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INVITED COMMENTARY

US Guidelines Fall Short on Short-Course Tuberculosis-Preventive Therapy

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The provision of tuberculosis-preventive therapy (TPT) to vulnerable populations is critical for global control. Shorter-course TPT regimens are highly effective and improve completion rates. Despite incorporation of 1 month of rifapentine and isoniazid into global guidelines, current US TPT guidelines do not include this as a recommended regimen, but should.

Keywords. tuberculosis infection; 1HP; 1 month rifapentine and isoniazid; tuberculosis preventive therapy.

Up to one-quarter of the world has *Mycobacterium tuberculosis* infection, with an estimated 13 million individuals with tuberculosis (TB) infection (TBI) in the United States alone [1–3]. Between 5% and 15% of TBI will progress to TB disease (TBD) without TB-preventive therapy (TPT), and more in people with human immunodeficiency virus (HIV; PWH), accounting for significant morbidity and mortality worldwide; 1.6 million deaths were attributed to TB in 2021 [4–6]. The World Health Organization (WHO) has prioritized TPT for populations with the greatest risk of developing TBD, including contacts of people with TBD and PWH [7], but the initiation and completion of TPT contribute to major losses in the TB care cascade [8, 9]. Across 15 US health departments only 42% of individuals with TBI initiated therapy, and among those, only 76% completed treatment [10], highlighting the importance of bolstering US TPT uptake and completion. In the last 2 decades, we have witnessed a dramatic shift in the TPT landscape from a prolonged 6–9-month course of isoniazid (INH) to shorter-course WHO-recommended rifamycin-based regimens [7, 11]. Importantly, shorter regimens are associated with improved adherence and completion rates [12–15]. Several US drug shortages for TB treatment regimens, such as rifampin [16], have limited the ability of some health departments to initiate short-course TPT; thus, programs may benefit from additional treatment options.

Among the studied short-course regimens, 1 month of daily INH and rifapentine (1HP) has multiple advantages. 1HP is efficacious, well tolerated, and safe, with extremely high rates of adherence and treatment completion. The regimen was studied in Rifapentine-Isoniazid Efficacy for TB Prevention (BRIEF-TB)/A5279, a multicenter, randomized, open-label, phase III clinical trial of 3000 PWH who received either 1HP for 4 weeks or daily INH for 36 weeks (9H) as TPT [14]. Followed for more than 3 years (median), 1HP was noninferior to 9H and, importantly, the proportion of participants completing treatment was significantly higher in the 1HP group than in the 9H group (97% vs 90%; $P < .001$). Of note, Richard E. Chaisson, a co-author of this commentary, was the BRIEF-TB Co-Chair and Chair/Co-Chair of several studies of 3 months of weekly INH and rifapentine (3HP), and thus has an interest in the translation of trial results into practice.

The findings of BRIEF-TB shifted policy worldwide, with the WHO recommending 1HP as an alternative TPT regimen, along with 6–9 months of INH (6H/9H), 3HP, 4 months of daily rifampin (4R), or 3 months of daily INH-rifampin (3HR), regardless of HIV status [6, 7]. Despite this, 1HP has yet to be incorporated into the most widely used US TPT guidelines. The 2020 Centers for Disease Control and Prevention/National Tuberculosis Controllers Association (CDC/NTCA) TBI guidelines note that "short-course (3–4 months) rifamycin-based treatment regimens are preferred over the longer-course (6–9 months) INH monotherapy for treatment of LTBI," but fall short of endorsing 1HP, even for PWH [17]. The CDC/NTCA guidelines relied on a literature review through August 2018. While BRIEF-TB data were not published in a journal, the results were widely known following presentation at a major conference in March 2018, and thus were available to the guidelines committee when drafting its recommendations [18]. The guidelines acknowledge the data by stating, "These guidelines do not address other empiric TB prevention strategies (eg, 1 month of INH plus rifapentine among HIV-positive persons living in settings with a high TB incidence regardless of results from the TST or an interferon-gamma release assay)." The omission of 1HP is therefore puzzling, as is the characterization of the 1HP regimen as "empiric." As a result, the guidelines are now 5 years out of date. Department of Health and Human Services (DHHS) guidelines for treating

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and preventing opportunistic infections in PWH do recommend 1HP as an alternative TPT regimen, but note the exclusion of 1HP in the CDC/NTCA guidelines [19]. As most US public health departments follow the CDC/NTCA guidelines, we will address some perceived limitations of applying this regimen broadly for US-based populations who require TPT.

ARGUMENTS AGAINST 1HP

BRIEF-TB Was Conducted Outside the United States

BRIEF-TB did enroll participants from 20 US sites, where PWH remain a high-risk population, with 91 (3%) individuals contributing to the study [14]. Additionally, 3 BRIEF-TB international sites were not in WHO-defined high-TB- or HIV/TB-burden countries [20]. Furthermore, precedent exists for extrapolating results of TB studies conducted overseas to the United States. The CDC/NTCA guidelines recommended 3HR as a preferred regimen based on trials conducted entirely overseas, for example [21–23]. The Study 31/A5349 trial of a 4-month rifapentine-based regimen containing moxifloxacin had only 27 US participants but was endorsed as an alternative regimen by the CDC [24, 25]. Furthermore, studies of bedaquiline, pretomanid, and linezolid for drug-resistant TB were conducted completely overseas, but the regimen has been approved by the Food and Drug Administration and CDC [26–29]. If a regimen is effective, there should not be a threshold for how many US citizens need be included in a trial for US approval.

BRIEF-TB Only Enrolled Persons With HIV

The DHHS guidelines explicitly note that "CDC/NCTA guidelines do not include 1HP as a preferred or alternative regimen given that the BRIEF-TB study was performed largely in people with HIV…" [19]. While this is true, there is extensive experience with rifapentine and INH use in people without HIV, with no evidence of increased toxicity [24]. Ongoing trials of 1HP in HIV-negative household contacts show no evidence of safety concerns thus far and further studies are planned [30, 31]. Moreover, there are published data on the safety and efficacy of 1HP in HIV-negative children; 408 child household contacts 2–19 years old given 1HP had a 94% completion rate, with only 1 case of TBD and 1 discontinuation for "burning sensation" [32]. Therefore, we have no reason to expect that 1HP would pose additional safety concerns or be less efficacious in a non-PWH population aged 2 years or older, and it should clearly be recommended for PWH. We note, however, that the WHO recommends 1HP only for adults and adolescents older than 12 years of age.

BRIEF-TB Enrolled Individuals Without Confirmed Tuberculosis Infection

Studies in high-burden settings have documented the benefits of TPT in people with negative tuberculin skin tests (TSTs) or interferon-gamma release assays (IGRAs) [33]. BRIEF-TB enrolled participants with negative TST/IGRAs if they lived in a high-TB-prevalence area [19]. BRIEF-TB did include 693 TST/IGRA-positive individuals at enrollment. In a subanalysis, 1HP was shown to be noninferior to 9H in TST/IGRA-positive individuals for preventing the primary endpoint (1HP incidence rate of 0.90/100 person-years vs 9H incidence rate of 0.97/100 person-years), even meeting the more stringent PREVENT TB (Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection) trial noninferiority margin [13, 14]. PREVENT TB enrolled far fewer PWH than BRIEF-TB (N = 205), and thus had fewer TST/IGRA-positive PWH. Tuberculin skin tests and IGRAs have diminished sensitivity in immunocompromised PWH [34–36]; therefore, the proportions of TBI-positive individuals are likely underestimated in BRIEF-TB, especially in those with CD4+ counts of 250 cells/mm^3 or less.

There Are Drug–Drug Interactions With Rifamycin-Based Regimens and Antiretrovirals

Historically, co-administration challenges of antiretrovirals (ARVs) and rifamycins have led to a preference for INH as TPT in PWH. In recent years, US and global guidelines have shifted to recommending rifamycin-based regimens over INH because of better adherence and feasibility, and drug–drug interactions can be managed. 1HP can be safely administered with efavirenz [37], and a study in Taiwan showed that bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) in 48 PWH given with 1HP was well tolerated [38]. Although BIC trough concentrations were reduced, plasma viral load levels were maintained at less than 50 copies/mL in 72.9% and 93.5% of participants at 15 days and 29 days of 1HP, respectively, and all participants had plasma viral loads of less than 50 copies/mL at 3 and 6 months. This suggests that 1HP could potentially be a viable co-administration strategy for PWH on BIC/TAF/FTC, although further studies are needed. Furthermore, while 3HP is known to be safely co-administered with dolutegravir-based regimens [39], there is accumulating evidence that 1HP can be safely administered with twice-daily dolutegravir [40]. Of note, 1HP cannot be used with protease inhibitors and some nonnucleoside reverse transcriptase inhibitors, and the safety in pregnancy is unknown.

1HP Is More Expensive Than Other Regimens

Cost-effectiveness was noted by the authors to not be considered when drafting the CDC/NTCA latent TB infection treatment guidelines [17]. Drug prices are highly fluid, especially if there is increased use to support increased production. While the cost of both 3HP and 1HP is considerably greater than INH, price negotiations have led to substantial reductions in the cost of rifapentine, and future reductions are likely. Furthermore, several studies have found that short-course TPT regimens, including 1HP, are in fact cost-effective when considering both cost and quality-adjusted life-years gained [41–43].

In conclusion, we feel that the totality of evidence and prior precedent supports the incorporation of 1HP into US TPT

guidelines. With ongoing losses in the US TB care cascade, intermittent drug shortages, and no need for follow-up, 1HP would provide a key tool for TB prevention. It works. It is safe. It is easier to take and better adhered to than all other regimens. It is time for the United States to adopt this global strategy for TB prevention.

Notes

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