Correspondence

Impact of Antituberculosis Treatment on Virological Response to Highly Active Antiretroviral Therapy: Implications for Resource-Limited Settings?

To the Editor—Breen et al. [1] reported a retrospective analysis of virological responses to highly active antiretroviral treatment (HAART) among patients in London who were receiving concomitant treatment for tuberculosis (TB). Despite the potential for pharmacokinetic drug interactions and the increased risk of treatment interruptions due to drug intolerance or cotoxicity, virological responses in these patients were nevertheless similar to those observed in control subjects who did not have TB. This is an important finding. The authors reasoned that "specialist care provided by a team experienced in treating both tuberculosis and HIV could overcome the potential difficulties" (p. 1437) in the concurrent management of these 2 infections. Moreover, the fact that the group of patients with TB received 5 different drug regimens that contained 31 different drug combinations was perceived by the authors as reflecting a need for highly individualized care, which was potentially responsible for the positive outcomes. If highly individualized care delivered by specialists is required, then this has great implications for the provision of care to the huge number of patients with TB receiving HAART in resource-limited settings.

A majority of the global burden of HIV-associated TB is in sub-Saharan Africa [2], and rates in southern Africa have reached almost unprecedented levels [3]. Access to antiretroviral treatment in the region is expanding, but it can only be delivered using a simplified public-health approach, rather than individualized patient care. At a community-based public-sector antiretroviral treatment program in Cape Town, South Africa, which now treats >2000 patients, 25% of patients at entry to the program are already receiving anti-TB treatment or have active TB [4]. This burden of TB presents a huge challenge for the delivery of clinical care and has the potential to undermine program outcomes. However, similar to the findings of Breen et al., we recently reported that concurrent anti-TB treatment does not affect virological or immunological responses [4]. HIV loads were suppressed to <400 copies/mL in >94% of patients at 16 and 48 weeks whether the patients received concurrent treatment containing rifampicin for TB or not. HAART was delivered using a simplified public-health approach, in accordance with World Health Organization guidelines [5], with a nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based first-line regimen. Thus, excellent virological outcomes among antiretroviral-naive patients receiving anti-TB treatment can be achieved on a large scale without specialist care and using a single standard HAART regimen.

The coadministration of rifampicin is known to reduce plasma concentrations of NNRTIs [6], which has led to debate over the optimal doses of NNRTIs for patients receiving rifampicin. Breen et al. did not report the doses used in patients who received NNRTI-based regimen in their study [1]. Studies in Thailand, however, have shown that standard doses of efavirenz and nevirapine achieve adequate plasma concentrations in most patients receiving rifampicin [7, 8]—when such patients were randomized to receive either 600 or 800 mg of efavirenz daily, equivalent virological responses were observed at 48 weeks [9]. Our data from South Africa agree with these findings; excellent virological responses were achieved when a standard daily dose of 600 mg of efavirenz was used in patients receiving treatment for TB [4].

A further critical issue for clinicians treating patients with HIV-associated TB is the decision of when to commence HAART during anti-TB treatment. Although early initiation might reduce risk of HIV-associated morbidity or mortality, this may increase the risks of immune reconstitution disease, cotoxicity, and pharmacokinetic interactions [6, 10]. However, the data of Breen et al. and those from our study in Cape Town indicate that no improvement in immunological or virological outcomes is derived from delaying HAART. These data therefore add weight to the argument favoring the early initiation of HAART.

In summary, excellent virological responses to HAART can be achieved among patients receiving concurrent anti-TB treatment using a standard dose efavirenz-based regimen delivered by a simplified public-health approach in resource-limited settings, without specialized care. The fact that virological responses are not undermined by the early initiation of HAART during anti-TB treatment supports policies favoring the early initiation of HAART.

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Reply to Lawn and Wood

To the Editor—We thank Lawn and Wood for their interest in our data and for the valuable information they provide regarding the successful management of tuberculosis (TB) and HIV coinfection in an antiretroviral program in Cape Town. Despite the 31 different drug combinations used in our cohort, 62% of individuals who received highly active antiretroviral therapy (HAART) concurrently with anti-TB therapy were prescribed a regimen that contained a single nonnucleoside reverse-transcriptase inhibitor (NNRTI), as is most widely available in resource-poor settings [1]. The large number of drug combinations that we used partly reflects the fact that, during the time period studied, the number of available antiretroviral agents and their suggested effective combinations changed. In addition, 26% of our patients were receiving HAART at the time when they received their diagnosis of TB, and a significant number had previously received antiretrovirals; it is these individuals in particular whom we suggest benefited from specialized care.

The dosing of NNRTIs administered concomitantly with rifampicin is undoubtedly an important area that has yet to be fully elucidated. In our cohort, we followed national guidelines based on published pharmacological data that suggested using efavirenz 800 mg daily in individuals weighing >50 kg and 600 mg daily in individuals weighing <50 kg [2, 3]. This produced excellent outcomes with no observed increase in rates of adverse events, compared with those in patients receiving other HAART regimens [4]. For reasons of practical ease and cost, it would be beneficial to be able to use a 600-mg dose in all cases, but this requires further study in all ethnic groups.

We agree that the timing of HAART initiation remains controversial and that data that inform this decision are welcome. The data reported from our cohort and that of Lawn and Wood certainly provide no reason to delay HAART, and we observed no increase in treatment-limiting adverse events according to whether HAART was commenced within 2 months of the TB diagnosis or later [4]. The risk of paradoxical reactions does, however, appear to be increased if HAART is started early [5, 6]. We believe that the effect of those variables that appear to be associated with clinical outcome should be assessed in a well-planned, prospective study.

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recent findings of several investigations [2–5] that call into question some long-held assumptions about this disorder. Her essay begins with the pronouncement that we have known for decades that the normal vagina is dominated by hydrogen peroxide–producing lactobacilli and then follows this with the declaration that decreases in the numbers of lactobacilli have been associated with a host of problems, including BV, gonorrhea, HIV infection, and cervicitis. However, several investigations conducted using cultivation-independent methods have shown that a significant proportion (∼30%) of healthy women lack appreciable numbers of Lactobacillus species.

A critical problem in studies of the etiology of BV is the diagnostic criteria used. Although numerous studies have shown that women with high numbers of Lactobacillus species do not have BV, it is a logical fallacy to conclude that women whose vaginal communities have few or no Lactobacillus species have BV. Formally, this is termed a “fallacy of propositional logic” (it is also known as “denial of the antecedent”). Unfortunately, this fallacy is the premise of the Nugent criteria [6] and is a component of the Amsel criteria [7], which are widely used for the diagnosis of BV—for these criteria, the degree of “healthiness” is assessed by scoring the abundance of Lactobacillus species by microscopic analysis of a Gram-stained smear or wet mount prepared from a vaginal sample.

We postulate that, because of this logical fallacy, BV is often misdiagnosed. This could partly account for the reported high incidence of so-called asymptomatic BV in reproductive-age women [8] and could also explain a proportion of BV treatment failures and apparent recurrences of BV in women. Acknowledgment that not all vaginal communities of healthy women are dominated by Lactobacillus species would also be in accordance with the observation that the vaginal communities of postmenopausal women (not receiving hormone-replacement therapy) often lack Lactobacillus species, yet these individuals do not exhibit other untoward symptoms.

We suspect that the causes of and cures for BV will continue to be enigmatic until it is recognized that, although “normal and healthy” can be equated with high numbers of lactobacilli, the converse—“unhealthy” being equated with low numbers of or no lactobacilli—is not necessarily true. We must be vigilant and recognize that, for a significant proportion of women, normal and healthy can also occur in the absence of appreciable numbers of Lactobacillus species.

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CORRESPONDENCE • JID 2006;194 (15 November) • 1469

Potential conflicts of interest: none reported.
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The Journal of Infectious Diseases 2006;194:1468–9 © 2006 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2006/19410-0019$15.00

Reply to Forney et al.

To the Editor—I could not agree more with Forney et al.’s reminder [1] that our understanding of what constitutes “normal” vaginal flora is incomplete and that the criterion standard for diagnosing bacterial vaginosis (BV)—the Nugent criteria [2]—may become tarnished as molecular methodologies redefine the ecosystem of the vaginal environment. In fact, my intention—perhaps an overly subtle one—in putting quotation marks around the term “normal” in the first paragraph of my editorial was to question what we currently believe contributes most to vaginal health. Although the focus of my editorial was on the natural history of BV as reported by Bradshaw et al. [3], whose analyses did not involve molecular analyses of subjects’ vaginal flora, it is useful to re-emphasize the Journal’s readers of the recent expansion of literature in this important area, which has been extensively reviewed elsewhere by Fredricks and myself [4]. As these studies progress, it will be critical to (1) determine whether the presence of vaginal bacteria (including previously undefined bacteria in the Clostridiales order, Atopobium vaginae, Eggerthella species, and Megasphaera species) that are detected more easily or solely by noncultivation techniques is associated with women’s own perceptions of abnormal vaginal symptoms and with examination findings that are suggestive of a disrupted vaginal environment; (2) perform the same analyses with respect to detection of individual vaginal Lactobacillus species; and (3) carefully assess the relationship between molecular profiles of vaginal bacteria and concurrently collected vaginal Gram stains as well...
as between these profiles and individual components of the Amsel criteria [5].

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Potential conflicts of interest: none reported.

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The Journal of Infectious Diseases 2006; 194:1469–70
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