Table 1. Continued

Variable	Short Arm (7 Days) (N = 91 Patients)	Long Arm (14 Days) (N = 82 Patients)	Risk Difference (95% CI)	*P* Value
New clinically or microbiologically documented infection	29 (31.9)	21 (25.6)	0.803 (0.499 to 1.293)	.404
Functional capacity needs assistance/dependent in ADL or bedridden at 30 days	24 (27.6)	23 (29.5)	−1.6 (−14.9 to 11.6)	.863
Resistance development	5 (5.5)	10 (12.2)	−6.7 (−15.1 to 1.7)	.175
Time to return to baseline activity in weeks (90 days)	3 (0–12), 60 pts	3 (1–12), 56 pts	…	.591
Total hospital days (90 days from randomization)—survivors	5 (1–12)	4 (1–10.3)	…	.195
Total hospital days (90 days from randomization)—all	5 (1–11), 80 pts	3 (1–10), 73 pts	…	.426
Duration of appropriate antibiotic therapy for bacteremia	7 (7–8)	14 (14–14)	…	<.001
Total antibiotic days from culture collection to day 90 postrandomization	14 (9–20), 80 pts	16 (15–25), 73 pts	…	<.001
Acute kidney injury	6 (6.6)	4 (4.9)	1.7 (−5.2 to 8.6)	.750
Liver function abnormalities	4 (4.4)	1 (1.2)	3.1 (−1.6 to 8.0)	.371
Diarrhea during hospital stay	2 (2.2)	4 (4.9)	−2.6 (−8.2 to 2.8)	.424
Diarrhea until day 90	9 (9.9)	10 (12.2)	−2.3 (−1.2 to 7.0)	.637
Rash	1 (1.1)	1 (1.2)	−0.1 (−3.3 to 3.0)	1
Clostridium difficile infection	0	0	…	…

Continuous data are presented in median (interquartile range); categorical data are presented in number (percentage).
Abbreviations: ADL, activities of daily living; CI, confidence interval; pts, patients; SOFA, Sequential Organ Failure Assessment score; spp., species.
[a]Immunosuppression – any immunosuppressive drugs, including prednisone ≥20mg/d or equivalent.
[b]Urinary device – including urinary catheter, nephrostomy tube or double J catheter.

these patients. The primary composite outcome at 90 days was experienced by 49 of 91 patients (53.8%) in the 7-day arm versus 39 of 82 patients (47.6%) in the 14-day arm (RD, 6.2%; 95% CI, −8.6% to 21.2%), exceeding the noninferiority margin of 10% planned for the original trial. The difference stemmed mainly from rehospitalizations: 43 of 91 patients (47.3%) in the 7-day arm versus 35 of 82 patients (42.7%) in the 14-day arm (RD, 4.5%; 95% CI, −10.2% to 19.3%). Relapse of bacteremia occurred in 5 patients in each group. Relapse of UTI without bacteremia was not evaluated in our trial. Mortality at 90 days was without significant difference (11 of 91 patients [12.1%] in the 7-day arm vs 9 of 82 patients [11.0%] in the 14-day arm; RD, 1.1%; 95% CI, −8.4% to 10.6%).

This post hoc subgroup analysis is limited by the small sample size, as reflected by the wide CIs. In addition, relapse of UTI specifically was not addressed in the original study, limiting our interpretation of results. Further randomized controlled trials are needed.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Change in Plasma Cryptococcal Antigen Titer Is Not Associated With Survival Among Human Immunodeficiency Virus–infected Persons Receiving Preemptive Therapy for Asymptomatic Cryptococcal Antigenemia

To the Editor—Current World Health Organization (WHO) guidelines recommend cryptococcal antigen (CrAg) screening in blood among those human immunodeficiency virus (HIV)-infected persons not receiving effective antiretroviral therapy (ART), with CD4 values <100 cells/μL, and to consider testing those not on ART with CD4 values between 100–200 cells/μL [1]. This recommendation is based on prior studies demonstrating that a "screen-and-treat" program identifying CrAg-positive persons and giving preemptive fluconazole therapy, in combination with an ART adherence intervention, prevents invasive cryptococcal disease and death [2].

There has been growing interest in the utility of serum/plasma CrAg as a prognostic tool in cryptococcal infection [3]. In 4 cohorts, patients with asymptomatic cryptococcal antigenemia and baseline serum/plasma titers of

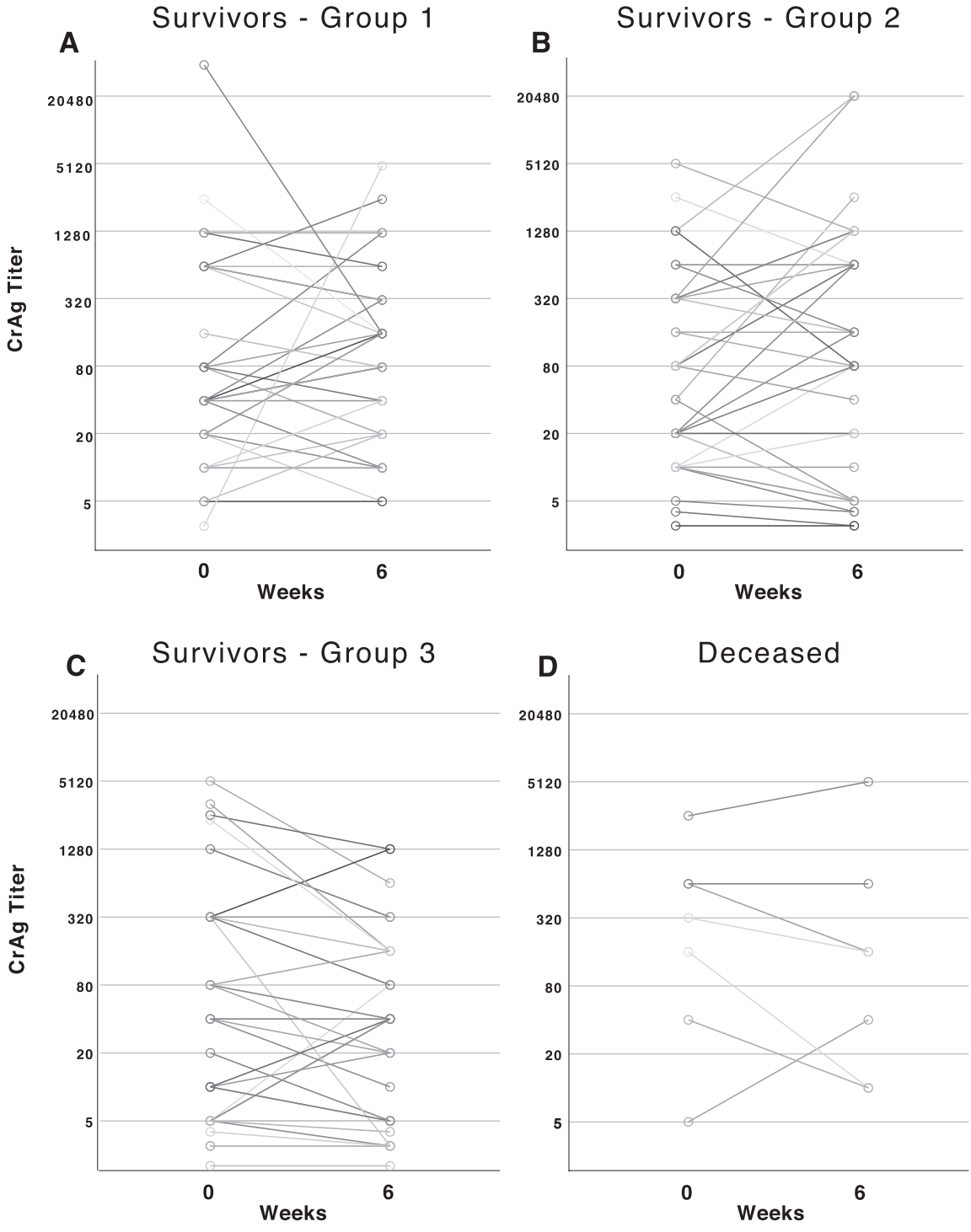

Figure 1. Change in plasma cryptococcal antigen over weeks of fluconazole therapy among those with asymptomatic antigenemia. Each plot displays the CrAg titer values for individual patients at enrollment (0 weeks) and at a 6-week follow-up. *A–C,* Those who survived to a 6-month follow-up, randomly distributed into 3 plots to allow better visualizations of individual responses. *D,* Those who did not survive to a 6-month follow-up. The median CrAg titer at 26 weeks was 40 (interquartile range 10–180) among all those who survived to 26 weeks. Abbreviation: CrAg, cryptococcal antigen.

≥1:160 experienced worse outcomes [3]. Those with baseline serum/plasma titers of ≤1:80 have an 80% chance of survival to 6 months, those with titers of 1:160–1:2560 have a 66% survival rate, and those with titers of ≥1:2560 have a 45% survival rate [3]. While higher titers portend worse outcomes, the value of monitoring sequential serum/plasma CrAg titers in asymptomatic CrAg-positive patients is unclear. In 2 cryptococcal meningitis cohorts, changes

in cerebrospinal fluid CrAg titers were unrelated to outcomes [4, 5]. This relationship between titers and prognoses have not been explored in asymptomatic cryptococcal antigenemia.

The data presented here, part of the work performed by the Operational Research for Cryptococcal Antigen Screening (ORCAS) study team from July 2012–December 2014, represent a cohort of HIV-infected, ART-naive Ugandans with CD4 values <100 cells/μL [6]. Exclusion criteria were overt signs of meningitis or cerebrospinal fluid being CrAg positive. Newly enrolled patients received a lab-based reflexive plasma CrAg lateral flow assay (LFA; Immy Inc., Norman, OK) if their CD4 value was <100 cells/μL. Eligible CrAg-positive patients received fluconazole therapy (800 mg/d for 2 weeks, followed by 400 mg/d for 8 weeks), per the WHO rapid advice at the time. ART was initiated after 2 weeks of fluconazole therapy. Patients were included in these analyses if they survived at least 6 weeks.

We measured plasma CrAg LFA at 0, 6, and 26 weeks of fluconazole therapy. Figure 1 displays the baseline and 6-week titers among those surviving to 6 months (n = 107; Figure 1A–C) and among those who survived at least 6 weeks but died prior to 26 weeks (n = 7; Figure 1D). There was no association between changes in baseline to 6-week titers and the chance of survival to 26 weeks, based on Mann-Whitney U-test analysis (P = .60). Among participants who died between 6 and 26 weeks, there was a median 2-fold increase in titers (interquartile range [IQR], 2-fold decrease to 4-fold increase). Visually, one can appreciate the variability on an individual patient level. Among 26-week survivors, there was a median of no change in titers (IQR, 4-fold decrease to 2-fold increase). Even among those whose titers increased between baseline and 6 weeks, the positive predictive value for death was low for a 2-fold (16%, 4/25) or 4-fold (18%, 3/17) increase. There was no statistically significant relationship between the chance of survival to 26 weeks and a change in CrAg LFA titers from baseline to 6 weeks among HIV-infected persons with asymptomatic cryptococcal antigenemia receiving fluconazole preemptive therapy. Among asymptomatic CrAg-positive patients enrolled in the ORCAS study, longitudinal plasma CrAg titers are not beneficial during fluconazole therapy.

Notes

Disclaimer. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the funding agencies.

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Letter to the Editor

To the Editor—We read with interest the recent publication by Rolfes et al regarding the influenza vaccine efficacy (VE) during the 2017–2018 season [1]. The authors used a test negative design to estimate VE in a population of 8436 participants aged ≥6 months seeking care for an influenza like illness (Figure 1). The study concluded that despite an adjusted VE of 38%, the vaccine prevented 7.1 million illnesses and 3.7 million medical visits. The availability of such information is critical in provaccination efforts; however, the way the information is presented to the lay public is of utmost importance.

The medical community has watched anxiously as outbreaks of vaccine-preventable diseases in the United States have occurred over the past decade [2, 3]. This highlights the communication gap between medical providers and patients regarding the benefits of vaccination. Although statistics such as VE are important for historical and epidemiologic comparisons, VE statistics are directly quoted from medical literature and presented to the lay public out of context [4–6]. For example, a headline released on the same day as an interim report of