for nonsuppression in both arms.

Conclusion: The SEARCH intervention resulted in higher population viral suppression among pregnant/postpartum women than a control of baseline universal testing with ART eligibility for pregnant/postpartum women.

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Keywords: Kenya, population viral suppression, postpartum, pregnant women, Uganda, universal test and treat

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Introduction

Antiretroviral therapy (ART) is critical to reducing morbidity and mortality in people living with HIV (PLHIV) [1,2], and preventing mother-to-child HIV transmission (MTCT) during pregnancy, delivery and breastfeeding [3,4]. With increasing ART access in sub-Saharan Africa (SSA) since the early 2000s, the proportion of pregnant and postpartum women receiving ART has markedly increased, with subsequent declines in perinatal infections [5]. HIV treatment guidelines in Kenya and Uganda have recommended lifelong ART for all pregnant and postpartum women ('Option B+') since 2012 [6,7], predating current guidelines that recommend ART for all PLHIV. Despite this progress, MTCT rates remain above global targets in SSA, with over half of HIV infections among children in East Africa in 2018 occurring during breastfeeding and approximately one-third of infections attributable to women stopping or being unable to access ART during pregnancy [5].

Pregnant and postpartum women living with HIV (WLHIV) in SSA face multiple barriers to achieving viral suppression. Inadequate access to antenatal care (ANC) due to distance, cost or lack of education regarding benefits of ANC results in missed opportunities for HIV testing and early diagnosis [8]. Many women who access ANC only attend one ANC visit during pregnancy, resulting in missed opportunities to identify women who seroconvert after an initial antenatal visit [9]. Once diagnosed with HIV, pregnant/postpartum women face challenges with ART access and adherence distinct from other PLHIV. For some, these barriers include fear and stigma when coping with a new HIV diagnosis alongside a new awareness of pregnancy – particularly if unintended – creating the challenge of dual disclosure to partners and family members [10]. Once on ART, adherence may be limited by symptoms during pregnancy, side effects associated with antiretrovirals and fear of stigma, particularly in situations wherein women have not disclosed their HIV status or are facing interpersonal violence or lack of support from partners [8,11]. Postpartum, transitioning from antenatal to HIV clinics can be stigmatizing and has been associated with loss to follow-up [12]. Competing priorities, including caring for a new child, and reduced concern regarding MTCT following an initial negative infant test, may contribute to increased ART nonadherence during breastfeeding compared with pregnancy [13]. These distinct barriers occur in addition to those faced by PLHIV in SSA, such as long distances to and waiting times at clinics, low perceived HIV risk and costs in accessing services [14,15].

Several recent universal HIV 'test and treat' (UTT) trials in SSA have tested the effects of population-wide HIV testing with universal ART on HIV care cascade outcomes, morbidity, mortality and incidence [16–19]. The Sustainable East Africa Research in Community Health (SEARCH) UTT trial compared an intervention of annual population-wide HIV testing with universal ART with a control of baseline population-wide HIV testing with ART by country standard, including ART eligibility for pregnant/postpartum women, in communities in Kenya and Uganda [17]. SEARCH's universal testing intervention was designed to increase knowledge of HIV status for all and re-engage PLHIV who knew their status but were out of care [20]. SEARCH's universal treatment intervention was designed to increase viral suppression among all PLHIV by reducing barriers to ART [21]. As such, the SEARCH intervention, in addition to increasing viral suppression among high-$CD4^+$ cell count individuals, offered the potential to improve the prevalence of viral suppression among pregnant/postpartum women, through frequent, community-based testing and re-engagement, and by reducing barriers to ART for all women of reproductive age. The trial's primary results have been published [17]. In this secondary analysis, we sought to determine whether the SEARCH intervention increased population-level viral suppression among pregnant/postpartum women, above and beyond baseline population-wide testing and the 'Option B+' strategy of universal ART eligibility for pregnant /postpartum women offered in control communities throughout the trial.

Materials and methods

The SEARCH UTT trial (NCT:01864603) was a community cluster randomized trial that compared annual population-wide, HIV testing at multidisease health fairs with universal ART eligibility via patient-centred care (intervention) to baseline population-wide HIV testing at multidisease health fairs with national-guideline based ART eligibility (control), in 32 rural communities in Kenya and Uganda over three years. The trial was conducted from 2013 to 2017, and the trial methods and primary outcome results have been published [17]. In brief, study communities underwent pair-matched randomization at baseline (2013–2014), with 16 communities randomized to intervention and 16 to control. We conducted door-to-door census enumeration of community residents at baseline, followed by 2-week health fairs that offered universal HIV testing integrated with multidisease services. Adult (≥15 years) residents who did not attend fairs were offered HIV testing at home, or locations of their choice [20].

In SEARCH intervention communities, population-wide testing occurred annually, and all PLHIV were given appointments to link to care for ART within 7 days of testing HIV positive, or within 48 h if pregnant or breastfeeding by self-report. All PLHIV were offered ART regardless of $CD4^+$ cell count, using a patient-centred, streamlined approach that included 3-month

visit intervals for stable patients, reduced waiting time and welcoming staff, mobile phone access to providers and flexible hours for accessing care [21]. This approach also included clinician-guided transitions between HIV clinics and ANC for pregnant WLHIV, and the option to continue receiving ART at HIV clinics while attending ANC for women already engaged in HIV care. In control communities, population-wide HIV testing was performed at baseline and after 3 years, and PLHIV were offered ART according to country guidelines, which changed over the course of the study, ultimately expanding to ART for all PLHIV in Kenya and Uganda [17]. However, Kenya and Uganda Ministry of Health guidelines recommended lifelong ART initiation for all HIV-infected pregnant women (Option B+) throughout the trial [6,7]. Therefore, in both intervention and control communities, we offered rapid referral with ART initiation within 48 h of HIV diagnosis for all pregnant/breastfeeding women during population-wide testing. During each round of population-level testing, all women aged 15–45 years were asked about current pregnancy (at time of testing) or any live births over the prior year, and WLHIV had plasma HIV viral load measured. We defined HIV testing coverage at baseline and at year 3 of the trial as the proportion of women of reproductive age who participated in HIV testing services provided by SEARCH (i.e. health fairs and home-based testing) at baseline and year 3, respectively.

In this post-hoc analysis, we first sought to determine whether the SEARCH UTT intervention resulted in increased prevalence of viral suppression compared with control among WLHIV of reproductive age who reported current pregnancy or live birth over the prior year at trial completion (year 3). Although these women were ART eligible in both trial arms, we hypothesized that viral suppression would be higher among pregnant/postpartum women in intervention than control due to annual, population-wide testing with rapid linkage to streamlined care. Second, we compared population-viral suppression at year 3 among all women of reproductive age (15–45 years) with HIV in intervention and control communities and third, evaluated predictors of viral suppression among these women by arm. For this latter analysis, we hypothesized that pregnancy or live birth over prior year would increase the probability of viral suppression in control communities, but not intervention communities wherein all HIV-infected women were ART eligible, regardless of current or prior pregnancy.

Statistical analyses

Our primary outcome was the population-level proportion of pregnant or postpartum WLHIV who were virally suppressed (HIV RNA <500 copies/ml) at trial completion. In each community separately, we first estimated the following HIV care cascade outcomes among female residents (inclusive of in-migrants), aged 15–45 years who reported a current pregnancy or live birth in the last year: proportion of PLHIV who knew their status, proportion of PLHIV with known status who had initiated ART, proportion of PLHIV with ART use who were virally suppressed and proportion of all PLHIV who were virally suppressed [22]. Targeted maximum likelihood estimation (TMLE) was used to adjust for differences in the characteristics of women with known versus unknown HIV status, and known versus missing viral suppression status, as previously described [17,23]; TMLE incorporates machine learning to avoid model misspecification bias and offers efficiency gains over alternative approaches, such as inverse-weighting [24]. In secondary analyses, we calculated unadjusted cascade estimates among women with known HIV status and measured viral load. We obtained estimates of cascade outcomes and population-level suppression at baseline and year 3 in both arms, and at years 1 and 2 in the intervention arm. Universal testing was not conducted at years 1 and 2 in the control arm.

We compared year 3 estimates by arm with community-level TMLE, accounting for the matched design and with data-adaptive selection of adjustment variables, as previously described [17,25]; prespecified candidates were limited to baseline suppression and proportion of young women (age 15–24 years) to avoid over-fitting in analyses with 16 matched pairs of communities. We repeated these analyses among all women of reproductive age (15–45 years). Finally, we used TMLE to assess arm-specific predictors of viral suppression among all women of reproductive age living with HIV at year 3. Further details are available in the Supplementary Materials, http://links.lww.com/QAD/B771.

Ethical considerations

We obtained approval from the ethics committee of the University of California, San Francisco Committee on Human Research, Kenya Medical Research Institute Ethical Review Committee, Ugandan National Council on Science and Technology and Makerere University School of Medicine Research and Ethics Committee in Uganda. Verbal consent was obtained at enrolment; written consent was obtained for persons in the intervention arm receiving ART not yet indicated by country guidelines.

Results

Testing, HIV prevalence and pregnancy/live birth at trial baseline

Of 150 395 adult (≥15 years) residents enumerated in 32 communities at baseline, 62 066 (41%) were women of reproductive age (15–45 years): 32 954 women in intervention and 29 112 women in control communities (Table 1). Among enumerated women of reproductive age at baseline, SEARCH achieved 91% (30 074/32 954) and 92% (26 895/29 112) HIV testing coverage in

Table 1. Characteristics of 15 to 45-year-old women residents of SEARCH Communities in rural Uganda and Kenya, stratified by SEARCH trial arm, at baseline and year three of the trial.

	Intervention		Control	
	Baseline *N* (%) *N* = 32 954	Year 3 *N* (%) *N* = 41 598	Baseline *N* (%) *N* = 29 112	Year 3 *N* (%) *N* = 36 264
Age in years, median (interquartile range)	25 (19–34)	24 (19–33)	26 (20–34)	25 (19–33)
Region				
Kenya	11 568 (35.1)	13 529 (32.5)	10 352 (35.6)	11 934 (32.9)
Uganda-West	10 453 (31.7)	13 992 (33.6)	9,304 (32)	12 129 (33.4)
Uganda-East	10 933 (33.2)	14 077 (33.8)	9,456 (32.5)	12 201 (33.6)
Educational attainment[a]				
Less than primary	20 627 (62.6)	28 013 (67.3)	18 653 (64.1)	24 126 (66.5)
Primary	5188 (15.7)	5,723 (13.8)	4,702 (16.2)	5,268 (14.5)
Secondary or higher	7139 (21.7)	7,862 (18.9)	5,757 (19.8)	6,870 (18.9)
Occupation[b]				
Formal sector	8493 (25.8)	7260 (17.5)	6612 (22.7)	6446 (17.8)
High-risk informal	744 (2.3)	660 (1.6)	1245 (4.3)	1076 (3)
Low-risk informal	21 177 (64.3)	21 456 (51.6)	18 847 (64.7)	19 215 (53)
Other	1035 (3.1)	1259 (3.9)	913 (3.1)	1160 (4)
No job or disabled	1424 (4.3)	1506 (4.7)	1435 (4.9)	1401 (4.8)
Marital status[c]				
Single	9587 (29.2)	8204 (25.5)	7645 (26.3)	7483 (25.5)
Married	20 399 (62)	21 531 (67)	18 757 (64.6)	19 477 (66.5)
Widowed, divorced or separated	2890 (8.8)	2404 (7.5)	2649 (9.1)	2341 (8)
Household wealth index quintile[d]				
First (lowest)	5161 (15.7)	5562 (14.4)	5057 (17.4)	5266 (16)
Second	5890 (17.9)	6720 (17.4)	5554 (19.2)	6093 (18.5)
Third	6602 (20.1)	7940 (20.5)	6084 (21)	7126 (21.6)
Fourth	7147 (21.7)	8610 (22.3)	6314 (21.8)	7402 (22.5)
Fifth (highest)	8062 (24.5)	9856 (25.5)	5975 (20.6)	7078 (21.5)
Alcohol use[e]	1712 (6.1)	1219 (3.6)	1469 (5.9)	984 (3.2)
Mobile[f]	4702 (14.3)	1483 (3.6)	3910 (13.4)	1300 (3.6)
Pregnancy or live birth[g]				
Reported current pregnancy	2776 (9.1)	2496 (7.5)	2528 (9.3)	2506 (8.3)
Reported live birth in prior year	8448 (27.6)	4431 (13.3)	7579 (27.7)	4038 (13.3)

[a]Education missing on 82 (0.1%) and 16 444 (21.1%) at baseline and year 3, respectively.
[b]Occupation missing on 141 (0.2%) and 16 423 (21.1%) at baseline and year 3, respectively.
[c]Marital status missing on 139 (0.2%) and 16 422 (21.1%) at baseline and year 3, respectively.
[d]Household wealth index, defined from principal component analysis of household item survey, missing on 220 (0.4%) and 6209 (8%) at baseline and year 3, respectively.
[e]Alcohol use missing on 8915 (14.4%) and 14 104 (18.1%) at baseline and year 3, respectively.
[f]Mobile, defined as spending one or more month away from the community in the past year, missing on 13 896 (17.8%) at year 3.
[g]Pregnancy or live birth status missing on 4253 (6.9%) and 14 449 (18.6%) at baseline and year 3, respectively.

intervention and control communities, respectively. Baseline HIV prevalence among women who tested varied by region: 23.8% in Western Kenya, 7.7% in Western Uganda and 3.7% in Eastern Uganda, with an overall baseline HIV prevalence of 12.4% (7047/56 969) among women who tested. At the time of baseline HIV testing, 93% (57 813/62 066) of all women of reproductive age and 99% (6995/7047) of HIV-positive women responded to the following pregnancy/live birth questions: 'are you pregnant now?' and 'how many live births have you had in the past year?' Among HIV-positive women aged 15–45 years, 33% (1252/3741) in intervention communities and 33% (1081/3254) in control communities reported a current pregnancy or at least one live birth in the prior year at baseline.

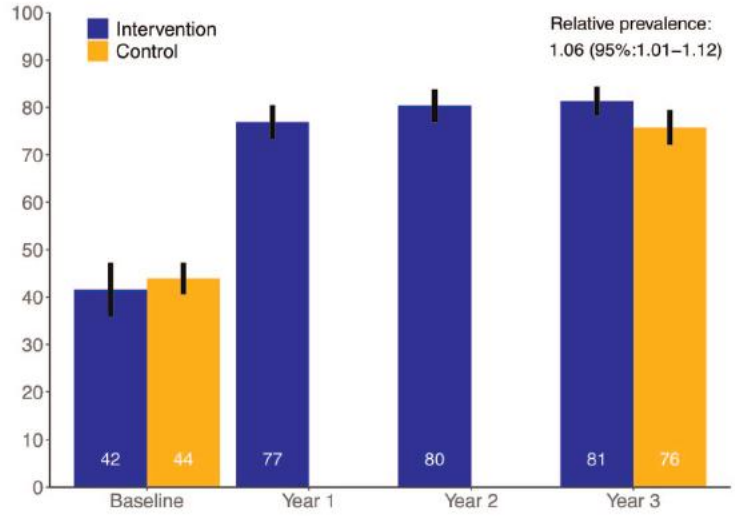
Testing, HIV prevalence and pregnancy/live birth at year 3 of the trial

During year 3 of the trial, there were 77 862 women age 15–45 years enumerated in the 32 study communities, inclusive of in-migrants and young women (12–14 years old at baseline) who turned 15 years during follow-up and excluding women who had aged out, died or out-migrated: 41 598 women in intervention and 36 264 women in control communities. Among these women, SEARCH achieved 80% (33 326/41 598) and 84% (30 282/36 264) HIV testing coverage in intervention and control communities, respectively, at year 3 of the trial. Year 3 HIV prevalence among women age 15–45 years who tested was 10.6% (3540/33 326) and 10.2% (3086/30 282) in intervention and control communities, respectively. At the time of year 3 testing, 81% (63 413/77 862) of all women of reproductive age and 99% (6557/6626) of HIV-positive women responded to the pregnancy/live birth questions. Among HIV-positive women, 14% (481/3505) reported a current pregnancy or a live birth in the prior year at year 3 of the trial in intervention communities, compared with 16% (487/3052) in control communities.

postpartum women

Among 15 to 45-year-old WLHIV who reported current pregnancy or live birth in the prior year at baseline, HIV viral suppression was 42% [95% confidence interval (CI): 36–47] in intervention, and 44% (95% CI: 41–47) in control communities, after adjusting for missingness in HIV status and viral load (Fig. 1). During subsequent annual rounds of offering universal HIV testing in intervention communities only, viral suppression estimates among pregnant/postpartum women were 77% years 1 and 2, respectively.

Among 15 to 45-year-old WLHIV reporting a current pregnancy or live birth in the prior year during year 3 of the trial, 95% (95% CI: 92–98) and 91% (95% CI: 89–93) knew their HIV status in intervention and control communities, respectively. Of those with a prior diagnosis of HIV, 98% (95% CI: 97–99) and 95% (95% CI: 94–97) were on ART in intervention and control communities, respectively. Of those on ART, 88% (95% CI: 85–91) and



	Intervention		Control	
	Adjusted*	Unadjusted**	Adjusted*	Unadjusted**
Baseline	536/1290 (42%)	417/952 (44%)	489/1113 (44%)	357/718 (50%)
Year 1	590/765 (77%)	568/724 (78%)		
Year 2	497/621 (80%)	480/586 (82%)		
Year 3	393/483 (81%)	384/464 (83%)	373/491 (76%)	366/476 (77%)

*Adjusted for missing measures on HIV status and viral suppression with TMLE for community, age group and mobility

**Unadjusted: Number measured viral suppression divided by number known to be HIV-positive with HIV RNA level measured.

Fig. 1. Estimates of population-level HIV viral suppression among women aged 15–45 years and reporting a current pregnancy or live birth over the prior year by study year in the SEARCH trial. Adjusted for incomplete measurement of HIV status and viral load measurement with targeted maximum likelihood estimation (TMLE); 95% confidence intervals indicated with black vertical lines. Absolute numbers given in the corresponding table.

87% (95% CI: 84–91) were virally suppressed, respectively. At year 3, overall population-level prevalence of viral suppression among 15 to 45-year-old women reporting a current pregnancy or live birth in the prior year had increased to 81% (95% CI: 78–84) in intervention compared with 76% (95% CI: 72–80) in control communities (Fig. 1). At year 3, population-level prevalence of viral suppression among women reporting current pregnancy or live birth in the prior year was 6% higher in intervention versus control communities (adjusted relative prevalence: 1.06, 95% CI: 1.01–1.12; $P=0.02$).

Prevalence of viral suppression among women of reproductive age

In comparison, population-level viral suppression estimates for all 15 to 45-year-old WLHIV (regardless of reported pregnancy or live birth) at year 3 was 77% (95% CI: 74–80) in intervention versus 68% (95% CI: 66–70) in control communities (adjusted relative prevalence: 1.13, 95% CI: 1.08–1.19; $P<0.001$).

Comparison of predictors of viral suppression by SEARCH trial arm

When determining predictors of viral suppression at year 3 among 15 to 45-year-old WLHIV, viral suppression at year 3 was not associated with self-reported current pregnancy or live birth in the prior year in intervention communities (aRR: 1.01, ref: no pregnancy/live birth, 95% CI: 0.98–1.05, $P=0.43$), whereas in control communities, women with a current pregnancy or live birth in the prior year were more likely to have viral suppression at year 3 than women without current pregnancy or live birth in prior year (aRR: 1.06, 95% CI: 1.01–1.12, $P=0.016$). In both intervention and control communities, older age consistently predicted viral suppression at year 3 compared with age 15–19 years (Fig. 2).

Discussion

The SEARCH UTT intervention resulted in a significantly higher prevalence of HIV viral suppression after 3 years among HIV-infected pregnant and recently postpartum women in intervention communities that offered repeat out-of-facility testing with rapid linkage to streamlined HIV care compared with standard clinical care in control communities, following baseline universal HIV testing in all communities. Although the absolute difference in prevalence of viral suppression in intervention versus control was relatively modest (6%), these gains occurred at a population level, in a group of PLHIV (pregnant/postpartum women) who were ART-eligible throughout the trial, and in communities (in both arms) that achieved prevalence of viral suppression in pregnant/postpartum women beyond the '73%' threshold of the UNAIDS '90–90–90' targets for 2020 [22]. The '90–90–90' targets aim to have 90% of PLHIV know their HIV status, 90% of PLHIV who know their status receive ART and 90% of those on ART achieve viral suppression: resulting in a goal that at least 73% of all PLHIV are virally suppressed. In a post 90–90–90 context, modest absolute gains in viral suppression will likely require testing and treating some of the hardest-to-reach subgroups and optimizing each '90'. Our results provide one of the first estimates of population-level prevalence of viral suppression among pregnant/postpartum women, independent of ANC access, in Kenya and Uganda. These findings add to the evidence demonstrating population-level health benefits conferred by UTT interventions, including reductions in HIV-associated mortality, tuberculosis and incidence [16,17,19].

There are several potential explanations for how the SEARCH intervention achieved a higher prevalence of viral suppression among peripartum women than control. First, annual, out-of-facility, population-wide HIV testing provided a platform to diagnose new infections that had occurred over the prior year, identify new in-migrants to the community who had not been diagnosed previously and re-engage PLHIV who had stopped ART. Community-based testing can also reach women who do not access ANC, deliver at home or do not engage in HIV testing while pregnant/postpartum. Thus, the proportion of peripartum women in year 3 of the trial who knew their HIV status was higher in intervention (95%) than control (91%) communities, even though in both, knowledge of HIV status exceeded 90%. Second, referrals to HIV care following annual testing prioritized pregnant and breastfeeding women by making appointments and starting ART within 48 h of testing positive, introducing women to clinic staff at testing sites, and closely following up women who missed appointments. As a result, the proportion of pregnant/postpartum women on ART was higher in intervention than control, even though in both arms this proportion was very high (98 and 95%, respectively). Third, the SEARCH intervention's streamlined model of care sought to reduce barriers to care, by reducing frequency of clinic visits and waiting times, providing a welcoming environment with flexible appointment scheduling and mobile phone access to clinicians, and actively tracking those lost to follow-up. For pregnant/postpartum women, particularly those caring for an infant, reducing these barriers to care and easing transitions between ANC and HIV clinics may explain the higher proportion of women on ART and suppressed in intervention communities. Finally, universal ART eligibility in intervention communities resulted in higher prevalence of suppression among women of reproductive age, providing an opportunity for viral suppression preconception, which also likely contributed to the higher prevalence of viral suppression in pregnant/postpartum women compared to control.

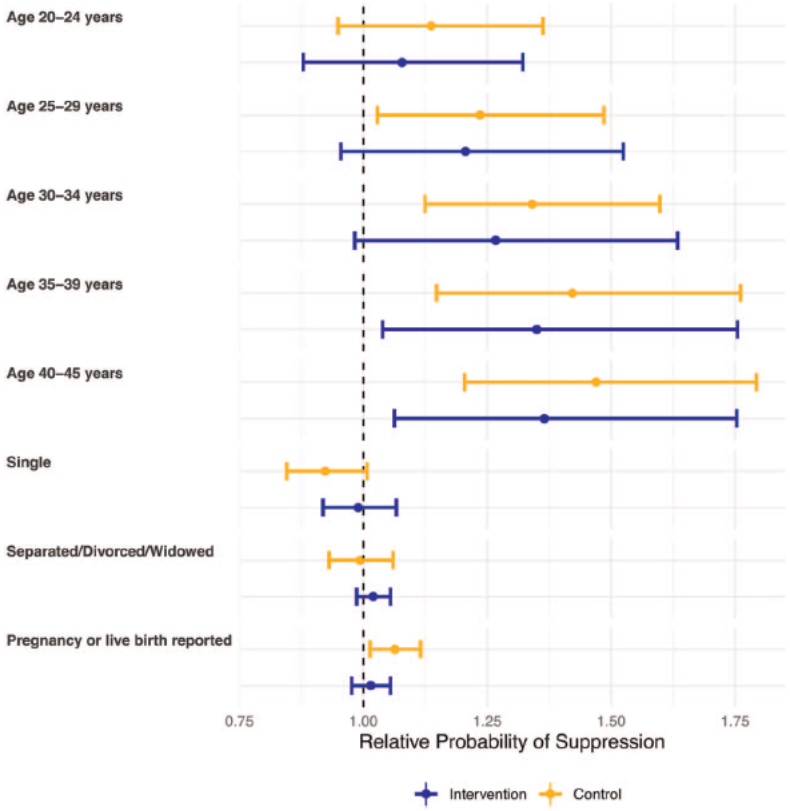


Fig. 2. Adjusted predictors of HIV viral suppression (HIV RNA <500 copies/ml) among HIV-positive women aged 15–45 years, as assessed during Year 3 of the SEARCH Study using targeted maximum likelihood estimation (TMLE) treating the community as the independent unit. Each relative probability is adjusted for the other predictors and region. Reference categories are age 15–19 years, marital status of married and not reporting a pregnancy or live birth in the prior year.

At present, as universal ART eligibility is the global standard and differentiated models of care are being widely adopted across SSA, the need for rapid, universal (i.e. nontargeted) testing initiatives and how often such initiatives may be needed remains under discussion. The higher knowledge of HIV status and higher levels of viral suppression achieved in pregnant/postpartum women may be potential benefits to implementing intermittent, large-scale HIV testing initiatives, in medium to high-prevalence settings such as rural Uganda and Western Kenya. Even as SEARCH control communities exceeded the UNAIDS '90–90–90' target of 73% among pregnant/breastfeeding women – with 76% viral suppression in this subgroup eligible for ART throughout the trial in control – the SEARCH intervention was able to achieve significantly higher levels of suppression (81%). It remains unclear whether efforts to push viral suppression further among the remaining 20–25% of unsuppressed PLHIV in communities that have surpassed '90–90–90' in SSA will require targeted outreach versus intermittent, nontargeted, population testing, or combination approaches. The higher levels of suppression

achieved among pregnant/postpartum women in intervention communities suggest that nontargeted, population testing can 'move the needle' in knowledge of HIV status and ART access, even among a group that was eligible for ART and targeted for HIV testing at ANCs throughout the trial.

Our results provide a population-level prevalence of viral suppression among pregnant/postpartum women, and all women of reproductive age, including measures of each step of the HIV care cascade. One advantage of population measures, compared with clinic-based measures, is that they are not conditional on accessing antenatal or postpartum HIV care. Published data on the prevalence of viral suppression in pregnant/postpartum women in SSA are sparse, and largely limited to clinic-based cohorts, with a large range of suppression estimates (30–98%) reported [26]. Our findings highlight ongoing challenges in adherence, even after exceeding the first two '90s', with 88% of pregnant/postpartum women on ART achieving viral suppression in intervention communities. In a recent study from South Africa, the vast majority (>90%) of instances of nonsuppression during pregnancy among women on ART were attributable to nonadherence rather than pretreatment drug resistance [27], demonstrating the need for adherence support interventions in pregnant/postpartum women. In addition, our finding of lower prevalence of viral suppression in younger women is consistent with prior literature [13,28], and emphasizes the need for specific, and integrated, interventions to support young women with both HIV and reproductive healthcare.

Our study has several limitations. First, classification of current pregnancy/live birth over the prior year was based on self-report. This may have resulted in some misclassification, though it seems unlikely that self-report would be inaccurate for pregnancy (particularly in second and third trimester) or the birth of a child, or that misclassification would have differed by trial arm. Second, incomplete viral load measures among PLHIV may have resulted in overestimates of population viral suppression. However, both HIV testing coverage and viral load measures among PLHIV were high (>80%), and we adjusted for differences between persons with and without viral load measures. Third, this analysis did not include measures of neonatal and childhood HIV incidence; analyses are ongoing to determine whether changes in maternal viral suppression resulted in reduced vertical transmission. However, maternal viral load during pregnancy, delivery and breastfeeding is clearly associated with likelihood of vertical transmission and increasing ART access for pregnant women has resulted in significant declines in the number of new child infections in multiple settings, including Kenya and Uganda [5].

In conclusion, the SEARCH UTT intervention resulted in significant gains in the prevalence of viral suppression among pregnant and postpartum women, compared with an active control that offered one-time universal testing and ART eligibility for all pregnant/postpartum women. The intervention also increased viral suppression among all women of reproductive age, extending the promise of ART to improve maternal health and further reduce new childhood HIV infections. As countries seek to eliminate MTCT and improve viral suppression among WLHIV, our findings provide insights into how to move closer towards achieving these important goals.

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Conflicts of interest

The authors have no competing interests.

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Appendix 2: Publication for Objective Three

Peer-mother counseling improves HIV treatment adherence and status disclosure over time among pregnant and postpartum women in rural Uganda

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Abstract

Adherence to antiretroviral therapy (ART) and disclosure of HIV status are critical for achieving HIV viral suppression and eliminating perinatal transmission of HIV. The ENHANCED-SPS intervention was designed to address barriers to viral suppression among pregnant and postpartum women with HIV and included standardized support and counseling though phone calls by peer-mothers. Using targeted minimum loss-based estimation (TMLE), we evaluated changes in adherence (≤1 dose of ART missed per month) and HIV status disclosure (to anyone and to a spouse or partner) among 505 pregnant and postpartum women with HIV who received the ENHANCED-SPS intervention in rural Uganda (2019-2021). ART adherence was 68% (95% CI, 62-74) at baseline and increased to 93% (95% CI, 81-100) after 12 months, corresponding to a 25% increase (95% CI, 9-40; P = .009). Largest improvements were among participants who were aged 15-24 years, breastfeeding, or without viral suppression at enrollment. At baseline, 80% (95% CI, 69-90) had disclosed their HIV status to anyone—increasing to 94% (95% CI, 89-99) after 12 months and corresponding to a 14% improvement (95% CI, 8-21; P = .003). Similar trends were observed for disclosure to a spouse or partner. Among pregnant and postpartum women with HIV in rural Uganda, the ENHANCED-SPS intervention was associated with meaningful improvements in ART adherence and HIV status disclosure after 1 year.

Key words: pregnancy and postpartum; HIV status disclosure; ART adherence; peer-led intervention; HIV care continuum and women; TMLE.

Introduction

Despite substantial progress in the prevention of vertical transmission of HIV, 130 000 children were born with HIV globally in 2022.[1] World Health Organization (WHO) policies have recommended lifelong antiretroviral therapy (ART) for pregnant women since 2012 and universal ART for all persons with HIV since 2016.[2] Expanded ART coverage for women with HIV has been realized in most countries of Sub-Saharan Africa.[3,4] In addition to extended treatment eligibility, ensuring knowledge of HIV status, early initiation and adherence to ART, and disclosure of HIV status have been associated with improved child and maternal outcomes.[1] Despite these efforts, global targets to eliminate vertical transmission of HIV are not on track.[5,6]

Pregnancy and postpartum remain the time when many women first learn about their HIV diagnosis and initiate ART for lifetime use.[7-9] Additionally, pregnancy and breastfeeding present unique challenges and vulnerabilities that may result in non-disclosure of HIV status, non-adherence to ART, and viral nonsuppression.[9-13] HIV disclosure among pregnant and postpartum women has been reported to be low, ranging from 16% to 86% in developing countries.[14] Additionally, the decision to disclose is mainly informed by perceptions of HIV stigma and, most importantly, the anticipated responses from individuals in

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their family and social networks.[10] While disclosure of HIV status has the potential to elicit negative reactions, positive experiences of disclosure can give individuals access to social support, which facilitates HIV care engagement both emotionally (through encouragement and advice) and practically (through reminders and financial assistance).[15] These positive experiences and the other documented benefits of HIV status disclosure have been reflected in the guidelines encouraging all women with HIV to disclose their status.[16–21] The benefits of ART adherence are well known; indeed, non-adherence to ART has been associated with poor maternal and child health outcomes[21–23] and, ultimately, an increased risk of vertical transmission of HIV.[23–25] Altogether, interventions to promote care engagement among pregnant and postpartum women are important in achieving the goal of zero infections among children born to women with HIV.[26–28]

Support and counseling from peers are crucial to addressing barriers to services for preventing vertical HIV transmission in Sub-Saharan Africa.[29–31] Use of community health workers have previously been recommended to increase awareness of viral load status as well as male partner engagement for safe disclosure and optimal ART adherence.[31,32] In particular, peer-mothers, who are lay women with HIV and trained to offer counseling and education on HIV prevention and treatment for pregnant women or mothers with HIV, have been increasingly incorporated in antenatal and postnatal clinics.[33,34] Furthermore, several mhealth interventions have been shown to improve adherence and retention in care.[35,36] In addition, prior studies of point-of-care HIV RNA viral load testing, which allows for rapid feedback of results and tailored counseling, have been associated with improved viral suppression among adults with HIV in the general population.[37] However, the combination of these interventions—specifically phone calls by peer-mothers to provide enhanced viral load and adherence counseling based on point-of-care viral load testing to pregnant and postpartum women with HIV—has not been rigorously evaluated.

Therefore, we developed the ENHANCED-SPS intervention, which combined peer-mother support, mhealth, and point-of-care viral load testing, to address barriers to viral suppression, including knowledge gaps, lack of tailored counseling, and poor support from partners and other peers.[38] We previously demonstrated the ENHANCED-SPS intervention was associated with significant improvements in viral suppression among pregnant and breastfeeding women with HIV in rural Uganda.[38] We hypothesized that the ENHANCED-SPS intervention would also be associated with improvements in ART adherence and HIV status disclosure.

Methods

Study design, population, and setting

This was a longitudinal analysis of participants in the intervention arm of the ENHANCED-SPS study, a cluster randomized trial of 14 health facilities with some of the highest seroprevalence of HIV in rural Southwestern Uganda.[38] All health facilities provided HIV care, were government-run with support from PEPFAR-implementing partners, and had existing peer-mothers to provide health education for pregnant and postpartum women in HIV care. Women with HIV aged 15-45 years and accessing care from these facilities were eligible for enrollment at[1] their first antenatal care visit or[2] a follow-up antenatal or postnatal care visit upon a new HIV diagnosis. Women in postnatal care were eligible for enrolment up until 6 weeks (42 days) after delivery. All women meeting the eligibility criteria were consecutively enrolled until the target sample size was reached. Enrolment started from September 1, 2019 and was completed on October 30, 2020, and participants were followed up for a period of 12 months.

All participants received standard-of-care services for pregnant and postpartum women: HIV testing, viral load testing, ART initiation, ART card documentation, general counseling, and adherence counseling every 3 months if not virally suppressing. The standard visit schedule for pregnant and postpartum women with HIV was monthly and followed in both arms. Women enrolled from intervention facilities also received the ENHANCED-SPS intervention, described next. There were no other interventions or changes in HIV care for pregnant or postpartum women during the study period.

Study intervention

The ENHANCED-SPS intervention was developed using the empirically validated PRECEDE framework, which is based on the idea that health promotion strategies are most effective when they are cocreated and implemented with the people affected.[20] First, we identified barriers to viral suppression from the literature, our prior experience in the SEARCH universal HIV test-and-treat trial,[39] and discussions with peer-mothers and providers at the different facilities during the prestudy assessment[38] (Figure S1). Next, we designed a counseling protocol on how to provide enhanced viral load counseling and individualized assessment of barriers to HIV status disclosure and ART adherence as well as how to jointly address those barriers. As previously described, this counseling protocol was flipchart-based with 6 themes: i) the role of HIV testing and the working of ART, ii) explanation of and implication of a high or low viral load in relation to adherence, iii) prevention of vertical HIV transmission, iv) what happens when the viral load is high, v) sharing your HIV status with the significant others, and finally, vi) the big catch—"A healthy mother, a healthy family."[38]

At each intervention clinic, 1 peer-mother and facility midwife were trained on the provision of viral load and adherence counseling using the flipchart. Through biweekly phone calls, peer-mothers provided viral suppression and adherence counseling to study participants. At routine clinic visits, peer-mothers and facility midwives used the flipchart to facilitate a guided discussion of barriers and facilitators to ART adherence and HIV status disclosure. Additional aspects of the multicomponent intervention included point-of-care viral load testing, which facilitated rapid feedback of results and enhanced viral load counseling, as well as feedback meetings with peer-mothers and midwives.

Outcome definition and measurement

Data on ART adherence were obtained through review of electronic medical records and Ugandan HIV care cards. Outcomes were assessed with respect to each participant's follow-up time in the study and regardless of their clinic visits. Specifically, we assessed adherence every 3 follow-up months via the clinic record closest to and within 45 days of 0 (baseline), 3, 6, 9, and 12 months of follow-up. At each timepoint, participants were classified as "adherent" if their record indicated missing $\leq$1 dose of ART per month, as "non-adherent" if their record indicated missing $\geq$ 2 doses of ART per month, and as "unknown" if their record was missing adherence data.

Using the same data sources, HIV status disclosure to anyone (eg, family or friend) was assessed at baseline and at every 3 months of follow-up for each participant. Specifically, we created a binary variable indicating if the participant had disclosed her HIV status by 0, 3, 6, 9, and 12 months of follow-up. This variable was subject to missingness if there were no disclosure data in the

Table 1. Baseline characteristics of the study participants; metrics in *n* (%) among measured.

	On ART <6 mo *n* = 181	On ART 6+ mo *n* = 316	Overall[a] *n* = 505
Age group[b] (y)			
15-24	62/138 (45%)	58/263 (22%)	123/407 (30%)
25-34	62/138 (45%)	156/263 (59%)	220/407 (54%)
35+	14/138 (10%)	49/263 (19%)	64/407 (16%)
Peripartum status			
Pregnant	160/181 (88%)	316/316 (100%)	483/505 (96%)
Breastfeeding	21/181 (12%)	0/316 (0%)	22/505 (4%)
Marital status[c]			
Never married	9/124 (7%)	31/234 (13%)	40/364 (11%)
Married	108/124 (87%)	164/234 (70%)	276/364 (76%)
Separated, divorced, widowed	7/124 (6%)	39/234 (17%)	48/364 (13%)
ART regimen[d]			
Efavirenz-based regimen	34/34 (100%)	219/235 (93%)	253/269 (94%)
Other regimen	0/34 (0%)	16/235 (7%)	16/269 (6%)
Viral suppression status[e]			
Suppressed (HIV RNA <1000 c/mL)	50/164 (30%)	265/286 (93%)	318/455 (70%)
Not suppressed (HIV RNA ≥1000 c/mL)	114/164 (70%)	21/286 (7%)	137/455 (30%)

[a]Data missing on duration of antiretroviral therapy (ART) for 8 (2%) participants.
[b]Data missing on age for 98 (19%) participants.
[c]Data missing on marital status for 141 (28%) participants.
[d]Data missing on ART regimen for 236 (47%) participants.
[e]Data missing on viral suppression status for 50 (10%) participants.

corresponding clinic record. HIV status disclosure specifically to a significant other (ie, partner or spouse) was defined and assessed in a similar fashion.

We additionally obtained demographics, measures of care engagement (eg, duration on ART), and viral load measures from medical records and study logs. Participants were classified into groups defined by their enrollment characteristics: age (15-24, 25-34, 35+ years), peripartum status (pregnant or breastfeeding), marital status (never married, currently married, previously married, or currently separated), time since HIV diagnosis (with "recent" as a diagnosis within 2 weeks of enrollment), ART status (on ART for <6 months or 6+ months), and viral suppression (HIV RNA <1000 c/mL). For all variables, reasons for missing data were complex and included no visit by the participant and, thus, no clinic record in the relevant follow-up window and/or poor documentation in their clinic record.

Statistical analysis

This was a secondary analysis of the ENHANCED-SPS study, which was designed to compare viral suppression at 12 months between randomized arms.[38] In this prespecified analysis among intervention participants, we used targeted minimum loss-based estimation (TMLE) to estimate the proportion of participants with ART adherence at baseline, 3, 6, 9, and 12 months of follow-up and to evaluate changes between baseline and 12 months of follow-up.[40,41] Targeted minimum loss-based estimation is a doubly robust, flexible, and efficient method for evaluating causal effects in randomized trials and observational studies. Targeted minimum loss-based estimation can account for clustering by clinic and repeated measures on participants. Targeted minimum loss-based estimation also employs machine learning to minimize modeling assumptions. Specifically, we used Super Learner, an ensemble machine learning method, to flexibly adjust for age, peripartum status, and care group (recently vs. previously diagnosed) and, thus, account for differences between participants with and without adherence measures. This approach corresponds to the following missing data assumption: within all values of age, peripartum status, and care group, adherence among participants with measurements is representative of adherence among participants without measurements. Using the influence curve and the Student t-distribution, we calculated 95% CIs and evaluated the null hypothesis that the ENHANCE-SPS intervention was not associated with changes in ART adherence from baseline to 12 months of follow-up with a two-sided test at the 5% significance level. Further details are available in the Statistical Analysis Plan (Appendix S1). Secondary analyses were unadjusted (ie, differences in the empirical proportions with adherence measures who were classified as adherent). These analyses were repeated for the secondary endpoints of disclosure to anyone and disclosure to a partner or spouse by baseline, 3, 6, 9, and 12 months of follow-up. All analyses were repeated within baseline subgroups defined by age group, peripartum status, ART duration, and viral suppression status at enrolment. All analyses accounted for repeated measures and clustering by clinic. Analyses were done in R, version 4.4.0, using the *ltmle* package.[42,43]

Ethical considerations

This study was approved by the Makerere University School of Medicine Research and Ethics Committee (SOMREC) in May 2019 with annual IRB renewal approvals. All participants involved provided written informed consent, and a waiver of consent for secondary data abstraction was obtained from the IRB.

Results

At 7 health facilities receiving the ENHANCED-SPS intervention in rural Uganda, we enrolled 505 pregnant and postpartum women with HIV; of whom, 316/497 (64%) were on ART for 6 or more months at enrollment (Table 1). Overall, participants had a median age of 28 years [IQR, 24-32]; 123/407 (30%) were aged 15-24 years; 483/505 (96%) were pregnant; 276/364 (76%) were married, and 318/455 (70%) were virally suppressed (HIV RNA <1000 c/mL) at enrollment.

As shown in Table 2, the estimated proportion of participants who were ART adherent was 68% (95% CI, 62-74) at baseline

Table 2. Estimated proportion adherent to antiretroviral therapy (ART) over time.[a]

	Baseline (95% CI)	3 mo (95% CI)	6 mo (95% CI)	9 mo (95% CI)	12 mo (95% CI)
Overall	68% (62-74)	93% (85-100)	93% (87-100)	93% (86-100)	93% (81-100)
Age group (y)					
15-24	56% (4072)	92% (84100)	90% (8397)	90% (78-100)	89% (72-100)
25-34	76% (7081)	95% (88100)	98% (94100)	94% (87-100)	94% (84-100)
35+	81% (75-87)	98% (92-100)	95% (88-100)	100% (100-100)	100% (100-100)
Peripartum status					
Pregnant	71% (68-74)	93% (85-100)	95% (88-100)	93% (86-100)	92% (80-100)
Breastfeeding	5% (0-24)	87% (68-100)	70% (25-100)	100% (100-100)	100% (100-100)
ART status					
On ART <6 mo	22% (10-34)	86% (67-100)	86% (72-100)	89% (79-99)	95% (87-100)
On ART 6+ mo	95% (92-98)	97% (94-100)	98% (94-100)	97% (90-100)	92% (79-100)
Viral suppression status					
Suppressed	88% (83-94)	96% (90-100)	97% (92-100)	98% (93-100)	97% (88-100)
Non-suppressed	20% (16-23)	83% (64-100)	83% (63-100)	81% (63-99)	85% (68-100)

[a]Estimates are from TMLE accounting for clustering by clinic, repeated measures, and differences between participants with and without adherence measurements.

and increased to 93% (95% CI, 85-100) after 3 months of the ENHANCED-SPS intervention. After 12 months, an estimated 93% (95% CI, 81-100) of participants were adherent, corresponding to an absolute increase of 25% (95% CI, 9-40; P = .009) from baseline (Figure 1). Baseline adherence varied by age group: 56% for 15- to 24-year-olds, 76% for 25- to 34-year-olds, and 81% for 35+ year-olds (Table 2). Over the 12-month follow-up, these proportions increased to 89%, 94%, and 100%, respectively; therefore, the largest changes in adherence were among the youngest women (Figure 1). Adherence among the pregnant women was 71% at baseline, and this proportion increased to 93% at 3 months and was largely sustained throughout the follow-up period. Only 5% of the breastfeeding women were classified as adherent at baseline, but this proportion reached 100% by endline. Participants on ART for 6+ months sustained high levels of adherence (≥92%) throughout the study. Adherence among participants on ART for less than 6 months was low at baseline at 22% and increased to 86% after 3 months and reached 95% at 12 months. Importantly, the majority of the participants who were virally suppressed at enrollment were adherent throughout; specifically, among this subgroup, the estimated proportion with adherence increased from 88% at baseline to 96% by 3 months and was sustained. Equally important, the proportion of participants without viral suppression at enrollment with poor adherence was reduced from 80% at baseline to 15% at 12 months. Similar results were observed in unadjusted analyses, which excluded participants without adherence measures (Tables S1 and S2).

As shown in Table 3, the estimated proportion of participants who had disclosed their HIV status to anyone (eg, family or friend) was 80% (95% CI, 69-90) at baseline and increased to 90% (95% CI, 84-97) by 3 months of the ENHANCED-SPS intervention. After 12 months, an estimated 94% (95% CI, 89-99) of participants had disclosed their status, corresponding to an absolute increase of 14% (95% CI, 8-21; P = .003; Figure 2). Changes in disclosure varied by baseline subgroup (Table 3). The largest improvements were for the youngest participants (15-24 years); specifically, the proportion who had disclosed increased from 73% at baseline to 92% by 12 months. Disclosure among women who were breastfeeding at enrollment consistently lagged behind disclosure among women who were pregnant at enrollment; after 12 months, the estimated proportions who had disclosed to anyone were 81% and 94%, respectively. Similar trends were seen for participants who were on ART for less than 6 months at enrollment and participants without viral suppression at enrollment; their disclosure rates increased to ~85% by 12 months from ~50% at baseline. Among participants on ART for 6+ months and those with viral suppression at enrollment, disclosure was >90% at baseline and exceeded 95% by the close of the follow-up period. Again, similar results were seen in unadjusted analyses, excluding participants without disclosure measures (Table S3).

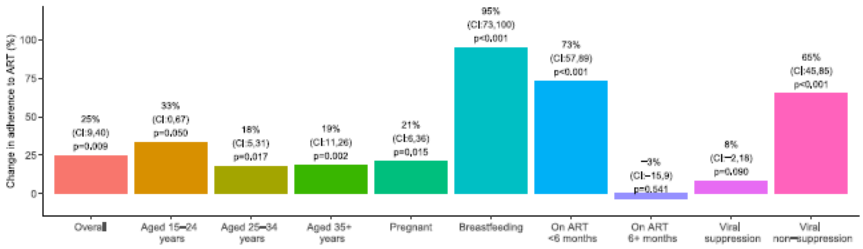

Figure 1. Change in antiretroviral therapy (ART) adherence from baseline to 12 months, overall and within subgroups.

Table 3. Estimated proportion disclosing their HIV status to anyone over time.[a]

	Baseline (95% CI)	3 mo (95% CI)	6 mo (95% CI)	9 mo (95% CI)	12 mo (95% CI)
Overall	80% (69-90)	90% (84-97)	91% (86-97)	94% (89-98)	94% (89-99)
Age group (y)					
15-24	73% (57-88)	89% (81-97)	90% (83-97)	92% (85-98)	92% (85-98)
25-34	83% (73-94)	93% (88-98)	94% (89-99)	96% (92-100)	97% (94-100)
35+	87% (83-90)	94% (90-98)	95% (91-100)	97% (93-100)	97% (93-100)
Peripartum status					
Pregnant	81% (72-91)	92% (86-97)	93% (88-98)	94% (90-99)	94% (90-99)
Breastfeeding	45% (9-81)	67% (39-94)	67% (39-94)	76% (52-100)	81% (60-100)
ART status					
On ART <6 mo	51% (28-73)	78% (66-89)	80% (70-91)	85% (75-95)	86% (76-96)
On ART 6+ mo	97% (92-100)	98% (94-100)	98% (94-100)	98% (95-100)	99% (96-100)
Viral suppression status					
Suppressed	93% (86-100)	97% (94-100)	97% (94-100)	98% (95-100)	98% (96-100)
Nonsuppressed	50% (31-70)	78% (64-91)	80% (67-93)	84% (73-95)	85% (74-96)

[a]Estimates are from TMLE accounting for clustering by clinic, repeated measures, and differences between participants with and without disclosure measurements.

Similar trends were observed for disclosure specifically to a spouse or partner (Tables S4 and S5). At baseline, spouse/partner disclosure was 74% (95% CI, 62-87) and increased to 86% (95% CI, 78-94) after 3 months of receiving the ENHANCED-SPS intervention. After 12 months, an estimated 91% (95% CI, 84-98) of the participants had disclosed to their spouse or partner, corresponding to an absolute increase of 16% (95% CI, 9-24; P = .002). As before, changes in spouse/partner disclosure varied by subgroups. Large improvements were observed among the youngest women (aged 15-24 years) whose disclosure rates increased from 68% to 89%; breastfeeding women whose disclosure rates increased from 40% to 76%, and virally nonsuppressed women whose disclosure rates increased from 45% to 81%.

Discussion

In this longitudinal study of pregnant and postpartum women with HIV in rural Southwestern Uganda, the ENHANCED-SPS intervention was associated with meaningful improvements in ART adherence from 65% at baseline to 93% at 12 months of follow-up. The levels of adherence reached in our study and among a particularly vulnerable group were notably higher than the among the general population of adults with HIV in Uganda. Specifically, the Ugandan Ministry of Health recently reported that adherence among persons with HIV *declined* from 96% in 2020 to 73% in 2022.[44] The ENHANCED-SPS intervention was also associated with improvements in HIV status disclosure to anyone from 80% at baseline to 94% after 12 months of follow-up. Improvements in disclosure were observed across all subgroups and, in particular, younger women. Disclosure rates among other young women (15-24 years) over the same timeframe and contextual setting were notably lower; only 55% of young women in the SEARCH-Youth study had disclosed to a partner and only 33% had disclosed to a friend.[45] As previously reported, our novel intervention was associated with significant improvements in HIV viral suppression from 70% at baseline to 95% at 12 months, corresponding to a difference of 25% (95% CI, 22-28; P <.0001).[38]

The ENHANCED-SPS intervention was grounded in the PRECEDE framework and built on the existing peer-mother program in public health facilities in rural Southwestern Uganda. We involved peer-mothers in the design and delivery of this intervention. Peer-mother programs, through which women with HIV provide peer support, have been increasingly incorporated into services to prevent vertical HIV transmission in many low- and middle-income countries. Prior work has shown that peer support interventions, both facility- and community-based, enhance maternal ART uptake and long-term retention of women in Option B+ programs.[46] Other qualitative studies have found that peer-mothers can foster engagement in HIV care and that they are a trusted source of information within the HIV clinics and community.[31,47] Although quantitative studies evaluating this approach

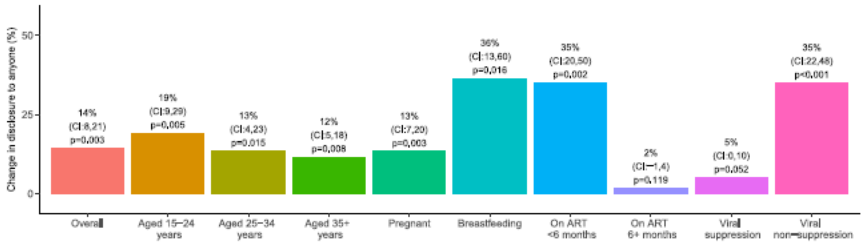

Figure 2. Change in disclosure of HIV status from baseline to 12 months, overall and within subgroups.

have been relatively limited, recent data have demonstrated an improved retention rate of 78% among pregnant women enrolled in peer-mother programs to prevent vertical HIV transmission in Tanzania.[37,47,48] Altogether, our findings add to the evidence base for the importance of peer-led models in expanding HIV care for pregnant and postpartum women with HIV within prevention of mother to child transmission of HIV (PMTCT) programs.[49]

Our intervention incorporated rapid viral load testing with tailored counseling to foster ART adherence and HIV status disclosure.[50] Because of delays of weeks to months in turnaround time for viral load results in many settings, the salience of viral load counseling may be limited when applied to prior behavior.[37] In contrast, point-of-care viral load testing with rapid return of results has previously been shown to improve viral suppression in adult populations with HIV.[37,47,51] Our study adds to the evidence base on the use of point-of-care viral loads during the critical time periods of pregnancy and breastfeeding. With ongoing scale-up of viral load testing, there are opportunities for integrating point-of-care testing strategies with peer-mother support models for counseling on ART adherence and to address workforce shortages in rural settings.[49]

The ENHANCED-SPS intervention provided peer-mothers with tools to provide structured counseling on viral load results and ART adherence. This motivational messaging may have created a desire in pregnant and breastfeeding women to stay healthy and have a healthy baby, thereby promoting adherence and disclosure.[52] Our findings highlight the additional benefits of behavioral interventions for pregnant and postpartum women with HIV. Discussions around HIV status disclosure with partners/spouses enhances male engagement, which was previously shown to increase clinic attendance and foster shared care responsibilities that contribute to improved adherence, retention, and ultimately, viral suppression.[53] Our intervention extends prior work by demonstrating that interventions with structured viral load counseling (ie, counseling describing viral load results and empowering patients with information on the effects of ART adherence) increase viral suppression.[39,54,55] The counseling flipchart is a tool with clear and simple messaging, which was reinforced at routine visits and via phone calls by peer-mothers, and could be incorporated into standard peer-mother programs.

Our intervention was associated with meaningful improvements in ART adherence as well as disclosure of HIV status to anyone and to a spouse or partner. Disclosure of HIV status lays a strong foundation for treatment support, reduces self-stigmatization, and improves treatment outcomes through facilitating adherence to ART.[53,56] Indeed, the relationship between disclosure of HIV status and adherence to ART is well documented, with disclosure improving adherence to ART[57] and early ART initiation improving disclosure[58]; implementation strategies exist to support either disclosure or adherence but rarely both. In a recent study in Nigeria, fear of disclosure of HIV status was cited as a potential deterrent to adherence; measured adherence was only 62.5%.[59] In a more recent exploratory qualitative study in Zambia,[50,60,61] women agreed that disclosure and partner support were necessary preconditions to ART initiation and their subsequent adherence to ART. Our study builds on this literature and suggests that interventions addressing both disclosure and adherence, rather than either in isolation, are associated with improvements in both disclosure and adherence to ART in this crucial population.

Our study examined adherence and disclosure among key subgroups, including younger women aged 15-24 years for whom outcomes have been suboptimal across many contexts.[62,63] The intervention was also associated with meaningful improvements among women on ART for fewer than 6 months; among these women, the estimated rates of adherence and disclosure were 95% and 86% after 12 months, respectively, suggesting the importance of early interventions and support for individuals who have recently received an HIV diagnosis. Similar improvements were observed for participants without viral suppression at baseline. Finally, multiple studies have demonstrated that retention in care and viral suppression drop in the postpartum period, threatening both maternal health and risking perinatal transmission during breastfeeding.[13,64,65] Although only 4% of this study population was postpartum (ie, breastfeeding), our results suggest that this intervention may be a promising approach to improve ART adherence and disclosure in this key group. Further study of the ENHANCED-SPS intervention is warranted.

Strengths of this study include engagement of peer-mothers throughout the study—from intervention development through delivery. This was among the first studies to evaluate an intervention combining point-of-care viral load testing with peer-led counseling among pregnant and breastfeeding women with HIV. Our study was implemented within routine care setting, representing real-world context. Furthermore, our intervention harnessed ongoing efforts provided peer-mothers and midwives to strengthen ART services and programs to prevent vertical HIV transmission.[44,66] The development and implementation of flipchart counseling tool for the peer-mothers is a major strength and is scalable to other programs in Sub-Saharan Africa. Specifically, this flipchart could be adapted and adopted by the Ministry of Health and implementing partners as a job aid to guide enhanced viral load and adherence counseling by peer-mothers.

The primary limitation of this study is the lack of a contemporaneous comparator group. Indeed, this was a longitudinal study evaluating changes over time among participants receiving the ENHANCED-SPS intervention. Self-controlled analyses, where each participant serves as their own comparator, can provide strong evidence of epidemiologic associations by eliminating confounding due to time-invariant variables. While we cannot eliminate the possibility that the observed improvements where due to secular trends, our study was implemented in routine settings where there were no other changes in HIV care for pregnant or postpartum women during follow-up. Furthermore, the levels of adherence observed after 12 months of the ENHANCED-SPS intervention far exceeded the current national program, which utilized the same data sources.[44] While we cannot rule out the possibility that disclosure rates improved simply because women had more time to share their status, the disclosure levels achieved by young (15-24 years) women in ENHANCED-SPS far exceeded the disclosure levels among their counterparts in the SEARCH-Youth study, also occurring in rural Southwestern Uganda over the same time.[45] An additional limitation is our reliance on routinely collected data, which was based on self-report and subject to missingness. However, routinely collected data are likely less prone to bias due to the Hawthorne effect or study participation, than data collected only for research purposes. In other words, we do not expect the observed changes in ART adherence or HIV status disclosure to be attributable to social desirability bias, because we obtained these measures from medical records. Additionally, TMLE was used to robustly control for missing data; specifically, our primary analyses assumed that within all values of age, peripartum status, and care group, participants with measured outcomes were representative of participants with missing

outcomes. This is a much more plausible assumption than missing-completely-at-random. Finally, our power to detect associations in certain subgroups (eg, breastfeeding women) was limited by small sample sizes. However, given the potential for enhanced counseling provided by peer-mothers to improve viral suppression via improvements in ART adherence and disclosure among pregnant and postpartum women with HIV in Sub-Saharan Africa,[38,67] we believe a larger trial is warranted to inform effectiveness and scalability.

In summary, the ENHANCED-SPS intervention, including enhanced HIV viral load counseling and standardized peer-mother support, was associated with meaningful improvements in ART adherence and HIV status disclosure among pregnant and breastfeeding women with HIV in rural Uganda. Our findings underscore that tailored peer support is a promising approach to advance health for women with HIV and strengthen programs to prevent vertical transmission in Uganda and Sub-Saharan Africa.

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Supplementary material

Supplementary material is available at *AJE Advances: Research in Epidemiology* online.

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Conflicts of interest

The authors report no conflict of interest in this work.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions on patient data.

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Original Contribution

Appendix 3: Publication for Objective Four

A Peer-Mother Counseling Intervention Improves Early Infant HIV Testing in Rural Uganda

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Background: Peer-led counseling interventions could improve early infant diagnosis of HIV by empowering mothers with knowledge and information on their role in preventing perinatal transmission. We hypothesized that a peer-led intervention would increase completion rates of infant HIV testing in rural Uganda.

Methods: From September 2019 to October 2021, we conducted the Enhanced viral load counseling with Standardized Peer-Support (ENHANCED-SPS) trial, which randomized 14 public health facilities to the intervention: peer-led counseling on HIV viral load and perinatal transmission, support for status disclosure and treatment adherence, and point-of-care viral load testing; or control: HIV care per national guidelines (NCT04122144). We retrospectively reviewed medical records of all infants born to ENHANCED-SPS participants during the 1-year follow-up and compared the proportions completing final testing (antibody rapid test at 18 months) between arms with targeted minimum loss-based estimation. Secondary outcomes included completion of earlier steps in the testing algorithm for the HIV-exposed infants.

Results: Among 464 children (intervention = 234 and control = 230) born to trial participants, the proportions completing final testing were 94.5% (95% CI: 91.6–97.5%) in the intervention and 83.3% (95% CI: 78.4–88.3%) in the control: a difference of 11.2% (CI: 5.4–17.0%; $P < 0.001$). There were no differences in the proportions completing the 1st test (at 4–6 weeks) or the 2nd test (at 9 months), but completion of the 3rd test (6 weeks after breastfeeding cessation) was 14.8% (95% CI: 7.9–21.8%; $P < 0.001$) higher in the intervention.

Conclusions: Peer-led counseling on the mother's role in ensuring a healthy baby reduced drop-offs in infant HIV testing, which is progress toward improved infant diagnosis and prompt linkage to care.

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Early diagnosis of HIV infection among infants and children is crucial, as it provides an entry point to pediatric HIV care and significantly improves long-term health outcomes.[1] However, globally in 2023, only 66% of children ages 0–14 years with HIV knew their status, and 42% living with HIV were not on antiretroviral treatment (ART) as a result of lack of timely diagnosis.[2] A schematic of the Uganda Ministry of Health standards for testing, adapted from the World Health Organization 2016 guidelines, is provided in Figure 1 and highlights the potential drop-offs in each step of the testing cascade.[3] These guidelines recommend that all infants born to women living with HIV (WLHIV) have their first HIV test at 4–6 weeks of age or as soon as the infant is identified as being HIV-exposed. In 2023, however, only 79% of children enrolled in the Ugandan Early Infant Diagnosis (EID) program received their first DNA polymerase chain reaction (PCR) in the first 2 months of life.[4] Furthermore, in 2023, only 80% of HIV-exposed children had their final status ascertained through a rapid antibody test at age 18 months.[5,6]

Ensuring timely and comprehensive testing for infants born to WLHIV is a complex endeavor, particularly in resource-limited settings where access to healthcare services remains limited.[7] Persistent challenges include knowledge gaps on preventing perinatal HIV transmission, maternal disengagement from HIV treatment and care, as well as poor participation in initiatives for the prevention of mother-to-child transmission (PMTCT).[8] Postpartum women are especially vulnerable to being lost-to-follow-up when they transfer from antenatal clinics to standard HIV care services. In addition, several missed opportunities exist due to a lack of data systems for linking mothers to their infants at follow-up clinic appointments.[9,10]

To address these challenges, we designed and implemented the Enhanced viral load counseling with Standardized Peer-Support (ENHANCED-SPS) intervention that combined peer-led counseling, guided by a study-created flipchart, and informed by point-of-care HIV viral load testing for pregnant and breastfeeding WLHIV. We previously demonstrated that the ENHANCED-SPS intervention improved HIV viral suppression (HIV RNA<1000 c/mL),[11] improved treatment adherence and HIV status disclosure[12] as well as addressed barriers identified by pregnant and postpartum WLHIV.[13] We now assess the effect of the intervention on the completion of HIV testing (antibody rapid test at 18 months) among HIV-exposed infants born to women enrolled in the ENHANCED-SPS study.

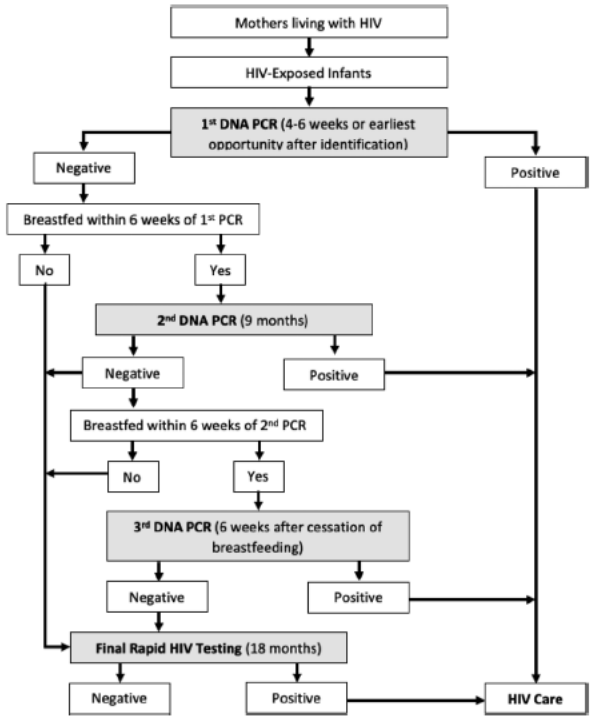

FIGURE 1. Schematic of the Ugandan testing algorithm for HIV-exposed infants. *This schematic is adapted from the "Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda – 2022".[13] According to these guidelines, up to 3 HIV DNA PCR tests are conducted for HIV-exposed infants. The first test should be done at 4–6 weeks after birth or immediately thereafter when identifying the infant who was HIV-exposed. Infants with a negative first test who have been breastfed within 6 weeks of the 1st PCR should be retested at 9 months. Those with a repeat negative PCR result who have been breastfed within 6 weeks of the 2nd PCR should be retested 6 weeks after the cessation of breastfeeding (recommended up to 12 months). All HIV-exposed children with negative PCR tests should receive a final rapid HIV antibody test at 18 months.

METHODS

Study Design and Setting

The ENHANCED-SPS study was a cluster randomized trial, implemented in the 14 public health facilities in Southwestern Uganda between September 2019 to October 2021. Participating facilities provided HIV care supported by the Elizabeth Glaser Pediatric AIDS Foundation, a U.S. President's Emergency Plan for AIDS Relief-implementing partner that facilitates HIV care in government-run clinics in Uganda. As the standard-of-care, these clinics provided a full array of women's health services, including antenatal care, ART for pregnant women, and PMTCT services. The clinics were selected based on their geographical location, HIV patient load, and absence of any ongoing and related projects. All facilities had peer-mothers, lay WLHIV who are trained to offer counseling on HIV prevention and treatment. Study participants were WLHIV, ages 15–45 years, and accessing care from these facilities. Additional inclusion criteria were (1) pregnant with a previous HIV diagnosis and attending the antenatal clinic for the first time or (2) pregnant or breastfeeding with a new HIV diagnosis at a follow-up visit for antenatal or postnatal care.

Facilities were randomized to the ENHANCED-SPS intervention or control in a 1:1 ratio using a computer-generated randomization scheme and within strata defined by distance, patient burden, and socioeconomic characteristics. We chose cluster-level randomization because the intervention changed clinical practices.

Study staff and participants were not blinded to the trial arm, but the study statistician (L.B.B.) remained blinded until trial completion and analytic unmasking. The 7 facilities randomized to the control arm received standard-of-care, as described above. The 7 facilities randomly assigned to the intervention arm received standard-of-care plus the multicomponent ENHANCED-SPS intervention, described next. The standard visit schedule for pregnant and breastfeeding WLHIV was monthly, and the same in both arms.

The ENHANCED-SPS intervention was designed to improve viral suppression and reduce perinatal transmission among pregnant and breastfeeding WLHIV. The intervention was a multi-component strategy and developed using the empirically validated PRECEDE framework.[14] First, through meetings with peer-mothers and midwives, we identified barriers to HIV viral suppression and PMTCT engagement for pregnant and postpartum WLHIV. These included maternal barriers: lack of knowledge and limited social support, resulting in nondisclosure and poor adherence. These also included structural barriers: lack of knowledge by providers, nontargeted counseling, delayed adoption of treatment guidelines, and limited viral load testing with long turnaround times for results.

Then we designed a flipchart for standardized delivery of a viral load counseling protocol.[11] Key messaging included the importance of viral suppression for PMTCT, HIV status disclosure, ART adherence, infant testing and the responsibility of the mother in having a healthy baby. Peer-mothers and midwives were trained on the counseling protocol and received mentoring from study staff and trained facility providers. Every 2 weeks, peer-mothers conducted phone calls to participants to provide viral load and adherence counseling. At each routine clinic visit, peer-mothers and midwives provided counseling, conducted an individualized assessment of barriers and discussed strategies to jointly address these barriers. Reinforcing components of the intervention included point-of-care viral load testing and feedback meetings with peer-mothers, midwives and study staff.

Study Measures and Endpoints

We conducted a retrospective evaluation of the EID testing cascade on all infants born to ENHANCED-SPS participants during the 1-year trial follow-up. We reviewed electronic medical records or Uganda EID care cards and extracted data on each step of the Ugandan EID testing algorithm. As shown in Figure 1, Ugandan EID guidelines recommend the first PCR test at 4–6 weeks (or at earliest identification of exposure thereafter), a second PCR at 9 months (if breastfeeding, within 6 weeks of the first PCR), a third PCR at the cessation of breastfeeding (if breastfeeding within 6 weeks of the second PCR), and a final HIV rapid antibody test at 18 months for all infants without a prior positive PCR.[15] Additional variables captured from the health records included maternal characteristics at trial enrollment: age, pregnancy status, care status and marital status. We considered a study participant to be recently diagnosed if she was diagnosed with HIV within 2 weeks of trial enrollment.

The primary outcome of this analysis was completion of the infant HIV testing algorithm, defined as the infant is having the final HIV antibody rapid test at 18 months of age or a prior positive PCR result. Secondary endpoints included completion of each of the tests recommended by national guidelines (Fig. 1).[15] For completion of the second and third PCR tests, we assumed all infants had been recently breastfed, in accordance with national guidelines.[15] For each testing endpoint, infants who previously had died or whose mothers had transferred care to a different clinic were excluded, while infants who were lost-to-follow-up were assumed not to have completed the relevant test. An additional outcome was perinatal transmission of HIV.

Statistical Analysis

The ENHANCED-SPS trial was designed to evaluate effectiveness on viral suppression (HIV RNA <1000 c/mL) at 12 months of follow-up. Accounting for cluster randomized design,[16] we anticipated having at least 80% power to detect a 15% or greater difference in average viral suppression with 14 health facilities (7 per arm), 70% suppression in the control, a harmonic mean of 70 participants per cluster, and a coefficient of variation k = 0.1.

In this secondary analysis, we prespecified using targeted minimum loss-based estimation to compare infant endpoints by arm. Targeted minimum loss-based estimation is a model-robust approach that can improve precision by adjusting for baseline outcome predictors.[17–19] Further details are available in the Statistical Analysis Plan (Text, Supplemental Digital Content 1, https://links.lww.com/INF/G262). We calculated 95% confidence intervals (CIs) and tested the null hypothesis with a 2-sided test at the 5% significance level. Prespecified subgroups were defined by maternal characteristics at study enrollment: age group (15–24 years, 25–34 years and 35+ years), care status (recently diagnosed, previously diagnosed) and marital status (never married, currently married, previously married or separated). We additionally reported on perinatal transmission rates during the follow-up period. All analyses were done in R, version 4.4.0.

Ethical Considerations

The study received ethical approval from the Makerere University School of Medicine Research and Ethics Committee, with annual institutional review board renewal approvals. All participants involved provided written informed consent for study participation and a waiver of consent for secondary data abstraction.

RESULTS

Study Accrual and Characteristics

A total of 464 infants born to participants of the ENHANCED-SPS study were included in this analysis, with 234 in the intervention arm and 230 in the control arm (Fig. 2). At trial enrollment, their mothers had a median age of 29 years with slightly over 50% ages 25–34 years; 90% were pregnant; 28% were recently diagnosed with HIV, and 77% were married (Table 1).

Completion of Final Antibody Rapid HIV Testing

After 18 months of follow-up, 13 infants had transferred care (9 intervention and 4 control), and 9 infants with unknown HIV status had died (5 intervention and 4 control; see Table, Supplemental Digital Content 2, https://links.lww.com/INF/G263). Of the remaining 442 infants (220 intervention and 222 control), none had a prior positive PCR, and the final antibody rapid HIV testing coverage (primary outcome) was significantly higher in the intervention arm at 94.5% (95% CI: 91.6–97.5%) compared with 83.3% (95% CI: 78.4–88.3%) in the control arm. Therefore, the intervention increased completion by 11.2% (95% CI: 5.4–17.0%; $P < 0.001$).

Intervention effectiveness for completion of final antibody rapid HIV testing varied by subgroups (Table 2). Testing coverage rates among infants born to the youngest women (ages 15–24 years) did not differ between arms and was 90.0% (95% CI: 82.3–97.7%) in the intervention and 93.0% (95% CI: 85.4–100%) in the control. However, a significantly higher proportion of infants born to intervention participants ages 25–34 years completed rapid antibody testing: 96.4% (95% CI: 93.0–99.8%) in the intervention versus

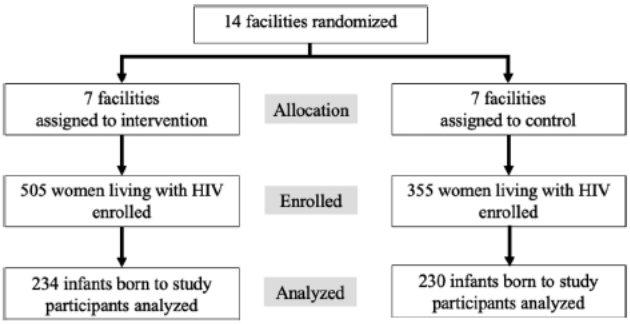

FIGURE 2. Study Consort diagram.

TABLE 1. Demographic Characteristics of the ENHANCED-SPS Participants Who Gave Birth to the 464 Infants Included in this Analysis

	Intervention (N = 234)	Control (N = 230)	Total (N = 464)
Age, median (Q1, Q3)	28 (24,32)	30 (25,35)	29 (24.2,34)
Age 15–24 yr	64/212 (30%)	46/226 (20%)	110/438 (25%)
Age 25–34 yr	119/212 (56%)	114/226 (50%)	233/438 (53%)
Age 35+ yr	29/212 (14%)	66/226 (29%)	95/438 (22%)
Peripartum status			
Pregnant	226/232 (97%)	223/227 (98%)	449/459 (98%)
Breastfeeding	6/232 (3%)	4/227 (2%)	10/459 (2%)
Care status			
Recently diagnosed*	54/232 (23%)	74/227 (33%)	128/459 (28%)
Previously diagnosed	178/232 (77%)	153/227 (67%)	331/459 (72%)
Marital status			
Never married	22/198 (11%)	21/217 (10%)	43/415 (10%)
Married	153/198 (77%)	167/217 (77%)	320/415 (77%)
Previously married or separated	23/198 (12%)	28/217 (13%)	51/415 (12%)

*Diagnosed within 2 weeks of study enrollment.

TABLE 2. Effectiveness on Completion of Final Antibody Rapid Test at 18 Months

	Intervention (95% CI)	Control (95% CI)	Effect (95% CI); *P* value
All	94.5% (91.6–97.5)	83.3% (78.4–88.3)	11.2% (5.4–17.0); <0.001
Age 15–24 yr	90.0% (82.3–97.7)	93.0% (85.4–100.0)	−3.0% (−13.9 to 7.8); 0.585
Age 25–34 yr	96.4% (93.0–99.8)	76.4% (68.4–84.3)	20.1% (11.4–28.7); <0.001
Age 35+ yr	100.0% (100.0–100.0)	87.7% (79.6–95.8)	12.3% (4.2–20.4); 0.003
Recently diagnosed	87.5% (78.0–97.0)	68.1% (57.1–79.2)	19.4% (4.8–33.9); 0.009
Previously diagnosed	96.5% (93.7–99.2)	90.0% (85.2–94.8)	6.5% (0.9–12.0); 0.022
Never married	90.9% (78.3–100.0)	70.0% (49.0–91.0)	20.9% (−3.6 to 45.4); 0.092
Married	94.3% (90.5–98.1)	84.4% (78.7–90.0)	10.0% (3.1–16.8); 0.004
Previously married or separated	100.0% (100.0–100.0)	89.3% (77.7–100.0)	10.7% (−0.9 to 22.3); 0.070

76.4% (95% CI: 68.4–84.3%) in the control arm, corresponding to a difference of 20.1% (95% CI: 11.4–28.7%; $P < 0.001$). Among infants born to participants ages 35 years and above, 100% completed rapid antibody testing in the intervention arm compared with 87.7% (95% CI: 79.6–95.8%) in the control arm, an increase of 12.3% (95% CI: 4.2–20.4%; $P = 0.003$).

Testing completion also varied by maternal time since HIV diagnosis. Specifically, completion rates among infants born to mothers with a recent HIV diagnosis were 85.7% (95% CI: 78.0–97.0%) in the intervention arm compared with 68.1% (95% CI: 57.1–79.2%) in the control arm, an increase of 19.4% (95% CI: 4.8–33.9%; $P = 0.009$). Completion among infants born to previously diagnosed mothers was notably higher in both arms but still significantly higher in the intervention than the control: 96.5% (95% CI: 93.7–99.2%) versus 90.0% (95% CI: 85.2–94.8%), respectively, for a difference of 6.5% (95% CI: 0.9–12.0%; $P = 0.02$). Finally, testing completion varied by marital status; infants born to women who were never married had the lower coverage in both arms but larger intervention effects (20.9% improvement), as compared with infants of women who were married (10.0%

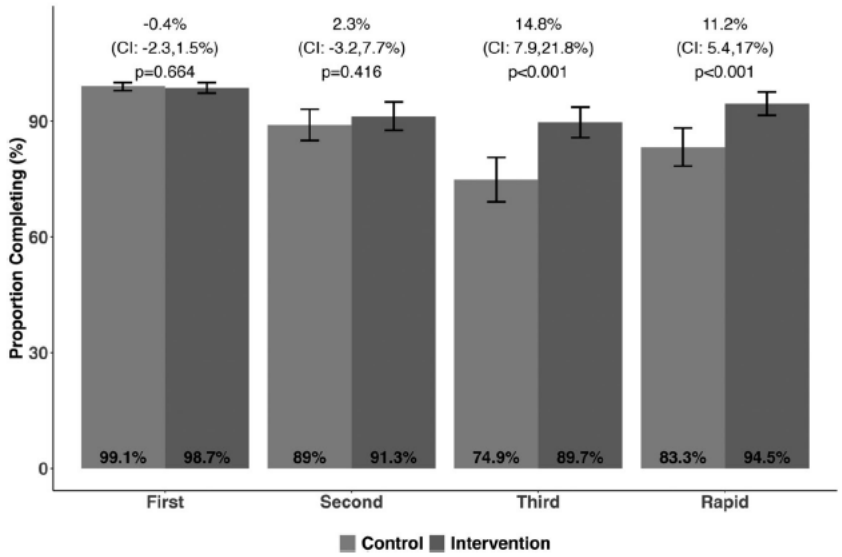

FIGURE 3. Effectiveness the ENHANCED-SPS intervention as compared with the standard-of-care (control) on completion of each step in the early infant diagnosis testing algorithm.

improvement) and infants of women who were previously married or separated (10.7% improvement).

Completion of Prior Steps of the EID Testing Algorithm

Coverage of the first PCR test was high in both arms: 98.7% (95% CI: 97.3–100%) in the intervention and 99.1% (95% CI: 97.9–100%) in the control (Fig. 3). The proportion of infants completing their second PCR test in the intervention arm was slightly, but not significantly, higher than in the control arm: 91.3% (95% CI: 87.6–95.0%) versus 89.0% (95% CI: 85.0–93.1%), respectively. However, the proportion of infants completing the third PCR test was significantly higher in the intervention arm compared with the control arm: 89.7% (95% CI: 85.8–93.7%) versus 74.9% (95% CI: 69.1–80.6%), respectively, and corresponding to a difference of 14.8% (95% CI: 7.9–21.8%; $P < 0.001$). The median age at third PCR completion (among those testing) was 13.8 months and similar by arm: 13.9 months in intervention and 13.7 months in control. The intervention significantly improved third PCR completion among infants born to women who were ages 25–34 years (18.2% improvement), ages 35+ years (18.1% improvement), previously diagnosed (14.8% improvement), married (13.7% improvement) and previously married or separated (20.7% improvement; see Table, Supplemental Digital Content 3, https://links.lww.com/INF/G264). There were no significant differences for infants born to women who were the youngest (5.7% improvement), recently diagnosed (13.2% improvement) or never married (15.9% improvement).

Perinatal Transmission of HIV

The perinatal transmission outcome was evaluated in 442 out of 464 (94%) infants who completed the final HIV rapid antibody testing at 18 months. All infants were negative for HIV and, thus, there were no transmissions during follow-up in either arm. It is worth noting, however, that 2 infants (1 control and 1 intervention) tested positive at the time their mothers enrolled in the ENHANCED-SPS trial.

DISCUSSION

The findings of this study highlight the effectiveness of an intervention aimed at improving outcomes among pregnant and breastfeeding WLHIV, including EID, in a resource-limited setting. Specifically, the ENHANCED-SPS intervention, a peer-led counseling model, significantly improved the proportion of HIV-exposed infants completing the recommended HIV rapid antibody testing (94.5%), as compared with the standard-of-care (83.3%; control). The 11.2% higher completion rate indicates sustained engagement with PMTCT services over time. Significant improvements in test completion were observed across most subgroups, suggesting the robustness and effectiveness of the intervention with different population groups.

These findings underscore the importance of interventions targeted at improving access to and uptake of PMTCT services.[14,20–22] They also align with previous research highlighting the effectiveness of multifaceted interventions in enhancing maternal and infant outcomes, particularly in settings where access to

healthcare services may be limited.[1,11,23] Tangible improvements in testing rates among HIV-exposed infants have been achieved by addressing identified barriers to HIV care, such as maternal engagement and knowledge.[24-26] The ENHANCED-SPS counseling protocol included targeted messaging about having a healthy baby, which likely generated a strong motivation to adhere to the testing algorithm. Additionally, through tailored engagement and counseling, the peer-led interventions, such as ENHANCED-SPS, help mothers feel connected to the process throughout the PMTCT cascade.[13,27]

The significant increase in test completion rates observed across most subgroups suggests that the intervention was effective in reaching and engaging a diverse range of mothers in the target population. However, in both the intervention and control arms, final infant HIV testing coverage was lowest among recently diagnosed WLHIV (87.5% and 68.1%, respectively), as compared with previously diagnosed WLHIV (96.5% and 90.0%, respectively). Within the intervention arm, coverage among the youngest mothers (15–24 years) was lower (90.0%) than coverage among mothers ages 25–34 years (96.4%) and mothers ages 35+ years (100%). However, the converse was observed in the control arm, where coverage among the youngest mothers was higher (93.0%) than coverage among mothers ages 25–34 years (76.4%) and mothers ages 35+ years (87.7%). Nonetheless, it is worth noting that the ENHANCED-SPS intervention resulted in the largest improvements in HIV viral suppression, status disclosure, and treatment adherence for the youngest WLHIV.[11,12] These findings underscore the importance of multi-component interventions to address specific barriers and preferences within subpopulations, thereby maximizing the reach and impact of PMTCT programs.[28]

Our findings contribute to the evidence on the positive impact of mHealth and telehealth interventions on maternal and infant outcomes, including improved antenatal attendance, PMTCT retention, EID test completion, exclusive breastfeeding and birthweight.[29-32] Phone counseling offers a practical approach to reach, engage and improve the health outcomes of pregnant and postpartum WLHIV. In a randomized trial conducted in Kenya, one-on-one counseling delivered via cell phone was effective in retaining mothers with HIV in care and in promoting infant HIV testing as well as antenatal and postnatal care attendance.[33,34] However, cell phone penetration is not 100% in most resource-limited settings, highlighting the important role of in-person counseling by peer-mothers and midwives at routine clinic visits in our study. Indeed, our findings further support the use of peer-mothers in improving timely testing of HIV-exposed infants and echo the results of other studies in sub-Saharan Africa.[35,36]

Importantly, there were no perinatal transmissions during follow-up in either arm, indicating huge successes with the existing PMTCT program in the standard-of-care. Unfortunately, however, 2 infants (1 in each arm) presented with HIV at the time their mother enrolled in the trial, indicating gaps remain. Likewise, 9 infants died during follow-up. While the causes for these deaths are unknown, they further indicate gaps in programs to improve and protect the health of HIV-exposed infants. Altogether, EID remains a key entry point into the pediatric HIV care cascade by ensuring the timely identification and treatment of infants with HIV in the earliest stages of life and resulting in improved health outcomes.[37,38]

A strength and weakness of our trial was reliance on routinely collected data, which reflects the "real-life" conditions of PMTCT programs in resource-limited settings but are also subject to quality issues.[39] Likewise, our intervention was multicomponent, designed with persons affected and to address multifaceted barriers to care engagement among WLHIV. Qualitative evaluations are ongoing to understand the mechanisms of intervention action. Additionally, our study was conducted in U.S. President's Emergency Plan for AIDS Relief-supported clinics and harnessed existing peer-mother programs. Therefore, we anticipate our intervention to be cost-effective and scalable. While formal costing analyses are ongoing, we have disseminated our findings and study protocols, including the counseling flipchart, to the Ugandan Ministry of Health for wider adoption. Finally, our power to detect associations in certain subgroups was limited by small sample sizes. Altogether, further research is needed to evaluate the impact of the ENHANCED-SPS intervention on clinical outcomes, including those beyond the 18-month follow-up period.[40]

In conclusion, the findings of this randomized trial contribute to the growing body of evidence supporting the effectiveness of targeted interventions to improve early infant testing rates among HIV-exposed infants. The ENHANCED-SPS intervention, which included peer-led counseling on the mother's role in preventing perinatal transmission and having a healthy baby, improved EID completion rates by 11.2% among infants born to WLHIV in rural Uganda. PMTCT services should continue to prioritize interventions aimed at improving EID testing uptake, especially among recently diagnosed mothers, while also recognizing the need for sustained engagement to achieve meaningful improvements in clinical outcomes over the long term.

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Appendix 4: Publication for Objective Five

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Research

"I desire to have an HIV-free baby": pregnant and breastfeeding mothers' perceptions of Viral load testing and suppression in HIV care in southwestern Uganda

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Abstract

Introduction Viral suppression is a critical component for preventing mother-to-child transmission of HIV(MTCT). Mothers' perceptions of viral load suppression is crucial in the attainment of successful outcomes in preventing mother to child transmission of HIV. We therefore aimed to explore the experiences and perceptions of women on viral suppression.

Methods This was a qualitative sub-study embedded in a cluster-randomized trial (NCT04122144) designed to improve viral load outcomes among pregnant and breastfeeding mothers living with HIV in four level III/IV health facilities in South-western Uganda. Thirty-two in-depth interviews were conducted with pregnant and breastfeeding women with HIV from 1st March 2020 to 30th September 2020 to explore their understanding and interpretation of viral suppression. Interviews were audio-recorded, transcribed, and coded in Dedoose software for analysis.

Results A total of 32 Women living with HIV were enrolled in this qualitative study. WLHIV explained viral suppression in the context of attaining good health and having HIV-free babies. Adherence to ART was presented as a key avenue to viral suppression. The level of engagement with providers was presented as a key attribute of attaining viral suppression. The participants narrated their experiences with viral load testing within the routine services. However, they revealed experiencing some proximate barriers to suppression including anticipated stigma, challenges with non-disclosure of HIV status, pregnancy distress, and distance to the health facility.

Conclusion The understanding and interpretation of viral suppression among pregnant and breastfeeding mothers living with HIV provides a basis for adopting behaviors leading to prevention of vertical transmission of HIV. Health care workers can support women by providing clear and culturally appropriate education about viral suppression, adherence strategies and creating a supportive and non-judgmental environment.

Keywords Viral suppression · Pregnant and breastfeeding women · Perceptions

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1 Introduction

In 2020, there were 1.3 million pregnant women with HIV, of which an estimated 85% received antiretroviral drugs for their own health and to prevent vertical transmission, still notably below the global target of 95% [1, 2]. The World Health Organization (WHO) recommended triple antiretroviral therapy (ART) for the elimination of mother-to-child transmission of HIV (MTCT) among pregnant and postpartum women living with HIV (WLHIV) [3]. Multiple countries have implemented and scaled up universal initiation of lifelong ART to all pregnant and breastfeeding women with HIV aiming to achieve viral suppression. The widespread scale-up of ART has specifically led to an increase in fertility intentions and pregnancy rates among WLHIV in sub-Saharan Africa (SSA) [2, 4–6]. Evidence from Uganda shows that among clients on long-term ART, the incidence of pregnancy increased from 4.6 per 100 person-years in the first year of ART to 7.9 per 100 person-years in the tenth year of ART [7].

Nonetheless, pregnancy presents unique challenges and vulnerabilities for women living with HIV [8]. It is associated with lower CD4 counts and increased risk of opportunistic infections due to immunosuppression. Additionally, evidence shows that viral load is associated with MTCT [9, 10]. However, the steady scale-up and improvement of services to prevent MTCT reduced the annual incidence of infections among children globally by 54% [11, 12]. In Uganda, the Ministry of Health (MoH) has revealed a remarkable reduction in the rates of MTCT from 20% in 2000 to 2.8% in 2022 [13]. Despite these remarkable milestones, vertical transmission rates remain below global targets in most SSA countries including Uganda [14, 15], and the rate of viral suppression remain lower among pregnant and breastfeeding women [3, 16].

Pregnant women living with HIV in SSA also face multiple barriers related to pregnancy and HIV infection including; reliability of ART access, psychosocial factors such as stigma and discrimination as well as ART adherence influencing viral suppression [17]. Studies have shown that maternal viral load is an important predictor of MTCT [9, 10, 18–20]. Retention in HIV care during the perinatal period remains a significant challenge and thus compromises viral suppression yet heightens the risk of vertical transmission [21]. Elsewhere in SSA, retention in programs on MTCT hovered between 50 and 73% which in-part explained the sub-optimal treatment outcomes including viral non suppression [22].

Viral load suppression in several SSA countries remains below the UNAIDS 95-95-95 targets [14, 15]. Known barriers to viral suppression include: health system barriers such as staff shortages, high turnaround time for viral load results; structural barriers such as transport needs also greatly affect women in the perinatal period [19]. However, pregnant women and breastfeeding mother's perceptions of, and experiences with viral suppression remain understudied despite influencing their decisions about HIV treatment and care in preventing MTCT. Understanding their interpretations of viral suppression is critical to ensuring optimal outcomes for both the mother and child. This study explored women's understanding and interpretation of viral suppression in relation to MTCT in selected public health facilities in Southwestern Uganda.

2 Materials and methods

2.1 Overview of study design

This was a qualitative sub-study conducted between 1st March 2020 and 30th September 2020. It was embedded in an ongoing cluster-randomized trial (ENHANCED-SPS-NCT04122144) designed to improve viral load outcomes among pregnant WLHIV and breastfeeding mothers in four level III/IV health facilities in South-western Uganda. The ENHANCED-SPS study evaluated the effect of the standardized peer mother support and viral load counseling intervention on viral suppression among pregnant women in 14 clinics in Southwestern Uganda.

2.2 Study setting

This study was conducted within public health facilities providing HIV care services to pregnant and postpartum women in Southwestern Uganda. All the clinics provide the standard of care HIV treatment services based on the Ugandan national HIV care and treatment guidelines. The guidelines recommend prompt ART for all identified pregnant and postpartum women and appropriate viral load monitoring (baseline, 6 months and 12 months) as standard of care.

2.3 Selection of study participants

We collected data from pregnant or breastfeeding women aged 18 years and above receiving HIV care from 7 public health facilities. Participants were purposively selected from 490 women enrolled in phase II of the ENHANCED -SPS (NCT0412214) trial to participate in this qualitative sub-study. These were pregnant and postpartum women who were enrolled in the trial and willing to participate in the interviews. Participants were stratified for selection according to their facility, enrollment category and viral suppression status (12-newly diagnosed; 08-virally suppressed; and 12- not virally suppressed at baseline). We obtained data saturation with the sample size of 32 women and we maintained it [23, 24].

2.4 Data collection procedures

We developed interview guides using information from previous studies. We pretested our semi structured interview guides on a sample of six women enrolled in the trial but not part of the qualitative sample and this helped us in adjusting and modifying on the questions developed to explore the women's perceptions of viral suppression. A team of experienced qualitative researchers (CA, JK, A.R.K) were involved in the development and review of these guides.

Data were collected from participants through in-person interviews using a semi-structured in-depth interview guide. The interview guides were developed in English and translated into Runyankole the language spoken and understood by the participants. Questions asked included knowledge and understanding of viral load, support received from providers during antenatal and postpartum periods as well general HIV care. The interviewers were research assistants fluent in both English and Runyankole and were experienced in conducting qualitative interviews. The research assistants were trained in qualitative interviewing. Interviews were conducted in private location within the facility, audio-recorded, transcribed and coded for analysis.

2.5 Interaction with the participants

We worked with health providers and study staff in the study clinics to identify the selected participants for the IDIs. We reached out to these adult HIV participants through phone calls and scheduled appointments for the interviews. Those who responded were given appointments and were consented to participate in the study. We also interviewed other participants who had come to the clinics on their routine clinic visit day. All participants enrolled in the study provided a verbal and written informed consent to participate in the study. Privacy was ensured by using private rooms for the interviews, participation was voluntary and no names or any patient identifiers were used during the interviews, neither are they used anywhere during the publication process.

2.6 Data management and analysis

In-depth Interviews were transcribed verbatim by the interviewers, then translated into English from the local language. Transcripts were checked against the audio files for accuracy. The first author (JK) read all the transcripts and the field notes to identify the meanings and patterns of the data relating the research questions. Thematic analysis was used to analyze the qualitative data. We adopted a hybrid of deductive and inductive analysis to generate themes from the data. Based on the six stages of thematic analysis suggested by Braun and Clarke, the transcripts were read and re-read by the researchers to gain deeper understanding of the meanings of the data. Initial codes were generated by a team of four researchers by studying fragments of data including words, lines and segments to understand their meaning [21]. The codebook was later presented with codes based on the lines of inquiry from the interview guide. Emerging themes were highlighted and the final codebook was completed with all data and the generated codes were imported into Dedoose software for coding and analysis. The results are presented in line with the emergent themes. Verbatim and rich quotes were extracted and presented to support the narratives describing the findings of each of the thematic areas.

2.7 Ethical consideration

The study was approved by the higher degrees' committee of Makerere University School of medicine (REC- 2018-0744), and the Ugandan National Council on Science and Technology in Uganda (UNCST-HS-2648) respectively. All participants provided written informed consent before the interviews. All data was de-identified, kept confidential, and analyzed using unique study identification numbers assigned to each participant. This study was conducted in accordance with

the declaration of Helsinki. The research team also sought administrative clearance from the district health officers and in charges of the participating facilities to allow the process of data collection within the study facilities. In addition, the confidentiality of participants was maintained by removing patient identifiers from the questionnaire and keeping the filled data secure.

3 Results

3.1 Demographic characteristics of the participants

Thirty-two pregnant and postpartum women were interviewed. The median age was 29 years; 46.9% aged between 18 and 24 years and 40.6% aged between 25 and 34 years. Majority of the participants were married at 90.6% while single and divorced/separated comprised only 9.4%. Of the participants interviewed, 25% of the participants were known to have HIV, in care and virally suppressed at first antenatal care (ANC) visit, 37.5% were known to have HIV and were in care but non-suppressed at their first ANC visit, while 37.5% were newly diagnosed with HIV at first ANC visit.

3.2 Women's understanding and motivations for attaining and maintaining viral suppression

Women described viral load in lay terms as *the number of viruses in the blood.* For example, *"a high viral load means an increase in the number of viruses in the blood and thus implies a weak body."* Pregnant women expressed their understanding of a "high and low" viral load and its implications for mother to child transmission of HIV. They described viral suppression as a state of having a very low amount of the virus in their blood and an important aspect for good health overall. They explained that if the viral load is high, it increased the chances of HIV transmission to the baby. They also understood that viral suppression serves as an indicator of whether one is taking their ARVs as prescribed or not.

> … *"If someone doesn't take his or her medication well, the amount of HIV virus increases in the blood, the immunity lowers down and the person gets other opportunistic infections. But if someone adheres well to HIV medication, the amount of HIV virus reduces and the immunity is boosted and other diseases are limited and chances of giving birth to a baby without HIV are high (19-year-old pregnant woman-already in care-not suppressed)."*

The desire to have an HIV free baby was a major motivation for WLHIV to work towards attaining viral suppression. Women explained their strategies for attaining suppression. They ensured to take their medication at the stipulated time, others set alarms at specific times, ensuring that they have their meals ready on time. For some, it was just a reflex action because of the strong desire to live and look after their families.

> *"It (viral load testing) has helped me to keep track of the time that I am supposed to take my medicine and not to exceed that specific time. It has helped me to make sure that before I take my medicine, I should not be stressed and that I should first eat well before I take my medicine and I think this will give me a better life (42-year-old pregnant woman-already in care-not suppressed)."*

Other women explained that they were aware that if they stopped their medication the virus would increase in their blood and would infect their unborn babies.

> *"I know that if I stop taking it (ART) then the HIV in my blood will increase and eventually I can infect my unborn baby…" (25-year-old pregnant woman-already in care-suppressed)."*

Women also reported that they were motivated to take their medications as prescribed because they were able to fulfil their fertility desires moreover free of HIV.

> *"… I wanted a child, so I knew that if I start HIV care and treatment even if I get pregnant, I will give birth to a baby who is not infected and God made it for me and I gave birth to a child without HIV (19-year-old pregnant woman-already in care-not suppressed)."*

Additionally, some participants shared experiences of mothers in their surroundings who were infected with HIV and adhered to their medicines as prescribed, that were virally suppressed and had babies without HIV. This gave hope of delivering HIV-free babies to the mothers and acted as a form of reassurance to the participants that if they adhere well to their medication, they would also have HIV free babies.

"… I have been seeing my colleagues who also have HIV and also get pregnant but because they take their medicines well and take advice from the nurses, they are able to produce babies without HIV. When they told me that I have HIV, I said to myself, "I am going to listen to the nurses and I will do whatever they ask me to do so that I live a good life and also have a healthy partner (42-year-old pregnant woman-already in care -not suppressed).".

3.3 Viral load testing experiences and provider support

Women perceived VL testing as part of routine care for WLHIV attending the health facility and there was less anxiety when testing for viral load compared to the HIV test.

"Everything went well because they got the blood sample the same way they had when testing for HIV except this time the anxiety was less … because this time, I was aware of my HIV status and I just wanted to know whether the amount of HIV has increased or reduced (23-year-old pregnant woman already in care-suppressed)".

Mothers described the processes of viral load testing at the health facility. They explained that their blood samples were taken and they received the results on a given return date. On that day, they received information on whether their viral load was high or low. They had concerns about the amount of blood taken for viral load testing, turn-around time of the results and questions about why viral load tests should be done routinely even when one is suppressed.

"… they teach us about viral load testing as a group after which each person goes to the doctor alone, they take blood sample for viral load testing and they tell us when to come back for viral load results…and they counsel us basing on whether the viral is high or low (27-year-old pregnant woman, already in care- suppressed)".

The providers availed WLHIV with information about their viral loads and viral suppression; in group sessions at the triage using illustrations such as the emoji, and individually counselled them after they received their results.

"…the provider pulled out two files with; one picture of a smiling face while another one had a picture of an annoyed face…who…didn't take their medication on schedule while one with smiling face took their medication on schedule and without missing. That demonstration made me happy (27-year-old pregnant woman, already in care-suppressed)".

Interactions with providers after receiving viral load test results included encouraging clients to adhere to their medication as prescribed or else their viral loads would surge. They explained to mothers with suppressed viral loads about the consequences of having an increased viral load.

"If viral load is low, they encourage us to continue adhering because when it is low, it means that the virus is just dormant /suppressed and if someone doesn't adhere, it multiplies again. And if viral load is high, it means that someone has been taking drugs poorly, they encourage him or her to start taking drugs on schedule without missing (27-year-old pregnant woman-already in care-suppressed)".

Not all women fully benefited from the same support from the providers. Some reported lack of clear information on viral loads from the providers. One participant revealed that she was not informed why her blood sample was taken and does not recall receiving her test results.

"Yes, the providers said they wanted to know the amount of the virus in my blood, but they did not tell me the results (19-year-old pregnant woman already in care-not suppressed)".

Awareness of the viral load test results determined refill time for the pregnant woman to return to the clinic. The turn-around time for receiving viral load results varied depending on the time each woman had until the next refill, and on whether they were suppressed or not.

"…I did not get my results right away, I waited for about 2 months to get them…on my return date, that's when the providers find the viral load results in your file. When you are suppressed…you are given 3 months' refill because you will have impressed the provider with your good adherence…those not suppressed and not adhering well are given 1-month refill, and they are also sent to a counsellor…" (32-year-old pregnant woman already in care-suppressed)".

Mothers reported their experiences with providers in addressing issues surrounding unsuppressed viral load and strategies for attaining suppression. They acknowledged that counselling was important during this time to support the mothers to achieve viral suppression as a primary goal of ART.

"You know I had tested for viral load, and I was not suppressing, when I went back after the counselling that I got, I was told that my viral load had lowered, and so that's why I was appraised and urged to continue adhering well (28-year-old pregnant woman-already in care-not suppressed).

One mother explained being advised by the provider that an unsuppressed viral load could accelerate illness which would result in stigma. This information was very helpful and encouraged mothers to strive to adhere in order to achieve good health.

"they say that when you do not adhere well on your medication, your viral load will go up and HIV symptoms will spring up too. Eventually will you develop stigma and start hiding from people (35-yearl-old pregnant woman-already in care-not suppressed)."

The providers helped the women to understand and address issues such as the scheduling of time for taking pills that may lead to a decrease in the viral load. A mother also explained that the health worker advised her to avoid stress and to maintain proper nutrition in order to keep her viral load down and remain unsuppressed. The providers also helped clients to get rid of the fear related to having a high viral load.

"I asked the nurse if it was possible to regain my immunity and lower my viral load when I adhere to HIV medication? "as long as you take your medicine on time and try to avoid stress, you will regain your health" she answered me…if I get angry and stressed, I will fail to eat and the medicine may not work for me." (42-year-old pregnant woman already in care- not suppressed)."

3.4 Challenges to achieving viral suppression

Despite the described benefits of viral suppression, women reported challenges to achieving viral suppression which included non-disclosure of HIV status, anticipated stigma and distance to clinics resulting in missed appointments. In addition, some women reported distress arising from being both pregnant and having HIV which created anxiety about the possibility of having an HIV infected baby. Other Challenges were related to the health care system such as variations in the relay of viral load test results. For instance, women expressed concerns about delays in the return of viral load test results, and the lack of general HIV counseling and education within the maternal and child health section of the health facility. All these challenges were reported to affect women negatively and hinder them from achieving viral suppression.

Fear of HIV- related stigma at the clinic visits was reported to hinder achieving viral suppression especially for women who had not yet disclosed to anyone. This was very common when the initial diagnosis of HIV was made at antenatal clinics. Stigma was reported as one of the key reasons for missed appointments and non-disclosure resulting in viral non-suppression. The fear to be seen by friends or other acquaintances resulted in several adjustments to clinic visits and resulted in delays or eventually missing of clinic visits.

"…some people fear to meet each other at the health center and they try their best to make sure that they do not reach there at the same time (unknown age, pregnant woman-newly diagnosed with HIV-not suppressed)."

In other instances, some pregnant women were skeptical about disclosing their HIV status for fear of being denied financial support from their partners during the pregnancy. Much as the women appreciated the importance of viral suppression, the fear of unknown consequences resulting from disclosure to their partners limited the ability to achieve viral suppression,

"I think that since I am already pregnant for him, once I disclose that I have HIV he may not give me any assistance like paying for my rent. Secondly, I fear that once he knows about it, he will tell all his sisters and the mother. Something that may not make them happy (27-year-old pregnant woman-already in care- suppressed)."

Distance to the health facility coupled with transport challenges hindered timely refills and adherence to clinic appointments. Participants reported transport challenges which were further complicated by pregnancy since they could not walk for long distances. Most times this resulted in missing their clinic appointments which eventually contributed to poor adherence and subsequent viral non suppression.

"Yes, I sometimes miss coming to collect my medicine because the transport is too high around shillings 20,000 and do not have energy to travel by foot (27-year-old pregnant woman-already in care—-not suppressed)."

Participants expressed concerns about the possibility of vertical transmission during breastfeeding. A client explained that after learning that she had a high viral load, her main concern was about the possibility of infecting her breastfeeding baby.

"I feared because I had given birth and I was breastfeeding my child, so I feared that my child might contract HIV from me (23-year-old pregnant woman-already in care- suppressed)."

Some clients expressed preference for receiving same day results after viral load testing with near point of care viral load testing.

"Of course, I would prefer to know the results on that same day of testing because I am always anxious to know whether the HIV in my body has increased or reduced and whether I am taking my medicine well or not (20-year-old pregnant woman-already in care-unknown viral load status)."

However, there were variations in how clients received their viral load test results. A participant revealed that her blood sample was taken two months ago but has not received her test results. Some clients expressed concern about not being informed about the reason for taking their blood samples and not being able to receive test results in a timely manner. Participants also express anxiety as far as delay to convey viral load test results is concerned as well as the lack of general HIV counselling and education within the maternal and child health section.

"The last time I was pregnant they did not tell me the results, may be some time back, they had tested me, and I was told that I had suppressed (32-year-old pregnant woman-already in care- suppressed)."
"…what I remember, I did not get my results right away, I waited for about 2 months to get them. So, on your return date, that's when the providers find your viral load results in your file (32-year-old pregnant woman-already in care- suppressed)."
"They didn't tell me what it (the viral load test) was for and up to now I have not yet known the results. They told me that I will know what came out of the test when I come back (25-year-old pregnant woman-already in care-suppressed)."

Long waiting hours with no provision of lunch for clients in the public health facilities was another barrier to accessing HIV care. Women reported that the average waiting time of 5–7 h when they visited to the clinic at times hindered their return for subsequent clinic visits.

"There's when we reach at the clinic at 8 am and leave at 6 pm, those are 10 h of waiting, we even fear to be looted along the way while going back home. The clients are always very many, and also the providers delay to start working (29-year-old pregnant woman-already in care- unknown viral load status)."

4 Discussion

This qualitative study sought to explore WLHIV perceptions of viral suppression and its implications during the perinatal period. The study found that women's interpretation and understanding of viral suppression influenced their HIV care decisions including adherence and retention in care.

These findings are presented within a context where attainment of fertility goals is deeply entrenched in traditional gender and socio-cultural norms that dictate women's fertility choices irrespective of the circumstances including HIV infection [15, 25]. Evidence indicates an increase in fertility intention rates among women living with HIV, hence the need for interventions to optimize viral suppression as the single most predictor to MTCT [4, 26, 27]. The advent of multidisciplinary strategies within PMTCT programs, including ART for all pregnant and breastfeeding mothers averted concerns around the possibility of MTCT [28]. This motivated mothers with HIV that with a suppressed viral load, they could have HIV free babies and attain positive health outcomes. However, our findings indicate the fear and anxiety among mothers to continue breastfeeding despite attaining viral suppression. This anxiety is exacerbated by the knowledge of HIV's transmission routes and the historical context of high MTCT rates before the widespread availability of antiretroviral therapy (ART) [29]. It is crucial to address these fears through continued counseling and reassurance from healthcare providers, emphasizing the effectiveness of ART and viral suppression in preventing MTCT especially during breastfeeding.

Nonetheless, barriers to retention within PMTCT programs in low resources settings persist [14, 15]. In this study, access to the health facility, non-disclosure and anticipated stigma were key hindrances to attaining viral suppression among pregnant and breastfeeding women. Non-disclosure of HIV status is proven to affect adherence to ART. Particularly

disclosure to sexual partners was revealed to be an important facilitator to viral load suppression [30]. The study was conducted in a setting where men overrule decision making in the household as well as resources. This may highlight that indirect male partner support influences retention in care among women living with HIV more specifically in the perinatal period [31, 32]. There is also need to test interventions aimed at leveraging male partner support for HIV care specifically in the perinatal period remains [32].

The turn-around time for receiving test results was another concern. Delays in obtaining results can cause anxiety and uncertainty, potentially affecting adherence to treatment and follow-up appointments [33]. Health facilities should strive to streamline the testing process to reduce waiting times. This could involve improving laboratory efficiency, leveraging faster diagnostic technologies, and optimizing logistical aspects of sample transportation and processing [33]. Mothers questioned the necessity of routine viral load tests, particularly when their viral loads are suppressed. This points to a potential gap in understanding the rationale behind regular monitoring. Healthcare providers should emphasize the importance of consistent monitoring, even when viral loads are low, to maintain optimal health outcomes. Enhanced communication strategies, including educational sessions and informational materials and peer support could help address these misconceptions [33].

The physical distance to health facilities was another significant barrier reported by women. For women in remote or underserved areas, the travel burden can be particularly challenging, exacerbating the difficulties in maintaining regular healthcare visits especially newly diagnosed and not suppressed. Addressing this barrier requires a multifaceted approach, the implementation of targeted outreaches and leveraging on peer support mechanisms to improve access to services at the community level. There is also need to advocate and modify the current DSD models to accommodate the needs of clients who are newly diagnosed and not virally suppressed.

The finding that participants acknowledged the role of viral suppression in preventing mother-to-child transmission (MTCT) of HIV highlights a significant understanding within the study population. This recognition indicates that participants are aware of the importance of maintaining low viral loads to minimize the risk of transmitting the virus to their children. Previous evidence from evaluation of PMTCT programs in Namibia highlighted knowledge as a key determinant to adherence [34]. This awareness among participants suggests that public health interventions and educational programs have successfully conveyed the critical link between viral suppression and MTCT prevention. It reflects the effectiveness of ongoing efforts to educate people living with HIV, particularly expectant mothers, about the importance of adhering to antiretroviral therapy (ART) to achieve and maintain viral suppression. Healthcare providers play a crucial role in ensuring that patients understand their treatment regimens and the significance of viral suppression in protecting their unborn or breastfeeding children. Continued support, counseling, and access to ART are essential to sustain viral suppression and, by extension, prevent MTCT. However due to over stretching of the healthcare work force, peer mothers can be supported.

Health education and routine counselling from the providers encouraged women to continue taking ART as prescribed. Previous studies have shown that poor interpersonal interaction between HIV clients and care providers can lead to poor engagement in care [31]. This arises from poor attitudes of providers coupled with clinic level challenges that interfere with the quality of care [35, 36]. On the contrary, women in this study attest to a positive attitude of the providers revealing support with counselling and information on adherence and its importance to achieving viral suppression. They further revealed how they eventually achieved suppression from previous non suppression due to the positive engagement of the providers in identifying and addressing of the barriers to viral suppression. The advent of client-centered care has also enabled HIV clients to efficiently navigate the structural barriers to viral suppression [37]. Training for the physicians and clinic workers in this area could further improve women's achievement of viral suppression.

With the scaling up of the 'treat all policy', women with HIV who are stable in care are most likely to attain or maintain viral suppression easily compared to those newly diagnosed with HIV [38]. Anti-retroviral therapy and other support services to enhance engagement in care through best practices such as streamlined HIV care [39, 40], option B + [15] and other differentiated care models, have led to subsequent improvement in viral load outcomes of HIV clients [41]. This also justifies the confidence displayed by mothers in this study that having a suppressed viral load could enable them to have HIV free babies and attain positive health outcomes. However, women diagnosed during the perinatal period are likely to face challenges while negotiating the HIV care system and may arise challenges of attaining suppression during pregnancy [38]. There is still need for multidimensional interventions to optimize viral suppression for this sub-population.

Our findings further reveal that viral load suppression is attainable within the context of the general HIV care setting. Strategies such as general counselling and group education, sharing of positive previous experiences about successful pregnancies and subsequent HIV free babies, ensuring sufficient drug stocks and deliveries which form part of the routine HIV care setting among others contribute to viral load suppression [31]. However, there is no

deliberate effort targeted to mothers in the perinatal period which leads to missed opportunities for attaining viral suppression [18], so as a result HIV infections are persistent among children.

5 Conclusion

The understanding and interpretation of viral suppression among pregnant and breastfeeding mothers living with HIV provides a basis for adopting behaviors leading to prevention of MTCT. Health care workers can support women by providing clear and culturally appropriate education about viral suppression, adherence strategies and creating a supportive and non-judgmental environment.

There is need to augment counseling sessions with messages on the importance of- viral load testing and suppression, stigma reduction information, and HIV status disclosure. Peer support is reported in previous evidence to play a significant role [42–44]. Counselling sessions also needs to be focused on enabling positive living during the pregnancy phase. The perceptions, understanding and interpretation of viral suppression among pregnant and breastfeeding women living with HIV provides a basis for adopting behaviors leading to prevention of MTCT. Health providers can support women by providing clear and culturally appropriate education about viral suppression, adherence strategies and creating a supportive and non-judgmental environment.

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Author contributions JK, conceptualization, investigation, formal analysis, methodology, writing-original draft. CA, conceptualization, investigation, formal analysis, writing-review and editing, supervision. JN, conceptualization, investigation, formal analysis, writing-review and editing. SP, conceptualization, formal analysis, writing-review and editing. EA, conceptualization, investigation, formal analysis, writing-review and editing. AB, conceptualization, investigation, formal analysis, writing-review and editing. SK, conceptualization, investigation, formal analysis, writing-review and editing. AM, conceptualization, investigation, formal analysis, writing-review and editing. FA, conceptualization, investigation, formal analysis, writing-review and editing. VM, Review and editing. JBM, Review and editing. PM, conceptualization, methodology, investigation. MRK, funding acquisition, Investigation, conceptualization, methodology. ARK, conceptualization, investigation, formal analysis, writing-review and editing. All authors read and approved the final manuscript.

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Data availability All the data needed for this manuscript have been included. In case there is a need for clarification, the corresponding author can be contacted. Codebooks used to analyze the data are available on request.

Declarations

Ethics approval and consent to participate The study was approved by the higher degrees' committee of Makerere University School of medicine (REC-2018-0744), and the Ugandan National Council on Science and Technology in Uganda (UNCST-HS-2648) respectively. All participants involved in this study signed a written informed consent form that allowed them to participate in the study and also authorized to publish the data after meaningful analysis. Consent forms were translated to the local language understood by participants. All participation was voluntary. All participant data was de-identified for confidentiality issues and avoiding unintentional disclosures.

Competing interests The authors declare no competing interests.

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Appendix 5: Manuscript under review for Objective Two

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Original Contribution

A multicomponent, peer-led intervention for pregnant and postpartum women with HIV improves viral suppression over time in rural Uganda

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Abstract

Achieving viral suppression among pregnant and breastfeeding women with HIV is essential to promoting their health and eliminating vertical transmission of HIV. We hypothesized that a multicomponent and peer-led intervention would increase viral suppression among pregnant and breastfeeding women with HIV in the rural Southwestern Uganda. The ENHANCED-SPS intervention included the development of a counseling protocol, point-of-care viral load testing, and standardized support delivered by peer-mothers. Among 505 pregnant and postpartum women receiving the ENHANCED-SPS intervention (2019-2021), we evaluated the change in viral suppression (HIV RNA < 1000 c/mL) from baseline to 12 months of follow-up with targeted minimum loss-based estimation, accounting for clustering and missing outcomes. The proportion with viral suppression was 70.0% (95% CI: 65.9, 74.1%) at baseline and 94.9% (95% CI: 92.5, 97.4%) at 12 months, corresponding to a 24.9% (95% CI: 21.6, 28.2%; P < 0.001) absolute increase over time. Significant improvements over time were observed across age groups (15-24 years, 25-34 years, and 35+ years) and for both pregnant and postpartum women. Approximately 95% of women in all age groups and pregnant women achieved viral suppression at 12 months. However, postpartum women lagged behind with only 75.7% viral suppression at 12 months, despite a 58.9% (95% CI: 27.4, 90.3%) increase from baseline. The multicomponent, peer-led ENHANCED-SPS intervention resulted in meaningful improvements in viral suppression for pregnant and breastfeeding women with HIV; however, additional support is needed during the postpartum period.

Key words: HIV care; peer-led intervention; pregnancy and postpartum; Uganda; viral suppression; TMLE.

Introduction

In 2016, the World Health Organization implemented option B+, which recommended lifelong antiretroviral therapy (ART) to all pregnant and postpartum women with HIV, and the current Test-and-Treat approach recommends ART to all persons with HIV.[1-3] There has been significant global progress in preventing vertical transmission of HIV, and ART coverage among pregnant women with HIV increased from 49% in 2010 to 84% in 2023.[4-8] These gains contributed to a 73% reduction in new HIV infections among children over the same period. Nonetheless, the burden remains high with an estimated 120 000 new pediatric HIV infections occurring in 2023, with more than 85% of these in sub-Saharan Africa.

In sub-Saharan Africa, women of childbearing age continue to be disproportionately affected by HIV and a significant number of pregnant and postpartum women do not receive ART during the pregnancy and postpartum period,[3,9,10] increasing risks of viral nonsuppression, pediatric infections, and poor maternal health outcomes.[4,11] In Uganda, viral suppression among pregnant and breastfeeding women has remained suboptimal and ranges between 68% and 80%, highlighting the gap in utilization of HIV treatment services.[12,13]

Pregnancy and breastfeeding present unique challenges and vulnerabilities for women. For example, fear and stigma of a new HIV diagnosis during these periods may affect care engagement and result in challenging disclosure to partners, family, and

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friends.[14] The rate of perinatal transmission is significantly higher among women who acquire HIV during pregnancy than among those who acquire HIV before pregnancy and is likely related to the high HIV RNA levels (ie, viral loads) in plasma and breast milk during acute infection.[7] However, comprehensive HIV care services for women of reproductive age can improve treatment coverage and viral suppression.[15] In Uganda, tailored services for preventing vertical transmission, including early enrollment into HIV care and adherence counseling, have contributed to a remarkable reduction in vertical transmission of HIV from 20% in 2000 to 2.8% in 2021.[16,17] Even so, work remains need to achieve the target of zero new infections in children by 2030.[1,4,15]

Peer support and counseling are increasingly being integrated in programs to prevent vertical transmission and have been reported to be crucial in addressing both the global and regional gaps in achieving viral suppression among women on ART.[17,18] Structured peer support initiatives that emphasize increased awareness of viral load status and male partner engagement for safe disclosure have been recommended.[19] In addition, mhealth interventions have enhanced healthcare service delivery through phone counseling, appointment reminders, and helping to address barriers to care engagement.[20] However, data on impact, implementation, and generalizability of these interventions have been limited. Overall and especially given recent changes in global funding,[21] there is an urgent need to develop and evaluate interventions that combine peer support and mhealth to optimize viral suppression among pregnant and postpartum women with HIV and to progress towards zero new HIV infections in children.

Using the PRECEDE model of behavior change, which emphasizes co-creating and implementing health promotion strategies with affected persons,[22] we designed and implemented a multicomponent intervention of Enhanced Viral Load Counseling and Standardized Peer-Mother Support (ENHANCED-SPS). We hypothesized the ENHANCED-SPS intervention would improve viral suppression over time for pregnant and postpartum women with HIV in rural Uganda.

Methods

Study setting, design, and population

This longitudinal analysis harnesses data from the ENHANCED-SPS study, which took place at 14 public health facilities with some of the highest seroprevalence of HIV in rural Southwestern Uganda (NCT04122144).[23] All facilities provided comprehensive HIV care, were supported by PEPFAR-implementing partners, and offered tailored services for pregnant and postpartum women: HIV testing, ART initiation, viral load testing at 6 months post ART initiation, ART card documentation, general counseling, and adherence counseling every 3 months if not virally suppressing. The facilities also had trained midwives, who provide standard antenatal and postnatal care, as well as peer-mothers, who are lay women with HIV and trained to support pregnant, postpartum, and other mothers with HIV. The standard visit schedule for pregnant and postpartum women with HIV was monthly. In addition to these routine services, we offered the ENHANCED-SPS intervention, which is described below. There were no other changes in HIV care for pregnant or postpartum women during the study period.

Women who had HIV, were aged 15-45 years, and accessed care from these facilities were eligible for enrollment in the ENHANCED-SPS study. Specifically, we consecutively enrolled eligible women at their first antenatal care visit or a follow-up care visit upon receiving a new HIV diagnosis. Women who were unable to provide consent were excluded from participation. Eligible and consenting women were followed for 12 months.

Intervention development and components

We designed the ENHANCED-SPS intervention to target the behaviors that would lead to or sustain viral suppression among pregnant and postpartum women with HIV. Following the PRECEDE framework, we first identified "predisposing" factors (ie, knowledge, attitudes, or beliefs) that impact behavior, "enabling" factors that facilitate behavior change by making it easier, and "reinforcing" factors that include consequences of following a behavior (Table S1).[22] The major intervention components were selected based on barriers to viral suppression identified from literature, our experience in the SEARCH Universal HIV Test-and-Treat trial,[11] and structured discussions with peer-mothers at nonstudy facilities on the contribution of viral suppression to maternal and child health.

Next, we developed a protocol on viral load counseling by midwives and peer-mothers. As shown in Figure 1, the counseling was in form of a simplified flipchart to provide key messages about viral suppression, its role in preventing vertical transmission, adherence scenarios that may result in viral suppression or nonsuppression, and how HIV status disclosure can support ART adherence and HIV-care engagement. The talking points were designed to aid peer-mothers in providing viral load and adherence counseling in a consistent and interpretable way.

For at least two midwives and one peer-mother from each facility, we conducted a joint two-day training on using the counseling flipchart, interpreting viral load results, and holding structured discussions about barriers and facilitators to ART adherence. The training included how to tailor counseling based on viral load results. For example, if viral suppression was not achieved, information should be provided about the risk of perinatal transmission to the child. The training also included role playing of counseling sessions under different adherence scenarios and barriers. Peer-mother were provided real-time feedback on their competency in offering structured, yet personalized counseling. We also conducted pre- and post-training evaluations to confirm peer-mothers' understanding of the intervention and its key components. As described below, this training was reinforced by one-day quarterly feedback meetings.

To guide counseling, all intervention participants received viral load testing using GeneXpert at baseline—regardless of their time since diagnosis—and again at the 12-month follow-up. Unlike routinely collected viral loads, which are returned to patients after weeks or months,[12] GeneXpert viral loads are considered "point-of-care" because results are available rapidly. To inform viral load counseling, all baseline results were returned to participants within three days of their enrollment visit. Some received their results in-person during their enrollment visit. Most received their results via a phone call from their peer-mother, while those without a phone received their results from an in-person home-visit by their peer-mother.

Irrespective of viral suppression status at baseline, all participants received enhanced viral load counseling supported by peer-mothers. Specifically, participants were offered viral load and adherence counseling by a phone call from peer-mothers every two weeks and at each clinic visit by midwives. Participants were also provided with a phone contact of their peer-mother to consult and ask questions. Additionally, at routine clinic visits, participants received an assessment of barriers to ART adherence

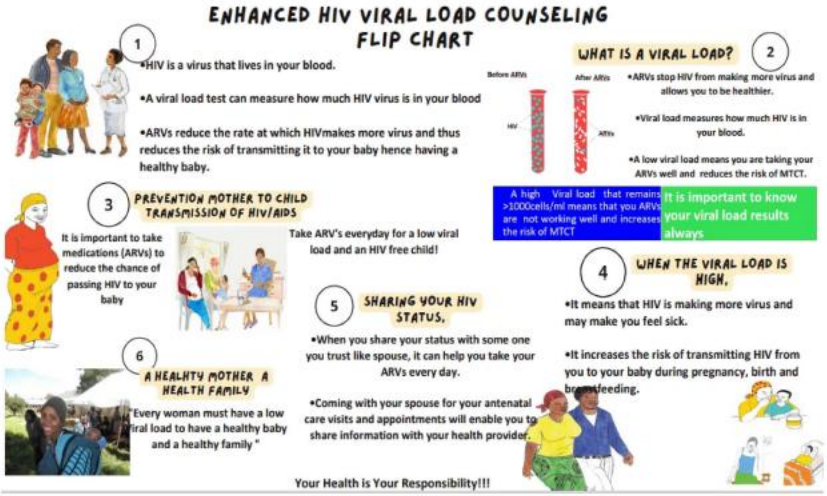

Figure 1. Flip chart developed as part of the ENHANCED-SPS intervention to facilitate counseling through key messages and graphics about viral suppression and its role in preventing vertical transmission of HIV.

as well as a discussion on personalized plans to address these barriers.

The final component of the ENHANCED-SPS intervention was feedback discussions between the peer-mothers, providers, and study staff. These meetings were conducted once every quarter to identify and address any barriers to viral suppression and overall implementation of the intervention.

Measures and statistical analysis

Among pregnant and breastfeeding women who received the ENHANCED-SPS intervention, we conducted a longitudinal analysis to evaluate changes in viral suppression, defined as HIV RNA < 1000 c/mL, from baseline to endline. A threshold of suppression of 1000 c/mL was prespecified to accommodate varying lower limits of detection across assays. This threshold is also the Ministry of Health standard.[24] For each participant, we defined baseline and endline as the viral load measure closest to and within 3.5 months of enrollment and 12 months of follow-up, respectively.

Through review of routinely collected clinic data as well as study logs, we obtained additional information on participant demographics as well as their HIV care status. We classified women into groups based on their characteristics at enrollment: age (15-24 years, 25-34 years, 35+ years), peripartum status (pregnant or breastfeeding), care status (with "recent" as a diagnosis within 2 weeks of enrollment), ART use, and marital status.

In this prespecified analysis, we used targeted minimum loss-based estimation (TMLE) to compare the change in the proportion with viral suppression from baseline to 12 months among women receiving the ENHANCED-SPS intervention.[25] We chose TMLE, because it facilitates flexible adjustment for differences between participants with measured versus missing outcomes, is appropriate for repeated measures, and accounts for the correlation of participants within clinics.[26,27] Our adjustment set included age, peripartum status (pregnant or breastfeeding), and care group (recently vs. previously diagnosed). Our corresponding missing data assumption was that within all values of age, peripartum status, care group, and time, viral suppression among participants with a measured viral load was representative of viral suppression among participants with missing viral loads. Within TMLE, Super Learner was used for flexible adjustment and to combine predictions from stepwise regression, main terms regression, and the mean. Secondary analyses were unadjusted (ie, contrasts of the raw proportion with viral suppression among those measured outcomes). Using the Student's t-distribution, we calculated two-sided 95% confidence intervals (CIs) and tested the null hypothesis that the ENHANCED-SPS intervention did not increase viral suppression over time with one-sided test at the 5% significance level. Further details are available in the Statistical Analysis Plan,[25] and a step-by-step description of TMLE for change over time analyses is given in our companion article.[28]

Subgroups included age group, peripartum status, marital status, and HIV care group. We also examined viral suppression among participants who switched versus did not switch to a dolutegravir-based regimen during follow-up. All analyses were done in R, version 4.3.3.

Ethical considerations

Ethical approval to conduct the study was received from the Makerere University School of Medicine Research and Ethics Committee (SOMREC) in May 2019, and annual IRB renewal approvals were obtained for this study. All participants involved provided written informed consent to participate in the study and a waiver of consent for secondary data abstraction.

Table 1. Baseline characteristics for the ENHANCED-SPS study participants in *N* (%) unless noted.

	Age 15-24 years *n* = 123	Age 25-34 years *n* = 220	Age 35+ years *n* = 64	Overall *n* = 505
Age, median [Q1, Q3][a]	22 [20,23]	29 [27,31]	38 [36,39]	28 [24,32]
Peripartum status				
Pregnant	118/123 (96%)	210/220 (95%)	63/64 (98%)	483/505 (96%)
Breastfeeding	5/123 (4%)	10/220 (5%)	1/64 (2%)	22/505 (4%)
Care status				
Recently diagnosed[b]	55/123 (45%)	55/220 (25%)	9/64 (14%)	157/505 (31%)
Previously diagnosed	68/123 (55%)	165/220 (75%)	55/64 (86%)	348/505 (69%)
ART status[c]				
Not on ART	50/120 (42%)	50/218 (23%)	11/63 (17%)	143/497 (29%)
On ART <6 months	12/120 (10%)	12/218 (6%)	3/63 (5%)	38/497 (8%)
On ART 6+ months	58/120 (48%)	156/218 (72%)	49/63 (78%)	316/497 (64%)
ART regimen[d]				
Efavirenz-based regimen	50/51 (98%)	121/124 (98%)	30/33 (91%)	253/269 (94%)
Other regimen	1/51 (2%)	3/124 (2%)	3/33 (9%)	16/269 (6%)
Marital status[e]				
Never married	18/108 (17%)	19/189 (10%)	1/56 (2%)	40/364 (11%)
Married	81/108 (75%)	145/189 (77%)	42/56 (75%)	276/364 (76%)
Separated, divorced, widowed	9/108 (8%)	25/189 (13%)	13/56 (23%)	48/364 (13%)

Abbreviation: ART, antiretroviral therapy.
[a]Data missing on age for 96 (19%) of participants.
[b]Diagnosed within 2 weeks of enrollment.
[c]Data missing on ART duration for 8 (2%) of participants.
[d]Data missing on 85/354 (24%) of participants on ART.
[e]Data missing on marital status for 141 (28%) of participants.

Results

Characteristics of the study population

This analysis included 505 pregnant and postpartum women receiving care at 7 health facilities with the ENHANCED-SPS intervention. Their median age was 28 years [IQR:24-32]; 96% were pregnant, and 69% were previously diagnosed with HIV (Table 1). At enrollment, 29% were not on ART; 8% had been on ART for <6 months, and 64% for 6 or more months. Among those on ART, the most common regimen was efavirenz based (94%).

Change in viral suppression from baseline to 12 months of follow-up

Among the 505 participants, 455 (90.1%) had a baseline viral load measurement and 354 (70.1%) had a follow-up viral load measurement. Accounting for possibly differential viral load ascertainment, the estimated proportion with viral suppression was 70.0% (95% CI: 65.9, 74.1%) at baseline. After 12 months of implementing the ENHANCED-SPS intervention, the estimated proportion with viral suppression was 94.9% (95% CI: 92.5, 97.4%), corresponding to an absolute increase of 24.9% (95% CI: 21.6, 28.2%; $P < 0.001$). In addition, 98% of the women who were suppressed at baseline maintained viral suppression after 12 months of receiving the intervention. Furthermore, 88% of women without viral suppression at baseline achieved suppression at the end of follow-up.

Significant improvements over time were observed within subgroups defined by age group, peripartum group, care status, ART status, and marital status (Figure 2; Table S2). By age group, the greatest increase in viral suppression was among the youngest participants (15-24 years) from 55.5% at baseline to 95.1% at 12 months and corresponding to an absolute increase of 39.5% (95% CI: 25, 54.1%; $P < 0.001$). Improvements in viral suppression decreased with increasing age: 18.1% (95% CI: 13, 23.3%; $P < 0.001$) increase among participants aged 25-34 years and 15.7% (95% CI: 1.8, 29.6%; $P = 0.017$) increase among participants aged 35 years and above.

Importantly, baseline and follow-up viral suppression rates varied by peripartum status and were notably lower among breastfeeding women. Specifically, only 16.8% of breastfeeding women had viral suppression at baseline and 75.7% after 12 months and corresponding to 58.9% increase (95% CI: 27.4%-90.3%; $P = 0.005$). In contrast, 72.4% of pregnant women had viral suppression at baseline, increasing to 95.6% after 12 months and corresponding to 23.1% increase (95% CI: 21.3, 25.0; $P < 0.001$). Observed improvements in viral suppression varied by marital status: 17.0% increase (95% CI: −4.8-38.9%; $P = 0.051$) for women who were never married; 28.1% increase (95% CI: 26.0, 30.1%; $P < 0.001$) for married women, and an 11.3% increase (95% CI: 1.5, 21.1%; $P = 0.016$) for women of other marital status.

Participants recently diagnosed with HIV had the greatest increase in viral suppression: 21.7% at baseline vs. 91.0% at 12 months for a difference of 69.3% (95% CI: 61.0, 77.6%; $P < 0.001$). Changes among previously diagnosed participants were smaller but still significant: 91.9% at baseline vs. 97.0% at 12 months for a difference of 5.0% (95% CI: 1.0, 9.0%; $P = 0.011$). During the 12-month follow-up period, 81 (23%) of participants switched to an ART combination with dolutegravir (DTG). Importantly, significant improvements in viral suppression were observed among participants who did and did not switch to a DTG-based regimen. Participants who switched to DTG-based regimen achieved the highest level of viral suppression at 98.4% corresponding to increase of 23.9% (95% CI: 14.0, 33.7%; $P < 0.001$) from 74.6% at baseline. However, participants who did not switch also achieved high viral suppression (95.2%) at the end of follow-up, representing a slightly larger absolute increase of 27.2% (95% CI: 19.2, 35.3%; $P < 0.001$) from 67.9% at baseline. Results were robust to the analytic approach (Table S3).

Discussion

In this longitudinal study of pregnant and postpartum women with HIV, significant improvements in viral suppression after 12

sustained viral suppression among women with more ART experience and is a strong contrast with the standard-of-care to only provide counseling to those failing on treatment.[30]

Our findings suggest that interventions including peer support and viral load counseling can have a positive impact on HIV viral suppression, and interventions tailored to pregnant and postpartum women with HIV can improve and sustain their viral suppression. These findings build on our prior analyses demonstrating that the ENHANCED-SPS improved HIV treatment adherence and status disclosure as well as completion of testing algorithms for HIV-exposed infants.[28] Overall, evidence from the ENHANCED-SPS Study can be used to improve maternal outcomes for women in HIV care and contribute to strengthening programs to prevent vertical transmission in Uganda and Sub-Saharan Africa.

The primary limitation of our study was lack of a concurrent comparator group who did not receive the ENHANCED-SPS intervention. Indeed, this was a longitudinal study evaluating changes over time among pregnant and postpartum women before and after they received the ENHANCED-SPS intervention. While previous studies have documented improvements in viral suppression in similar settings in the absence of any additional interventions,[11,12] 95% of our participants were virally suppressed after 12 months—consistently higher than the expected under the standard-of-care where estimates range from 70% among youth (age 15-24 years) to 76% among the women of reproductive age.[11] Furthermore, there were no other changes (beyond the ENHANCED-SPS intervention) to HIV care for pregnant or postpartum women during the study period. Additionally, significant increases were observed across age groups, for recently and previously diagnosed women, and among women who did and did not switch to dolutegravir during follow-up. For the recently diagnosed group, it is challenging to disentangle the impact of the ENHANCED-SPS intervention from ART initiation; however, it is likely the intervention facilitated HIV status disclosure as well as initiation and adherence to ART among these participants.[28] Nonetheless, the improvements in viral suppression over time cannot solely be attributed to the ENHANCED-SPS intervention. Altogether, given the lack of temporaneous control arm, we do not interpret our results causally.

Another limitation was that the study intervention was multicomponent, designed to address multiple barriers faced by pregnant and postpartum women, but also making it difficult to identify which elements had the greatest impact and benefit to the participants. However, our qualitative evaluations have indicated that engaging trusted peer-mothers with lived experience in delivering HIV-free children may have increased the motivation and desire in pregnant and breastfeeding women to stay healthy and have a healthy baby, thereby promoting adherence and ultimately resulting in viral suppression.[28,38,39] Additional qualitative evaluations with participants and providers will provide further insights into mechanisms. We also plan to conduct formal mediation analyses to understand the pathways of intervention action (eg, how disclosure and ART adherence mediated viral suppression outcomes).

Finally, we acknowledge that viral load measures were not available for 30% of participants at endline. This reflects the real-world challenges of conducting implementation studies in resource-limited settings. To minimize the potential for bias due to missing data, our primary analysis was conducted with TMLE, a doubly robust approach using machine learning to flexibly account for differences between participants with and without viral load measures.[11,25,27,40,41] That said, we acknowledge that there could be residual differences between participants with and without viral load measures.

In summary, the ENHANCED-SPS intervention, a multicomponent and peer-led package, significantly improved viral suppression over time among pregnant and postpartum women with HIV in rural Uganda. Despite the observed improvements after one year, viral suppression among breastfeeding women remained far below the UNAIDS target and vertical transmission rates remain high.[7,42] We need to optimize interventions during the postpartum period and further research to explore mechanisms.

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Supplementary material

Supplementary material is available at *AJE Advances: Research in Epidemiology* online.

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Conflicts of interest

The authors have no conflicts of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions on patient data.

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Original Contribution

Appendix 6: Statistical analysis plan for ENHANCED-SPS trial

Statistical Analysis Plan for the Primary and Selected Secondary Endpoints in the ENHANCED-SPS Study

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Abstract:

This document provides the statistical analytic plan (SAP) for the ENHANCED-SPS study, a cluster randomized trial to evaluate the effects of peer-led, multicomponent intervention on viral suppression and other care outcomes among pregnant and breastfeeding women with HIV in South Western Uganda (Clinicaltrials.gov: NCT04122144). The SAP was locked prior to unblinding and effect estimation. This SAP was embargoed until August 31, 2023 when it was submitted to medRxiv.

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1 Overview

ENHANCED-SPS is a cluster randomized trial designed to evaluate the effectiveness of an enhanced viral load (VL) counseling and standardized peer-mother support (SPS) on viral suppression and other care outcomes among pregnant and breastfeeding women with HIV in South Western Uganda (Clinicaltrials.gov: NCT04122144). The patient-centered intervention was developed using the PRECEDE model of behavioral change and was designed to address the structural barriers and unique needs of the target population. Details of the trial design and procedures can be found in the Study Protocol. This document provides the statistical analysis plan to evaluate the intervention effect on the primary endpoint of viral suppression and selected secondary endpoints, including retention in care, adherence to antiretroviral therapy (ART), and disclosure of HIV status. Analysis plans for qualitative outcomes and other endpoints are available elsewhere. A history of changes to this analysis plan is given in the Appendix.

1.1 Study design

ENHANCED-SPS is an Implementation Science study, designed to rigorously evaluate the effects of a multi-component intervention, including viral load counseling and peer support, on care outcomes among pregnant and breastfeeding women with HIV in South Western Uganda. Since the intervention involves clinic-level changes, 14 government-run HIV clinics were randomized to the intervention or the standard-of-care. Randomization was conducted by an independent statistician using a computer-based random number generator and within strata defined by distance, patient burden (HIV prevalence and the number of new HIV diagnoses), and other socioeconomic characteristics (e.g., main occupation of the catchment area of the study clinics).

To facilitate examination of secular trends, retrospective data were collected from all trial clinics (regardless of randomization arm) in the 18-months leading up to intervention initiation. For simplicity, we refer to the pre-intervention phase as "Phase 1" and the intervention phase as "Phase 2". This document focuses on analyses of Phase 2 data only; analyses of Phase 1 data will be described elsewhere.

The primary objective of this study is to determine whether the intervention improved viral suppression after 12 months of follow-up. Key secondary endpoints include disclosure of HIV status, ART adherence, and retention in care. We also plan to evaluate predictors of these endpoints and describe changes in ART regimen during follow-up.

1.2 Description of population and context

Throughout, the target population is pregnant and postpartum women with HIV and accessing care from public health facilities in South Western Uganda. Women with HIV accessing care at the study clinics were eligible for trial enrollment if they were (1) pregnant, previously diagnosed with HIV, and attending the antenatal clinic (ANC) for the first time; (2) pregnant and newly diagnosed with HIV at their first ANC visit; or (3) breastfeeding and newly diagnosed with HIV at the postnatal visit. All eligible and consenting women were consecutively enrolled until the desired clinic-specific sample size was attained (Appendix A.2).

We will provide a participant flow diagram (i.e., a CONSORT diagram) and describe the study population with summary measures of baseline participant characteristics, including age, marital status, enrollment group (pregnant and previously diagnosed; pregnant and newly diagnosed, or breastfeeding and newly diagnosed), ART regimen, and HIV viral suppression status (HIV RNA< 1000 c/mL). Throughout, "baseline" refers to the time of enrollment into Phase 2, when intervention delivery began. We will provide these summary measures overall and by arm. We may also provide these summary measures by clinic.

2 Primary endpoint: Virologic suppression after 12 months

For each participant, the primary endpoint is HIV viral suppression after 12 months of follow-up in Phase 2. In the intervention arm, HIV RNA measures (hereafter called "viral loads") will be obtained through the Ministry of Health (MoH) standard procedures as well as study-specific procedures (GeneXpert point-of-care viral load testing). In the control arm, viral loads will be obtained through MoH standard procedures and accessed via electronic health records (EHR). As a result, the assay used and corresponding lower limit of detection (LLOD) will vary across participants and over time. To be the most inclusive, the primary analysis will define viral suppression as <1000 copies/mL. Pending data availability, we may conduct sensitivity analyses defining viral suppression a <400 copies/mL. Throughout, we will define the "baseline" viral load as the one taken closest to and within 3.5 months of enrollment in Phase 2. Throughout, we will define the "endline" viral load as the one taken closest to and within 3.5 months of 12 months of follow-up in Phase 2.

2.1 Missing data

Despite regular viral load monitoring, offered every 6 months or more frequently for pregnant and breastfeeding women, viral load data may be subject to missingness at baseline and at

endline. For some women, this missingness may reflect being out of care. For others, this missingness may reflect shortages of viral load assays. Yet, for others, this missingness may reflect gaps in the data system. Given our reliance on routinely collected viral loads and on the EMR system, we anticipate missingness at baseline and endline will be greater in the control arm than the intervention arm.

Our ability to adjust for differential measurement is attenuated by the magnitude of missing outcomes. As a result, we pre-specify the following approach:

1. If 50% or greater of control participants have an endline viral load, we will compare endline viral suppression by arm, as detailed below.
2. If fewer than 50% of control participants have an endline viral load, we will compare the change in viral suppression from baseline to endline in the intervention arm only, as detailed below.

The approach taken for viral suppression, the primary endpoint, will determine the approach taken for the secondary endpoints, specified below.

2.2 By arm comparison

If there are sufficient data to support a by arm comparison of endline viral loads (Section 2.1), we will conduct the following analysis. Using targeted minimum loss-based estimation (TMLE),[1–5] we will compare the proportion of participants with viral suppression after 12 months of follow-up between arms. TMLE accounts for clustering and allows for flexible adjustment for the ways in which participants with measured outcomes could differ from participants missing outcomes. Our adjustment set will consist of study arm, age, enrollment group, and baseline viral suppression status. To minimize the risk of model misspecification bias, we will use Super Learner, an ensemble machine learning method, to combine predictions from generalized linear models, stepwise regression, and the mean.[6] In the primary analysis, we will use a *Single-stage TMLE* that pools across clinics to estimate and compare the proportion of participants with viral suppression between arms. In a sensitivity analysis, we will use *Two-Stage TMLE* to first estimate the proportion with viral suppression in each clinic, accounting for missing outcomes, and then compare the estimated clinic-specific proportions by arm. In an additional sensitivity analysis, we will conduct an *unadjusted, complete-case analysis*. Specifically, we will restrict to participants with measured outcomes and compare the proportion with viral suppression between arms. All analyses will exclude participants who are missing both baseline and endline viral loads.

All analyses will also account for dependence of participants within clinics. Specifically, for statistical inference, we will aggregate the influence curve to the clinic level,[4,5] and use the Student's t-distribution with 14-2=12 degrees of freedom as finite sample approximation to the standard normal distribution.[7] We test the *null hypothesis* that the ENHANCED-SPS intervention did *not* improve viral suppression, as compared to the standard-of-care, with a one-sided test at the 5% significance level. We will report point estimates and two-sided 95% confidence intervals for the arm-specific endpoints. The primary analysis will be on the difference scale and for the study population (i.e., the sample average treatment effect [SATE]).[2,8] We will also examine relative effects in secondary analyses.

2.3 Within arm comparison

If there are *not* sufficient data to support a by arm comparison of endline viral loads (Section 2.1), we will conduct the following analysis **within the intervention arm only**. In the primary analysis, we will use a *Single-Stage TMLE* to compare the proportion with viral suppression at

endline versus baseline, accounting for clustering and for the ways in which participants with measured viral loads could differ from participants with missing viral loads. As described in Section 2.2, we will use Super Learner for flexible estimation; here, our adjustment set will include age and enrollment group. In a sensitivity analysis, we will use *Two-Stage TMLE* to first estimate the proportion with viral suppression at baseline and endline in each clinic (accounting for missing viral loads) and then compare the estimated clinic-specific proportions over time. In an additional sensitivity analysis, we will conduct an *unadjusted, complete-case analysis*. As before, all analyses will exclude participants who are missing both baseline and endline viral loads. We will use the same approach for statistical inference and test the *null hypothesis* that the ENHANCED-SPS intervention did *not* improve viral suppression over time with a one-sided test at the 5% significance level.

2.4 Subgroups

To understand effect heterogeneity, we will repeat the above analyses within the following pre-specified baseline subgroups: age group (15-24 years, 25-34 years, >35 years), enrollment group, and marital status. If conducting a by arm analysis, we will also include baseline viral suppression status as a subgroup. Additionally, given the rollout of dolutegravir (DTG) during the study, we will repeat these analyses stratified by women who did and did not switch to DTG during follow-up. Participants with missing data on the variable determining their subgroup classification will be excluded from that analysis.

2.5 Predictors

In addition to subgroup analyses, we will report the number and proportion of participants who were not suppressed at baseline and achieved viral suppression at endline – overall and within subgroups. Likewise, we will report the number and proportion of participants who sustained viral suppression (i.e., had viral suppression at both baseline and endline). Additionally, we may conduct the following analyses to understand predictors of viral non-suppression at endline. Within each arm separately, we will estimate unadjusted associations and adjusted associations of viral non-suppression using as predictors: age, enrollment group, marital status, baseline ART regimen, and baseline HIV viral suppression. All analyses will be implemented with the Single-Stage TMLE and yield associations on the relative scale (statistical analogs of the causal risk ratio).

3.0 Secondary Endpoints

Evaluation of the intervention effect on the below secondary endpoints will follow from the primary analysis. As detailed in Section 2.1, if we conduct a by arm comparison of viral suppression at endline, then we will compare the secondary endpoints by arm at endline. Alternatively, if we evaluate the change in viral suppression over time in the intervention arm, then we will compare the secondary endpoints between baseline and endline within the intervention arm only.

Key secondary endpoints include

- Disclosure of HIV status, overall and to a partner or spouse
- Adherence to ART
- In-care indicators: an indicator of having at least one clinical visit within {42,60,90} days of {6, 12} months of follow-up

- Time-in-care: the proportion of the 12 month follow-up where the participant is engaged in clinical care. "Out-of-care" time starts 14 days after a missed visit and ends at re-engagement.
- ART covered time: the proportion of the 12 month follow-up where the participant had a full regimen of ART.

Data for the secondary endpoints will be obtained from routine clinical records and study records. For the disclosure and adherence endpoints, we will evaluate the intervention effect using TMLE to account for clustering and for missing outcomes, as described for the primary endpoint (Section 2). For endpoints related to retention in care (i.e., in-care indicators, time-in-care, and ART covered time), we will conduct an unadjusted, complete-case analysis account for clustering. For all secondary endpoints, we will test the null hypothesis of no improvement due to the ENHANCED-SPS intervention with a one-sided test at the 5% significance level. We will also implement analogous subgroup and predictor analyses.

Appendix:

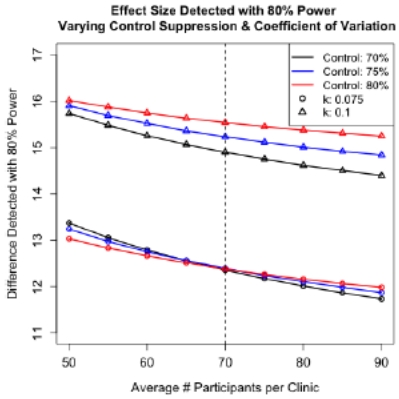
A.1 History of changes

This document provides the pre-specified analyses for the primary endpoint of viral suppression and secondary endpoints of disclosure, adherence, and retention in care. For these endpoints, this document supersedes any prior analytic plans (e.g., in the Study Protocol). This document does not cover additional analyses specified in the Study Protocol for pre-post analyses including Phase 1, vertical transmission, costing, or qualitative assessment of facilitators and barriers. Separate statistical analysis plans will be developed for these endpoints.

A.2 Power calculations

Sample size and power calculations were based on the standard formulas for cluster randomized trials with proportion endpoints.[7] We expect these calculations to be conservative, because of the precision gained through our pre-specified choice of a one-sided hypothesis test.

We estimated 14 clinics (7 clinics per arm) would provide 80% power to detect at least a 15% absolute increase in viral suppression at 12 months (the primary outcome) from 70% in the standard-of-care, using a two-sided test and assuming a coefficient of variation of $k=0.1$ (informed by the START trial) and average of 70 participants/clinic. As shown in the following Figure, these calculations are fairly insensitive to the number of participants and viral suppression in the control arm.



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Appendix 7: ENHANCED-SPS- Study follow up form

CRF for the Enhanced - SPS Study		
1	**Dates**	
Dates	a) Vist date	……..
	b) ART Start date	……..
	c) Date of the last V/L specimen	……..
	d) Date of last V/L results	…….
	e) Date for next V/L specimen	……..
2	**Follow-up assessment (Today's Visit)**	
ART Status	a) ART naïve	
	b) Pre-ART	
	c) ART ≥ 6months	
Adherence	a) Not on ART	
	b) Poor adherence	
	c) Good (≥ 95%)	
Disclosure	Yes	
	No	parents
		Spouse …….
		Friend ……
	If yes, to whom did you disclose?	Significant others ……
Use of Herbs/Herbal Products	Yes	
	No	
	If yes, why?	…….
3	**Intervention**	
a) Peer mother support (visit or phone call	Yes	
	No	
		Visit ……
	If yes specify	Phonecall …….
b) Enhanced VL Counseling Done	Yes	
	No	
c) Did you receive any phone call since the last visit	Yes	1……
	No	2……..
Provider Comments: BP……, Wt…… MUAC, Acohol use: Yes/No and smoking :Yes/No Initials of data entrants 1 ……2 ……..		

Appendix 8: ENHANCED-SPS study qualitative evaluation phase II: draft interview guides

Introduction: These Semi-Structured In-Depth Interview (IDI) guides are to guide data collection in three different groups over the study period

- IDI Guide A: HIV+ WOMEN WITH INCOMPLETE ENGAGEMENT IN HIV CARE (In care, but with detectable viral load)
- IDI Guide B: HIV+ WOMEN DROPPED OUT OF HIV CARE (Missed ALL scheduled visits/ not seen in clinic in past ≥ 6 months)
- IDI Guide C: HIV+ WOMEN SUCCESSFULLY RETAINED IN HIV CARE (Did not miss scheduled visits/ viral suppression achieved)

The purpose of these semi-structured guides are to better understand the factors that contribute to women's challenges related to care engagement, and the factors that help facilitate successful engagement in care, in study clinics/ communities. The guides include specific probes and follow-up questions, but interviewers will insert additional probes and follow up questions as needed in order to clarify participants' responses or further explore discussion points that are salient to the research questions.

Note to interviewers: Instructions for interviewers are in italicized text; the script to guide questioning is in plain text. Do not read IDI guide section headers aloud to participants. Take your time to make sure the participant has understood your questions, and rephrase as needed; ask follow up questions as needed to make sure the participant responds fully to each question.

IDI Guide A: HIV+ ADULTS WITH INCOMPLETE ENGAGEMENT IN HIV CARE

My name is _____. I work for the ENHANCED-SPS study as a researcher. We would like talk to you to learn about your experiences as an HIV-positive person who is a member of this community. We are interested in the needs and preferences of men and women in this community related to seeking HIV care and treatment. We would like to learn about how you feel about seeking HIV care and treatment, and what factors you consider in your decision whether or not to go to the clinic for treatment of HIV. We are also interested in learning about what other factors in your life help you to access care at the clinic, or challenges that interfere with your ability to stay in HIV care.

The information that you provide will be used to inform efforts to improve programs and services for people in Uganda and other countries. This discussion will take around one hour. If you have questions you want to ask on other topics, I can try to answer them after the end of the discussion. In order not to lose any of the valuable information you tell me, I will record our conversation. After a transcript of the audio recording is typed up, the recording will be destroyed. Your name will not be attached to the recording or the transcript, and only members of the study team will be permitted to listen to what you say.

NOTE TO INTERVIEWER: Read the consent form for in-depth interviews out loud in the participant's preferred language and give him/her a copy. Ask if s/he has any questions, and answer them. Ask him/her to sign if s/he agrees to participate. If s/he consents to participate, you may start recording here, without recording any names or identifying information.

I. Experiences with HIV testing and disclosure of HIV status

1. I want to start by asking you some questions about your experiences with HIV testing. Please tell me, when did you learn that you were HIV-positive?

2. And how did that make you feel, at that time?

3. And how are you feeling now? *Probe for physical and emotional feelings.*

4. I'd like to ask you a little more about your testing experience. Why did you decide to test?

5. Can you tell me please about whether you talked to anyone about your decision to test, before you got tested that time? *Probes: If no, why s/he decided to not tell anyone? If yes, Why s/he chose that person to talk with about testing?*

6. How did you feel about your testing experience?

a. Did you feel that you got the support you needed during your counseling sessions?

b. Did the counselor answer all of the questions?

c. What would you have changed about the testing experience if you could change one thing?

7. Can you tell me about your experiences sharing your HIV test results with other people?

a. After you first were tested, did you talk to anyone about your experience with testing?

b. Have you shared your HIV test results with anyone?

- *If yes:*

- Who was the first person you disclosed your status to?

- Please tell me about your decision to share your test results: Why did you choose this person to

disclose to?

- Please tell me about their reaction when you shared your test results.
- Were there other people you wanted to disclose your status to, but felt you couldn't? Please tell me more about that.

o *If no:* What makes it difficult for you to share your results?

8. Is there anyone whom you do not want to know your HIV test results? *Probe as needed to find out if there was someone among their family and/or friends whom they wanted to disclose to but could* not.

a. Can you tell me why you do not wish to disclose your test results to this person?

Probe as needed: What makes it difficult for you to share your results with this person?

9. I want to ask you more about your main intimate and family relationships, and about how you and your partner(s) have handled discussions around getting treatment for HIV. First, please tell me about your marital status, and about any girlfriends/boyfriends? *Probe for whether respondent has a husband/wife or main partner with whom s/he resides, and any other sexual partners s/he sees regularly.*

10. Sometimes people in marital relationships, or in non-marital sexual partners, struggle with the decision whether or not to tell a partner that they are HIV-positive. Can you tell me, please, how did you feel about that decision, whether or not to disclose your HIV status?

Note that if participant mentions more than one partner, begin with main partner, then ask these questions again about any additional sexual partners.

a. Did you find it possible to talk with your spouse/partner?

- *If yes:* what was your partner's reaction?
  - How did it feel to discuss testing for HIV with your partner?
  - Did your partner discuss his status/testing with you?
  - Did you test with your partner?
  - How has it affected your relationship?
  - *Probe as needed with follow up questions if participant offers additional information about positive or negative consequences of disclosure*
- *If no:* What made it difficult to talk with your partner/spouse about your HIV status?
  - What are your thoughts about how you may handle this in the future?
  - What would help make it easier to talk with your partner about your HIV status?

II. Perceptions, attitudes and preferences related to enrollment in HIV care

11. Thank you. Now I would like to ask you some questions about your experiences with HIV care and treatment. First, have you ever received any care or treatment for HIV?

a. *If the participant responds that he or she has NOT previously received care for HIV:* Can you tell me the main reasons why you have not yet received HIV care?

- Are there any other problems or issues that have kept you from enrolling in care?
- Please tell me, what would make it easier for you to enroll in HIV care and treatment?

12. Please tell me, what were the issues you considered when you first decided to go to a clinic to start HIV care and treatment?

a. Think back to before you started receiving HIV care and treatment. What worries or concerns did you have about getting treatment for HIV?

- What were the main reasons you decided to start HIV care despite these concerns?
- Please tell me about any concerns you still have about receiving care and treatment for HIV?
- Please tell me about any other alternatives to HIV care? have you taken traditional medicines or herbal preparations to treat your HIV infection?

b. When you decided to enroll in HIV care, did you talk about this decision with anyone?

- *If yes:* Why did you choose this person?
  - How did they respond?
  - Was there someone you wanted to talk with about this decision, but felt that you couldn't? Please tell me more about that.
- *If no:* Was there someone you wanted to talk with about this decision, but felt that you couldn't? Please tell me more about that.

c. Let me ask you more about your decision whether or not to come to the clinic [*name clinic*] to seek HIV care and treatment. What were the main reasons why you decided to come to the clinic for HIV care and treatment? *Probe*: Were there any other reasons?

d. Did you receive any treatment from other providers such as herbalists or traditional healers?

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

e. Did you receive any phone call reminders or visits from clinic staff about coming to the clinic? *Probe: this could include other staff, VHTs, counselors etc.*

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

13. Have you ever had to change where you access HIV care at any point since you tested positive? *If yes, probe for main reasons why.*

III. ***Experiences with HIV care and treatment***

14. I want to ask you some questions now about your experiences with HIV care and treatment at [*clinic name*]. Please remember that everything you tell me is confidential, to be shared only with the research team and combined with information collected from many other people in this community—nothing that you tell me will affect the care you receive in any way. First of all, when you go to the clinic for an appointment, how satisfied do you feel about the amount of time you have to wait to be seen?

a. Has this changed over time? *Probe for whether waiting times have decreased or are about the same.*

15. Please tell me about the care that you receive at the clinic. Walk me through from the moment you arrive at the health facility, what are the processes that you go through?

a. Do you tend to see one particular health care provider, or have you been seeing different providers at [*clinic name*]?

b. How do you feel about that? *Probe for whether participant prefers to see one particular provider-the person who provides the drugs/medication.*

16. Please tell me a bit about the counseling and advice you've received when you access care at [clinic name]. How informative and helpful has it been?

a. Were there questions you remember asking the provider? *Probe: this is the person who provides the counseling and medication.* Please tell me about that.

b. How did you feel about the information that you were provided? *Probe*: Please tell me about that, *was it adequate or inadequate?*

- How comfortable do you feel about asking those questions, in the future?

17. Please tell me about any positive or negative experiences you had at [*clinic name*], in terms of how you felt you were treated by staff and providers. *Probe for levels of friendliness, respect, or other aspects of quality of care.*

a. Has this changed over time? *Probe for whether treatment by staff or providers has improved, worsened, or is about the same.*

18. Now I want to ask you about the medications you've received. Can you tell me please about the drug treatment you are receiving for HIV/AIDS? *Probe whether informant knows what ARV meds are, whether they know what meds they are taking.*

a. *If receiving ARV therapy*: Please tell me about how you learned you were eligible for ARV therapy. Where and when did you learn you were eligible to begin taking ARVs?

- Who spoke to you about your eligibility for ARV therapy*? Probe for cadre of health care provider and health centre. Probe as needed to ask about experiences and feelings among patients about learning they were eligible under NEW guidelines.*

- Please tell me about worries or concerns you had about started ARV medication. *Probe for whether or not s/he still has some concerns.*
- How has taking ARVs affected your life?
- Please tell me about any challenges you have with adhering to your HIV medications? *Probe for ALL reasons.*
- What would make it easier for you to adhere to taking your HIV medications?

b. Can you please tell me about your experience learning about your HIV "viral load"?

- When and where did you first learn about viral load, and what it means?
- What words did your health care provider use, to describe what viral load means?
- How has it affected you, to know about your viral load?
- How important is it to you, to know your viral load?

19. Some people may have challenges keeping HIV care appointments. Now I am going to ask you some questions about challenges that you have had with making all of your scheduled appointments in the past year. Please tell me about that.

a. What were the circumstances that led this to happen?

b. For about how long was your care interrupted?

20. How are you feeling now, about getting to the clinic for HIV care and treatment?

a. Please tell me about your scheduled clinic visits in the 9months/18months. About how many visits did you have scheduled, and about how many of the scheduled visits have you missed?

b. Next I'd like to ask you about the events that led up to your missing your scheduled appointment[s]. What was happening in your life, or at the clinic, that made it hard for you to make that appointment? *Probe for reasons for each clinic visit missed, if more than one.*

c. Would you say that you are still interested in getting treatment for HIV, or would you say you have dropped out of care for now? *Probe*: Please tell me more about that.

- [*If s/he says s/he has dropped out*:] What else affected your dropping out of care? *Probe for personal factors (e.g. fear of disclosure), as well as factors at the clinic (e.g. long wait times), that affected respondent's disengagement from care.*

- How concerned are you about your ability to make your clinic appointments in the future? *Probe*: Please tell me more about that.

- [*If s/he says s/he intends to stay engaged in care*:] Please tell me, what do you think would make it easier for you to make your clinic appointments?

- What else do you think would help you to stay in care in the future?

IV. Relationship, family and other contextual factors related to HIV care-seeking

21. Now I want to ask you about how other people in your community feel about getting treatment for HIV, especially your friends or family close to you. How do you think most of them feel about getting care and treatment for HIV?

a. To what extent do you and your friends/family talk about HIV treatment? What kinds of things do your friends/family say about it?

b. What are the main motivations for people to enroll in HIV care programs?

- And what about staying enrolled in HIV care?

c. Please tell me, what do you think are the main reasons why people do not seek care and treatment for HIV?

- What other barriers do people face, related to starting HIV treatment

d. And what about staying enrolled in HIV care and treatment—making clinic appointments. What are the main barriers to staying in care, for most people?

- What about adhering to medications—what are the main things that make it hard for people to adhere to ARV regimens?

- What about other medical services—how do most people in this community, especially your friends/family, feel about accessing medical care?

22. I want to ask you more about your main intimate and family relationships, and about how you and your partner[*s*] have handled discussions around getting treatment for HIV. First, is HIV treatment something you and your partner/spouse have talked about? Please tell me about that.

a. What are the things that make it hard to discuss HIV treatment with him/her?

b. What do you think might make it easier?

c. *If s/he has discussed treatment with their partner*: How has it affected your relationship to talk together about HIV care and treatment?

Probe as needed with additional spouse/partners, if mentioned previously.

23. We would like to understand the importance of the peer mother support and how their relationship

a. How was your relationship with the peer mother at your facility?

b. Is there anything you'd like to share with me, about your experiences with the peer mothers? or about this study? ; Were you able to receive SMS messages on your phone? How helpful were the SMS messages in reminding you of the care engagement and ART.?

THANK THE RESPONDENT FOR HIS/HER PARTICIPATION, AND COMPLETE REFERRAL PROCESS AS NEEDED.

Appendix 9: IDI Guide B: HIV+ adults dropped out of HIV care or never linked

My name is _____. I work for the ENHANCED-SPS study as a researcher. We would like talk to you to learn about your experiences as an HIV-positive person who is a member of this community. We are interested in the needs and preferences of women in this community related to seeking HIV care and treatment. We would like to learn about how you feel about seeking HIV care and treatment, and what factors you consider in your decision whether or not to go to the clinic for treatment of HIV. We are also interested in learning about challenges that interfere with your ability to enroll or stay in HIV care.

The information that you provide will be used to inform efforts to improve programs and services for people in Uganda and other countries. This discussion will take around one hour. If you have questions you want to ask on other topics, I can try to answer them after the end of the discussion. In order not to lose any of the valuable information you tell me, I will record our conversation. After a transcript of the audio recording is typed up, the recording will be destroyed. Your name will not be attached to the recording or the transcript, and only members of the study team will be permitted to listen to what you say.

NOTE TO INTERVIEWER: Read the consent form for in-depth interviews out loud in the participant's preferred language and give him/her a copy. Ask if s/he has any questions, and answer them. Ask her to sign if s/he agrees to participate. If s/he consents to participate, you may start recording here, without recording any names or identifying information.

I. Experiences with HIV testing and disclosure of HIV status

1. I want to start by asking you some questions about your experiences with HIV testing. Please tell me, when did you learn that you were HIV-positive?
2. And how did that make you feel, at that time?
3. And how are you feeling now? *Probe for physical and emotional feelings.*

4. Can you tell me please about whether you talked to anyone about your decision to test, before you got tested that time? *Probes: If no, why she decided to not tell anyone? If yes, why she chose that person to talk with about testing?*
5. Where did you test? *Probe for whether HIV+ result given at health facility or within the community (at clinic or other venue).*

a. *If testing occurred at facility*: How did it happen that you were tested at facility? Please tell me about that.

- Please tell me about the reasons you decided to get tested at facility.

b. Did you ever test for HIV before the first time you tested from this [*clinic name/ other venue*] please tell me what your motivator to test was?

6. How did you feel about your testing experience?

a. Did you feel that you got the support you needed during your counseling sessions?

b. Did the counselor answer all of the questions?

c. What would you have changed about the testing experience if you could change one thing?

7. Can you tell me about your experiences sharing your HIV test results with other people?

a. After you first were tested, did you talk to anyone about your experience with testing?

b. Have you shared your HIV test results with anyone?

- *If yes:*

- Who was the first person you disclosed your status to?
- Please tell me about your decision to share your test results: Why did you choose this person to disclose to?
- Please tell me about their reaction when you shared your test results.
- Were there other people you wanted to disclose your status to, but felt you couldn't? Please tell me

more about that.

- *If no:* What makes it difficult for you to share your results?

8. Is there anyone whom you do not want to know your HIV test results? *Probe as needed to find out if there was someone among their family and/or friends whom they wanted to disclose to but could* not.

a. Can you tell me why you do not wish to disclose your test results to this person?

Probe as needed: What makes it difficult for you to share your results with this person?

9. I want to ask you more about your main intimate and family relationships, and about how you and your partner(s) have handled discussions around getting treatment for HIV. First, please tell me about your marital status, and about any girlfriends/boyfriends? *Probe for whether respondent has a husband/wife or main partner with whom s/he resides, and any other sexual partners s/he sees regularly.*

10. Sometimes people in marital relationships, or in non-marital sexual partners, struggle with the decision whether or not to tell a partner that they are HIV-positive. Can you tell me, please, how did you feel about that decision, whether or not to disclose your HIV status?

Note that if participant mentions more than one partner, begin with main partner, then ask these questions again about any additional sexual partners.

a. Did you find it possible to talk with your spouse/partner?

- *If yes:* what was your partner's reaction?

- How did it feel to discuss testing for HIV with your partner?
- Did your partner discuss his status/testing with you?
- Did you test with your partner?
- How has it affected your relationship?
- *Probe as needed with follow up questions if participant offers additional information about positive*

or negative consequences of disclosure

- *If no:* What made it difficult to talk with your partner/spouse about your HIV status?
- What are your thoughts about how you may handle this in the future?
- What would help make it easier to talk with your partner about your HIV status?

II. Perceptions, attitudes and preferences related to enrollment in HIV care

11. Thank you. Now I would like to ask you some questions about your experiences with HIV care and treatment. First, have you ever received any care or treatment for HIV?

a. *If the participant responds that he or she has NOT previously received care for HIV:* Can you tell me the main reasons why you have not yet received HIV care?

- Are there any other problems or issues that have kept you from enrolling in care?
- Please tell me, what would make it easier for you to enroll in HIV care and treatment?

12. Please tell me, what were the issues you considered when you first decided to go to a clinic to start HIV care and treatment?

a. Think back to before you started receiving HIV care and treatment. What worries or concerns did you have about getting treatment for HIV?

- What were the main reasons you decided to start HIV care despite these concerns?
- Please tell me about any concerns you still have about receiving care and treatment for HIV?

b. When you decided to enroll in HIV care, did you talk about this decision with anyone?

- *If yes:* Why did you choose this person?
- How did they respond?
- Was there someone you wanted to talk with about this decision, but felt that you couldn't? Please tell me more about that.
- *If no:* Was there someone you wanted to talk with about this decision, but felt that you couldn't?

Please tell me more about that.

c. Let me ask you more about your decision whether or not to come to the clinic [*name clinic*] to seek HIV care and treatment. What were the main reasons why you decided to come to the clinic for HIV care and treatment? *Probe*: Were there any other reasons?

d. Did you receive a transport voucher?

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

e. Did you receive any phone call reminders or visits from ENHANCED-SPS Study staff about coming to the clinic? *Probe: this could include other staff, VHTs, peer mother etc.*

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

13. Have you ever had to change where you access HIV care at any point since you tested positive? *If yes, probe for main reasons why.*

III. Experiences with HIV care and treatment

14. I want to ask you some questions now about your experiences with HIV care and treatment at [*clinic name*]. Please remember that everything you tell me is confidential, to be shared only with the research team and combined with information collected from many other people in this community—nothing that you tell me will affect the care you receive in any way. First of all, when you go to the clinic for an appointment, how satisfied do you feel about the amount of time you have to wait to be seen?

a. Has this changed over time? *Probe for whether waiting times have decreased or are about the same.*

15. Please tell me about the care that you receive at the clinic. Walk me through from the moment you arrive at the health facility, what are the processes that you go through?

a. Do you tend to see one particular health care provider, or have you been seeing different providers at [*clinic name*]?

b. How do you feel about that? *Probe for whether participant prefers to see one particular provider- the person who provides the drugs/medication.*

16. Please tell me a bit about the counseling and advice you've received when you access care at [clinic name]. How informative and helpful has it been?

a. Were there questions you remember asking the provider? *Probe: this is the person who provides the counseling and medication.* Please tell me about that.

b. How did you feel about the information that you were provided? *Probe*: Please tell me about that, *was it adequate or inadequate?*

- How comfortable do you feel about asking those questions, in the future?

17. Please tell me about any positive or negative experiences you had at [*clinic name*], in terms of how you felt you were treated by staff and providers. *Probe for levels of friendliness, respect, or other aspects of quality of care.*

a. Has this changed over time? *Probe for whether treatment by staff or providers has improved, worsened, or is about the same.*

18. Now I want to ask you about the medications you've received. Can you tell me please about the drug treatment you are receiving for HIV/AIDS? *Probe whether informant knows what ARV meds are, whether they know what meds they are taking.*

a. *If receiving ARV therapy*: Please tell me about how you learned you were eligible for ARV therapy. Where and when did you learn you were eligible to begin taking ARVs?

- Who spoke to you about your eligibility for ARV therapy*? Probe for cadre of health care provider and health centre. Probe as needed to ask about experiences and feelings among women about learning they were eligible under NEW guidelines.*

- Please tell me about worries or concerns you had about started ARV medication. *Probe for whether or not s/he still has some concerns.*
- How has taking ARVs affected your life?
- Please tell me about any challenges you have with adhering to your HIV medications? *Probe for ALL reasons.*
- What would make it easier for you to adhere to taking your HIV medications?

b. *If not on ARV therapy*: Can you tell me what you have been told about your eligibility for ARV therapy?

- *If previously told s/he is eligible for ARV therapy, but has not yet started*: Can you please tell about your reasons for not starting ARV therapy?
- Are there any other reasons you have not started taking ARVs? *Probe for ALL reasons.*

c. Can you please tell me about your experience learning about your HIV "viral load"?

- When and where did you first learn about viral load, and what it means?
- What words did your health care provider use, to describe what viral load means?
- How has it affected you, to know about your viral load?
- How important is it to you, to know your viral load?

19. Some people may have challenges keeping HIV care appointments. Now I am going to ask you some questions about challenges that you have had with making all of your scheduled appointments. Records from the clinic showed that you were among a group of people in this community who may have missed some appointments in the past six months. Please tell me about that.

a. What were the circumstances that led this to happen?

b. For about how long was your care interrupted?

20. How are you feeling now, about getting to the clinic for HIV care and treatment?

a. Please tell me about your scheduled clinic visits in the last year. About how many visits did you have scheduled, and about how many of the scheduled visits have you missed?

b. Next I'd like to ask you about the events that led up to your missing your scheduled appointment[s]. What was happening in your life, or at the clinic, that made it hard for you to make that appointment? *Probe for reasons for each clinic visit missed, if more than one.*

c. Would you say that you are still interested in getting treatment for HIV, or would you say you have dropped out of care for now? *Probe*: Please tell me more about that.

- [*If s/he says s/he has dropped out*:] What else affected your dropping out of care? *Probe for personal factors (e.g. fear of disclosure), as well as factors at the clinic (e.g. long wait times), that affected respondent's disengagement from care.*

- How concerned are you about your ability to make your clinic appointments in the future? *Probe*: Please tell me more about that.

- [*If s/he says s/he intends to stay engaged in care*:] Please tell me, what do you think would make it easier for you to make your clinic appointments?

- What else do you think would help you to stay in care in the future?

21. ***Ask only if participant not currently enrolled in care:*** Can you tell me the main reasons you're not receiving care currently? *Probe for ALL reasons*.

- *If respondent was previously enrolled in an HIV care and treatment program, but dropped out of care:* Please tell me about the events that led up to your dropping out of care. What was happening in your life, or at the clinic, that made it hard for you to stay in care?

- *Probe*: What else affected your dropping out of care? Please tell me more about that. *Probe for personal factors (e.g. fear of disclosure), as well as factors at the clinic (e.g. long wait times), that affected respondent's disengagement from care.*

- Please tell me, what would make it easier for you to enroll again in HIV care and treatment?

IV. Relationship, family and other contextual factors related to HIV care-seeking

22. Now I want to ask you about how other people in your community feel about getting treatment for HIV, especially your friends or family close to you. How do you think most of them feel about getting care and treatment for HIV?

a. To what extent do you and your friends/family talk about HIV treatment? What kinds of things do your friends/family say about it?

b. What are the main motivations for people to enroll in HIV care programs?

- And what about staying enrolled in HIV care?

c. Please tell me, what do you think are the main reasons why people do not seek care and treatment for HIV?

- What other barriers do people face, related to starting HIV treatment

d. And what about staying enrolled in HIV care and treatment—making clinic appointments. What are the main barriers to staying in care, for most people?

- What about adhering to medications—what are the main things that make it hard for people to adhere to ARV regimens?

- What about other medical services—how do most people in this community, especially your friends/family, feel about accessing medical care?

23. I want to ask you more about your main intimate and family relationships, and about how you and your partner[*s*] have handled discussions around getting treatment for HIV. First, is HIV treatment something you and your partner/spouse have talked about? Please tell me about that.

    24. What are the things that make it hard to discuss HIV treatment with him/her?

    25. What do you think might make it easier?

a. *If s/he has discussed treatment with their partner*: How has it affected your relationship, to talk together about HIV care and treatment?

    Probe as needed with additional spouse/partners, if mentioned previously.

26. Is there anything else you'd like to share with me, about your experiences with HIV care and treatment, or about the ENHANCED-SPS study?

Appendix 10: IDI Guide C: HIV+ adults successfully retained in HIV care

My name is _____. I work for the ENHANCED-SPS study as a researcher. We would like talk to you to learn about your experiences as an HIV-positive person who is a member of this community. We are interested in the needs and preferences women in this community related to seeking HIV care and treatment. We would like to learn about how you feel about seeking HIV care and treatment, and what factors you consider in your decision whether or not to go to the clinic for treatment of HIV. We are also interested in learning about what other factors in your life help you to access care at the clinic, or challenges that interfere with your ability to stay in HIV care.

The information that you provide will be used to inform efforts to improve programs and services for people in *Uganda* and other countries. This discussion will take around one hour. If you have questions you want to ask on other topics, I can try to answer them after the end of the discussion. In order not to lose any of the valuable information you tell me, I will record our conversation. After a transcript of the audio recording is typed up, the recording will be destroyed. Your name will not be attached to the recording or the transcript, and only members of the study team will be permitted to listen to what you say.

NOTE TO INTERVIEWER: Read the consent form for in-depth interviews out loud in the participant's preferred language and give him/her a copy. Ask if s/he has any questions, and answer them. Ask him/her to sign if s/he agrees to participate. If s/he consents to participate, you may start recording here, without recording any names or identifying information.

I. Experiences with HIV testing and disclosure of HIV status

1. I want to start by asking you some questions about your experiences with HIV testing. Please tell me, when did you learn that you were HIV-positive?
2. And how did that make you feel, at that time?
3. And how are you feeling now? *Probe for physical and emotional feelings.*
4. I'd like to ask you a little more about your testing experience. Why did you decide to test?
5. Can you tell me please about whether you talked to anyone about your decision to test, before you got tested that time? *Probes: If no, why s/he decided to not tell anyone? If yes, Why s/he chose that person to talk with about testing?*
6. Where did you test from? *Probe for whether HIV+ result given at home or facility*

- How do you think other members of this community felt about getting tested for HIV at convenient places?

7. How did you feel about your testing experience?

a. Did you feel that you got the support you needed during your counseling sessions?

b. Did the counselor answer all of the questions?

c. What would you have changed about the testing experience if you could change one thing?

8. Can you tell me about your experiences sharing your HIV test results with other people after you were last tested?

a. After you were tested, did you talk to anyone about your experience with testing?

b. Have you shared your HIV test results with anyone?

- *If yes:* whom?

- Please tell me about your decision to share your test results: Why did you choose this person to disclose to?
- Please tell me about their reaction when you shared your test results.

- Were there other people you wanted to disclose your status to, but felt you couldn't? Please tell me more about that.

o *If no:* What makes it difficult for you to share your results?

9. Is there anyone whom you do not want to know your HIV test results?

a. Can you tell me why you do not wish to disclose your test results to this person?

Probe as needed: What makes it difficult for you to share your results with him/her?

10. I want to ask you more about your main intimate and family relationships, and about how you and your partners have handled discussions around getting treatment for HIV. First, please tell me about your marital status, and about any girlfriends/boyfriends? *Probe for whether respondent has a husband/wife or main partner with whom s/he resides, and any other sexual partners s/he sees regularly.*

11. Sometimes people in marital relationships, or in non-marital sexual partners, struggle with the decision whether or not to tell a partner that they are HIV-positive. Can you tell me, please, how did you feel about that decision, whether or not to disclose your HIV status? *Note that if participant mentions more than one partner, begin with main partner, then ask these questions again about any additional sexual partners.*

a. Did you find it possible to talk with your spouse/partner?

o *If yes:* what was your partner's reaction?

- How did it feel to discuss testing for HIV with your partner?
- How has it affected your relationship?
- *Probe as needed with follow up questions if participant offers additional information about positive or negative consequences of disclosure*

o *If no:* What made it difficult to talk with your partner/spouse about your HIV status?

- What are your thoughts about how you may handle this in the future?
- What would help make it easier to talk with your partner about your HIV status?

II. Perceptions, attitudes and preferences related to enrollment in HIV care

12. Thank you. Now I would like to ask you some questions about your experiences with HIV care and treatment. Please tell me, what were the issues you considered when you first decided to go to a clinic to start HIV care and treatment?

a. Think back to before you started receiving HIV care and treatment. What worries or concerns did you have about getting treatment for HIV?

- What were the main reasons you decided to start HIV care despite these concerns?
- Please tell me about any concerns you still have about receiving care and treatment for HIV?

b. When you decided to enroll in HIV care, did you talk about this decision with anyone?

- *If yes:* Why did you choose this person?
- How did they respond?
- Was there someone you wanted to talk with about this decision, but felt that you couldn't? Please tell me more about that.
- *If no:* Was there someone you wanted to talk with about this decision, but felt that you couldn't? Please tell me more about that.

c. Let me ask you more about your decision whether or not to come to the clinic [*name clinic*] to seek HIV care and treatment. What were the main reasons why you decided to come to the clinic for HIV care and treatment? *Probe*: Were there any other reasons?

d. Did you receive a transport voucher?

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

e. Did you receive any phone call reminders or visits from ENHANCED-SPS staff about coming to the clinic?

- *If yes:* How did it affect your decision-making about whether or not to come to this clinic to get treatment for HIV?

13. Have you ever had to change where you access HIV care at any point since you tested positive? *If yes, probe for main reasons why.*

III. Experiences with HIV care and treatment

14. Where are you currently receiving care and treatment for HIV? *Probe for clinic name. Ask about all locations where s/he seeks care.*

a. How has receiving HIV care affected your life?

15. I want to ask you some questions now about your experiences with HIV care and treatment at [*clinic name*]. Please remember that everything you tell me is confidential, to be shared only with the research team and combined with information collected from many other people in this community—nothing that you tell me will affect the care you receive in any way. First of all, when you go to the clinic for an appointment, how satisfied do you feel about the amount of time you have to wait to be seen?

a. Has this changed over time? *Probe for whether waiting times have decreased or are about the same.*

16. Do you tend to see one particular health care provider, or have you been seeing different providers at [*clinic name*]?

a. How do you feel about that? *Probe for whether participant prefers to see one particular provider.*

17. Please tell me a bit about the counseling and advice you've received when you access care at [clinic name]. How informative and helpful has it been?

a. Were there questions you remember asking the provider? Please tell me about that.

b. Were there other questions you had about HIV, or about HIV care and treatment that you did not ask the provider about? *If yes*: Please tell me about that.

- How comfortable do you feel about asking those questions, in the future?

18. Please tell me about any positive or negative experiences you had at [*clinic name*], in terms of how you felt you were treated by staff and providers. *Probe for levels of friendliness, respect, or other aspects of quality of care.*

a. Has this changed over time? *Probe for whether treatment by staff or providers has improved, worsened, or is about the same.*

19. Now I want to ask you about the medications you've received. Can you tell me please about the drug treatment you are receiving for HIV/AIDS? *Probe whether informant knows what ARV meds are, whether they know what meds they are taking.*

a. *If receiving ARV therapy*: Please tell me about how you learned you were eligible for ARV therapy. Where and when did you learn you were eligible to begin taking ARVs?

- Who spoke to you about your eligibility for ARV therapy*? Probe for cadre of health care provider and health centre. Probe as needed to ask about experiences about learning they were eligible under NEW guidelines.*

- Please tell me about worries or concerns you had about started ARV medication. *Probe for whether or not s/he still has some concerns.*
- How has taking ARVs affected your life?
- Please tell me about any challenges you have with adhering to your HIV medications? *Probe for ALL*

reasons.

- What are the things that have helped you to adhere to your medications?

b. Can you please tell me about your experience learning about your HIV "viral load"?

- When and where did you first learn about viral load, and what it means?
- What words did your health care provider use, to describe what viral load means?
- How has it affected you, to know about your viral load?
- How important is it to you, to know your viral load?

20. Have you ever missed HIV care appointments, or dropped out of care for a time? Please tell me about that.

a. What were the circumstances that led this to happen?

b. For about how long was your care interrupted?

21. How are you feeling now, about getting to the clinic for HIV care and treatment?

a. How concerned are you about your ability to make your clinic appointments in the future? *Probe*: Please tell me more about that.

- [*If she says she intends to stay engaged in care*:] Please tell me, what do you think would make it easier for you to make your clinic appointments?
- What else do you think would help you to stay in care in the future?

IV. ***Relationship, family and other contextual factors related to HIV care-seeking***

22. Now I want to ask you about how other people in your community feel about getting treatment for HIV, especially your friends or family close to you. How do you think most of them feel about getting care and treatment for HIV?

a. To what extent do you and your friends /family talk about HIV treatment? What kinds of things do your friends/family say about it?

b. What are the main motivations for people to enroll in HIV care programs?

- And what about staying enrolled in HIV care?

c. Please tell me, what do you think are the main reasons why people do not seek care and treatment for HIV?

- What other barriers do people face, related to starting HIV treatment

d. And what about staying enrolled in HIV care and treatment—making clinic appointments. What are the main barriers to staying in care, for most people?

- What about adhering to medications—what are the main things that make it hard for people to adhere to ARV regimens?
- What about other medical services—how do most people in this community, especially your friends, feel about accessing medical care?

23. I want to ask you more about your main intimate and family relationships, and about how you and your partner[*s*] have handled discussions around getting treatment for HIV. First, is HIV treatment something you and your partner/spouse have talked about? Please tell me about that.

a. What are the things that make it hard to discuss HIV treatment with him/her?

b. What do you think might make it easier?

c. *If s/he has discussed treatment with their partner*: How has it affected your relationship, to talk together about HIV care and treatment?

Probe as needed with additional spouse/partners, if mentioned previously.

24. Is there anything else you'd like to share with me, about your experiences with HIV care and treatment, or about this study?

Appendix 11: ENHANCED-SPS Study. In-depth Interview Guide - Provider's follow-up Interview guide

Thank you for accepting to do this interview. We are here to discuss your experience with providing care to patients with HIV. We want to understand your experiences and your point of view, and are not here to criticize, so please feel free to share your real experiences with us.

I. Experiences providing HIV care

We want to learn a little bit about your work experiences providing care to HIV/AIDS patients.

- How long have you worked at this particular clinic?
- Please tell us about the activities that make up your day-to-day routine work providing counseling, care and treatment to HIV-infected patients, at the current time. About how many patients do you counsel about ART initiation or adherence each week?
- Do you provide counseling to individuals, couples or groups?
- Do patients tend to come alone, or with family members? Does this vary by gender and age? [*If so*: Can you tell me more about that?]
- What do you feel are the most rewarding and fulfilling aspects of your job?
- What are the things that make it hard for you to do your best work, or that decrease your motivation and morale?

II. General ART initiation counseling content

We would like you to tell us about your conversations with patients who were eligible for antiretroviral therapy either immediately before ART initiation or during the first weeks and months of ART to understand how you provide support and care.

- Which types of patients truly merit antiretroviral therapy, in your opinion?

- When discussing ART initiation with patients who are eligible for ART but not on ART already, what are the topics are the most important and most frequently discussed?
- How have these topics changed over time?
- What special issues do women face when discussing ART initiation? What about men?

III. Enhanced Viral load counseling

Note: Ask these questions for all intervention clinic providers. For control clinic providers, first ask about whether VL testing and counseling happens at the health center, and for which patients. If viral load testing and counseling happens at site, proceed (otherwise, skip to section IV).

- What has been the patients' experience regarding learning about their viral loads?
- Can you tell me please, how do you explain to patients what viral load testing means? Please give me an example of how you typically describe HIV viral load to patients.
  - What kinds of questions do patients have about viral load testing?
- How has the patient knowing their viral load affected them?
- How has knowing the patient's viral load level affected your care of the patient?

IV. a. Patient-based factors in ART initiation and maintenance

Now I'd like to ask you some questions about your experiences with patients, and the barriers they face with initiating ART and staying engaged in HIV care and treatment, at the present time. [*Recap from interview summary main points of what provider said in previous interview*.]

- First of all, what do most patients know about ART, before they initiate ART?
  - What are the main misconceptions they have?
  - How has this changed since we last spoke, if it has changed?
- What do you think most patients believe to be the benefits or drawbacks of ART?
  - How has this changed since we last spoke, if it has changed?

- You mentioned that [*recap what provider said about patients' most common misconceptions or areas where they lack information*].
  - How do you respond when patients have this misconception or need information?
  - Can you please give me an example from among patients you have seen recently?
- Please tell me your opinion about the main differences between male and female patients in their knowledge, beliefs and attitudes about ART.
  - Which are more common among women?
  - What differences do you see among people in different age groups?
- What do you think most patients need to have or to believe in order to stay enrolled in care and treatment?
- And what do they need to have and to know in order to adhere to medications?
  - *Probe for the main challenges in care that patients present.*
  - *Probe for whether they are mostly medical, psychosocial, or logistical*
  - How have these barriers changed since we last spoke, if they have changed?

<u>For providers in intervention communities:</u>

- What are the main challenges you have faced, so far, with implementing the Enhanced-SPS study intervention?

- Are there certain types of mothers that you've especially had difficulty enrolling for ART? (For instance, has your experience varied by health status, gender, age, or other characteristic of the patients?)

IV. b. Clinic-based factors in ART initiation and maintenance

We would like to learn more about the kinds of barriers that might exist *at the clinic* to ART initiation and engagement in care and treatment, at the present time. From your point of view, what are the most important things that you see at the clinic, that might make it hard for patients to initiate ART?

- Please tell me about most people's experience with waiting times.
- What are the interactions like with the staff who work here?

- What do you think the clinic can do to make ART initiation easier for patients?
- What about staying engaged in care and treatment, specifically—what could the clinic do to help patients attend their regular appointments and adhere to medications?

IV. Structural factors in ART initiation

- Patients often have difficulty starting ART, because of problems due to lack of money, transportation, work or child care – What do you think are the biggest problems for patients in this clinic?
- **Wrap-up:** Can you tell us about perhaps the best example of a difficult case you've had, with a patient was having problems starting ART, that that you were able to address?

Appendix 12: Approved Copy of the ENHANCED-SPS Flipchart

EKIPANDDE EKYO KUBUULIRIRA KUKUPIIMA OBUNGI/OMUWENDO GWAKAWUKA AKALEETA SIRIIMU.

- Siriimu kawuka akabeera mu musaayi gwo.
- Okukebera kw'obungi bwa kawuka kusobola okupima obungi bwakawuka ka siriimu mu musaayi gwo.
- Eddagala lya ARVs likeendeeza kungeri siriimu gyakolamu obuwuka obulala era nekikeendeeza kubulabe obw'okusiiga akawuka eri omwana wo nekiviiramu okuba n'omwana omulamu.

OKUZIYIZA OKUSIIGA OKAWUKA KA SIRIIMU OKUVA KU MAAMA OKUTUUKA KUMWANA.

Kirungi okumira eddagala lyo (ARVs) okusobola okukeendeeza emikisa gyokusiiga omwanawo akawuka.

Mila eddagala lyo (ARV's) buli lunaku okendeeze ku kawuuka era obeele n'mwana omulamu.

Enhanced -Ps study: Ebifo awokolerwa okubuuliirwa kw'obungi bwakawuka mu musaayi

- Eddagala lya ARVs likomya siriimu okukola obuwuka obulala era likusobozesa okubeera n'obulamu obweyagaza, omwana atalina kawuka wamu n'okulabirila amakka go.
- Okupiima omuwendo gwakawuka akali mumusaayi gwo kuyamba kumanya obungi bwa kawuka mu musaayi gwo.
- Omuwendo gwakawuka oguli wansi kiegeeza nti omirra eddagala lyo bulungi era kikendeeza n'obulabe bwokusiiga omwana wo oba MTCT.

Omuwendo gwakawuka oguli wagulu wa olukumi/1000cells/ml kitegeeza nti eddagala lyo elyakawuka terikola bulungi era nekyongeza n'obulabe bwókusiiga omwana wo.

Okugabana ka ngeri gyo yimilidde kunsoonga zakawuka kasiimu wamu n'omwagalwa wo oba omuntu gwewesiga kisobola okuyamba ekumira eddagala lyo buli lunaku okukendeeza kubungi bwakawuuka kasiimu.

NGA OMUWENDO GWA'KAWUKA GULI WAGGULU,

- Kitegeeza nti ekilwadde kya siriimu kikola obuwuka obulala bungi era kiyinza n'okuviiramu okulwala.

- Kyongeza ku bulabe bwokusiiga akawuka ka siriimu okuva ku gwe okugenda kumwana mukiseera nga oli olubuto,nga ozaala oba nga oyoonsa.

OKUBAAKO BOBULILA KUNGERI GYOÝIMILIDDE KU NSONGA ZA'AWUKA KA SIRIIMU.

- Bwogabana ebikwatako n'omuntu gwewesiga nga omwagalwa wo , kisobola okukuyamba okumira eddagala lyo (ARVs) buli lunaku.
- Okujja n'omwagalwa wo okunywa eddagala ly'olubuto wamu n'okukyala okutegekeddwa kijja kusobozesa okugabana obubaka nabasawo bo.

Okubulilira ku'kupiima omuweendo gwakawuka ka sirimu mumubiri.

"buli mukyala alina okuba nomuweendo gw'akawuuka nga guli wansi okusobola okubeera n'omwana omulamu wamu namakka amalugi"

Obulamu bwo buvunanyizibwa bwo!!!

Mira eddagala lyo elya'ARV's buli lunaku okondeeze ku muwendo gwa kawuuka mumubiri osobole okubeela no'omwana omulamu/ atalina kawuka ka siriimu!

Appendix 13: Participant Card with appointment dates and Motivational messages