taking ART and we acknowledge that ART-experienced persons with VL nonsuppression are at risk for cryptococcosis [5]. Yet, the authors failed to present data that a novel, VL-directed screening approach with an appropriate intervention clearly improved outcomes. We believe the evaluation of VL-directed CrAg screening and its impact on morbidity and mortality should be addressed prospectively. Also, operational matters need attention before changing guidelines (eg, VL results turnaround time) and ensuring anyone at risk of cryptococcal disease has rapid CD4 access, including those on ART with virological failure.

We commend the authors for their description of CrAg prevalence in those on ART with VL nonsuppression, however, more data would be needed to justify a recommendation that the WHO should change CrAg screening in PLHIV with an isolated high VL result.

Notes

Disclaimer. The findings and conclusions in this letter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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.

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Reply to the Author

TO THE EDITOR—We have read the commentary by Heather and Raizes on our recent publication with interest. Given that this was one of the first studies to determine cryptococcal antigen (CrAg) prevalence among individuals with suspected antiretroviral therapy (ART) with a viral load (VL) >1000 copies/mL in the public health system in Uganda, the conclusions we draw may have been overstated in relation to implementing this guidance for country programs.

We agree that we had small numbers of patients to demonstrate improvement in outcomes, however, despite the small numbers in our study, and based on prior studies in Uganda and South Africa, a CrAg prevalence of >0.6% followed by pre-emptive antifungal therapy for those with cryptococcal antigenemia is cost effective [1, 2]. We believe that a CrAg prevalence of 3% among individuals with VL >1000 copies/mL warrants the need to do larger evaluation studies, particularly in sub-Saharan Africa where cryptococcal disease remains a significant cause of AIDS-related mortality. Second, given that the proportion of HIV-infected individuals presenting with cryptococcal meningitis is increasingly skewed to those who are ART experienced, there is a need to do studies on CrAg prevalence among this population of individuals likely failing their ART regimen by using the VL test as a CrAg screening entry point to define the

prevalence, outcomes, and cost effectiveness in other settings.

Given the reasons above, we agree with the authors that further studies are needed to review viral load based CrAg screening in HIV patients with virologic failure in order to prevent and reduce cryptococcosis related mortality.

Note

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The Detrimental Effects of Oral Vancomycin

TO THE EDITOR—In the 1 September 2020 issue of *Clinical Infectious Diseases*, Johnson and colleagues [1] evaluated oral vancomycin prophylaxis in a randomized trial for prevention of *Clostridioides difficile* infection (CDI). We agree with and wish to elaborate on 2 of Professor Garey's editorial comments that (1) one important concern for oral vancomycin as a prophylactic agent is its “profound effect on the microbiome that by itself decreases colonization resistance to *C. difficile*,

vancomycin-resistant *Enterococcus*, and other multidrug-resistant organisms” and (2) that “CDI may develop at the same rate or higher in patients given oral vancomycin as primary prophylaxis but be simply delayed during the vancomycin administration time period” [2].

The degree of microbial-community disruption caused by oral vancomycin is substantial and should not be discounted. The potent anti-anaerobic activity of oral vancomycin parallels or exceeds that of many other conventional antibiotics in terms of magnitude and duration [3–5]. This helps to explain why CDI recurrences following treatment are so common, and why early attempts at treating asymptomatic carriage of *C. difficile* with oral vancomycin demonstrated a temporary suppression that was followed by paradoxically increased susceptibility to both colonization and true infection [6]. This is consistent with our clinical experience, in which we have observed CDIs immediately following the cessation of prophylactic courses of oral vancomycin.

Given this risk of this rebound effect, risks of oral vancomycin should be carefully considered before adopting a routine prophylaxis strategy, with an emphasis on the period after cessation of prophylaxis. Johnson and colleagues attempted to evaluate subjects after discharge, though it was unclear if this corresponded well to treatment cessation. Unfortunately, follow-up was only completed in less than half of the trial participants (48% vancomycin prophylaxis, 44% no prophylaxis); a true CDI difference of 15%, for example, would not have been detectable at this power.

The article by Johnson and colleagues did not report on the effects of vancomycin on fecal microbial composition, and we caution that this unexamined aspect of the study may belie potentially ominous consequences to the intestinal microbiome. Besides fecal microbiota transplantation (FMT) from a healthy donor, several other nonantibiotic approaches to CDI are in development, including banked autologous FMT [7], spore-enriched fractions

of healthy-donor stool (ClinicalTrials.gov number, NCT03183128), rationally designed probiotics (ClinicalTrials.gov number, NCT03788434), a charcoal-based antibiotic adsorbent [8], and intraluminal enzymatic digestion of antibiotics [9]. We welcome clinical trials of any approach against CDI that aims to spare or improve the commensal community and thereby avoid the risk that oral vancomycin might throw out the baby with the bathwater.

Note

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Is the World Health Organization Hepatitis B Virus (HBV) DNA Standard Appropriate for Standardizing Serum HBV RNA Assays?

To THE EDITOR—We read with great interest the article by Anderson and colleagues using a dual-target quantitative polymerase chain reaction (qPCR) assay to demonstrate that full-length pregenomic RNA is the major circulating hepatitis B virus (HBV) RNA species in patients with chronic hepatitis B [1]. Interestingly, the dual-target qPCR assay in this study was standardized according to the World Health Organization (WHO) HBV DNA standard, which raises an important question regarding whether the WHO HBV DNA standard is appropriate for standardizing HBV RNA assays.

According to the calibration hierarchy of biological standards, WHO international standards are the highest-order calibrators for nucleic acid amplification