HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

AIDS. 2020 January 01; 34(1): 63–71. doi:10.1097/QAD.0000000000002380.

Adherence to tuberculosis preventive therapy measured by urine metabolite testing among people with HIV

Emily A Kendall[1,*], **Betina Durovni**[2,3], **Neil A Martinson**[4], **Solange Cavalacante**[3,5], **Katlego Masonoke**[4], **Valeria Saraceni**[3], **Limakatso Lebina**[4], **Anne Efron**[1], **Silvia Cohn**[1], **Sandy Chon**[1], **Richard E Chaisson**[1], **David W Dowdy**[6], **Jonathan E Golub**[1], **THRio and TEKO teams**

[1]Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

[2]Center for Strategic Studies, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil.

[3]Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro, Brazil.

[4]Perinatal HIV Research Unit (PHRU), South African Medical Research Council (SAMRC) Soweto Matlosana Collaborating Centre for HIV/AIDS and TB, University of Witwatersrand, Johannesburg, South Africa

[5]Evandro Chagas National Institute of Infectious Diseases - Fiocruz, Rio de Janeiro, Brazil.

[6]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Abstract

Objectives: Tuberculosis preventive therapy for people living with HIV is effective, widely recommended, and increasingly prescribed, but completion rates are less than ideal, and adherence is not typically monitored. We sought to quantify adherence to isoniazid preventive therapy using a urine metabolite assay.

Design: Two cross-sectional surveys

Setting: Rio de Janeiro, Brazil, 2008–2009; and Northwest Province, South Africa, 2018–2019

Participants: 203 Brazilian and 93 South African patients attending HIV clinics with active prescriptions for isoniazid preventive therapy

Main outcome measures: Self-reported isoniazid adherence, paired with semiquantitative measurement of urine isoniazid metabolites.

[*]Corresponding author. ekendall@jhmi.edu.

Authors' roles

EAK, NAM, DWD, JEG designed the South Africa adherence study. NAM, KM, LL, SaC implemented the South Africa adherence study. EAK, JEG provided oversight of the South Africa study.

BD, SC, VS, AE, REC, JEG designed the Brazil adherence study. BD, SC, VS, AE implemented the Brazil study. VS, JEG provided oversight of the Brazil study.

SiC managed and cleaned data for both Brazil and South Africa studies.

EAK analyzed the data from both studies and drafted the manuscript. All authors critically revised the manuscript and approved the final version to be published.

Results: By self-report, 90% of patients (95% confidence interval [CI] 86–93%) reported having taken a dose of isoniazid on the day of enrollment or the preceding day, and 91% (95% CI 87–94%) reported missing an average of one dose or fewer per week. By urine testing, only 65% (95% CI 59–70%) of all patients, and 69% (95% CI 63–74%) of those who reported having taken isoniazid on the current or preceding day, had detectable urine metabolites (expected in 95% of patients at 24 hours). Longer time since starting preventive therapy was independently associated with a negative urine test for isoniazid metabolites (adjusted prevalence ratio 1.11 per month of isoniazid, 95% CI 1.05–1.18).

Conclusions: Adherence to isoniazid preventive therapy among patients with HIV in Brazil and South Africa is inadequate, is overestimated by self-report, and declines with time on treatment. Shorter regimens for TB preventive therapy may improve adherence and completion, but adherence support for all patients may be necessary.

Keywords

Tuberculosis; preventive therapy; medication adherence; people living with HIV

Introduction

TB is the leading cause of death among people living with HIV, responsible for approximately one third of HIV-related deaths in 2017 [1]. TB preventive therapy (TPT) reduces TB incidence and all-cause mortality among ART recipients [2–4] and is widely recommended for people with HIV in high- and moderate-TB-burden countries [5]. A large expansion of TPT is among the principal goals established by the 2018 United Nations High Level Meeting on tuberculosis [6].

While gaps are recognized in the cascade of care prior to initiating TPT, some countries now report high levels of TPT coverage, including a reported 53% of people newly enrolled in HIV care in South Africa in 2017 [7]. As many as 50% of those who initiate TPT do not complete it, however [8]. Policymakers, recognizing that rising initiation rates are insufficient in isolation, have proposed TPT completion as an additional monitoring and evaluation indicator [9,10]. Low rates of completion have also been a motivation in developing shorter TPT regimens, including twelve-week, once-weekly and four-week, once-daily regimens of rifapentine and isoniazid [11,12].

Direct observation of TPT is infeasible, and TPT completion is most often assessed based on prescriptions and patient-reported adherence. However, patients to whom TPT is prescribed may over-estimate or inaccurately report their own adherence. Better estimates of patient adherence to TPT could aid in appropriately measuring TPT completion, in understanding needs for adherence education and support, and in estimating the full potential value of shorter TPT regimens. To assess patient-reported adherence, we performed cross-sectional evaluations of adherence using patient questionnaires and urine isoniazid metabolite testing among adults with HIV receiving routine isoniazid preventive therapy after periods of local TPT scale-up in Brazil and South Africa.

Methods

Patient enrollment

We recruited HIV-seropositive adults currently prescribed isoniazid as TPT in two settings: 26 HIV clinics in Rio de Janeiro, Brazil, in the years 2008–2009, and 6 HIV clinics in South Africa's North West province in 2018–2019; these enrollment windows corresponded to periods of preventive therapy scale-up in each setting, including training in preventive therapy for clinic personnel [13].

Patients recruited for enrollment were randomly selected from among the eligible patients attending each clinic for HIV care: from a register of all patient currently on IPT at each Brazilian clinic, and from a list of patients with scheduled follow-up visits on arbitrarily-selected recruitment days at the South African clinics (with age, HIV diagnosis, and lack of documented TB diagnosis first verified from the medical record). Patients were eligible if they were 18 years or older, had a current prescription for isoniazid as TPT, had not been diagnosed with active TB since initiating isoniazid, and provided a urine specimen on the day of enrollment. Recruitment was limited to patients with recently-diagnosed HIV (within the past year) in South Africa but not in Brazil.

The selected patients were approached in person during their next routine HIV clinic visit in Brazil, and in person or by phone call (with a request that they come to speak in person with the research team) on the day of their visit in South Africa, without advance notice of isoniazid adherence as the research topic. Once in-person contact was made and eligibility confirmed, participants provided informed consent to be interviewed, provide a urine sample, and have data extracted from their medical record.

Enrolled participants answered a brief questionnaire focused on recent isoniazid adherence. Patients were asked to report their recent adherence, including the date of their most recent dose. They were also asked to estimate how many of the last thirty doses they had missed (Brazil) or how many doses they missed in a typical week (South Africa), and the reasons for any missed doses. There were minor site differences in the variables included in the questionnaire: patients were asked about smoking status in Brazil, and about alcohol use, education, and employment status in South Africa. Age, sex, timing of HIV diagnosis, most recent CD4 count, ART prescription, and time since isoniazid initiation were collected at both sites. For South African patients, the times of the last isoniazid dose and of urine collection were documented to allow calculation of hours since last dose, and in Brazil, medical records were later reviewed for documentation of TPT completion.

The protocols were approved by the Johns Hopkins Medicine institutional review board and the research ethics committees of the Rio de Janeiro City Health Secretariat and the University of Witswatersrand.

Urine testing for isoniazid metabolites

Urine was provided by participants and tested on site by trained research staff immediately after completion of the questionnaire. The Isoscreen (GFC Diagnostics) point-of-care test, a colorimetric test based on the Arkansas method [14], was used according to manufacturer-

recommended methods previously validated in Brazil [15]. In the presence of isoniazid metabolites, this test causes urine to change color from yellow to green to indicate low levels detected (termed “weakly positive” in this report) or to blue-black to indicate high levels detected (“strongly positive”); urine remains yellow with no visible color change at five minutes if no isoniazid metabolites are detected (“negative”). The sensitivity of any positive result has been estimated as 95–99% at 24 hours and 85% (95% binomial confidence interval 76–91%) at 48 hours after the last dose of 300mg of isoniazid [15,16]. The sensitivity of a strongly positive result is estimated to be >99% at 12 hours [16], 68–82% at 24 hours [15,16], and 5% at 48 hours [16]. Results are negative 72 hours after the last dose in 87% (78–92%) of patients [16].

In our primary analyses, any positive urine result was considered evidence of having taken isoniazid on the day of testing or the preceding day. In a sensitivity analysis, we considered only strongly positive urine results to be consistent with a same-day dose (but accepted any positive result as evidence of a previous-day dose).

Statistical analysis

Poisson regression with robust standard errors (which can provide unbiased estimates of prevalence ratios when log-binomial models fail to converge[17]) was used to analyze risk factors for nonadherence. The primary analysis included all patients and considered nonadherence as indicated by a negative urine result as the outcome of interest. Two sensitivity analyses considered consistency between reported and measured recent adherence. (1) We modeled the prevalence of a negative urine result among only those patients who reported having taken an isoniazid dose on the day of testing or the preceding day. (2) Because patients who had taken a dose of isoniazid on the day of urine testing were expected to have a strongly-positive result (and those who reported a same-day dose but had only a weakly positive result were likely over-stating their adherence), we modeled the prevalence of over-stated adherence, as defined by either a negative result from a patient who reported a dose on the preceding day, or a negative or weakly positive result from a patient who reported taking a dose on the day of testing.

Missing data (age [n=1], time since HIV diagnosis [n=23], most recent CD4 count [n=26], and time on isoniazid [n=1]) were estimated using multiple imputation with predictive mean matching pooled across 20 imputed models.

Representations of continuous independent variables were chosen to balance robustness, interpretability, and parsimony. Age was represented categorically due to its non-monotonic relationship with the primary outcome; tertiles were used after verifying that other cutoffs or natural cubic splines did not meaningfully change results. The time since HIV diagnosis and the CD4 count each had skewed distributions and monotonic relationships with the primary outcome within and across sites; these were represented in the final models as ordinal variables corresponding to the quintiles of their distributions, after verifying that log-transformed continuous variables or categorical variables with other cutoffs produced similar results. Because time since isoniazid initiation had a more uniform distribution and a monotonic relationship to outcome (Figure 1), it was modeled as a continuous variable for maximal interpretability; we verified that log transformation or discretization as a

categorical variable did not meaningfully affect results. We also considered patient-reported adherence as a covariate. Patients were classified as reporting good adherence if they reported generally missing no more than one dose per week (South Africa), five doses out of the last 30 (Brazil), or one dose out of the past four days if data on the last thirty days were missing (N=7, Brazil). Where we limited number of included covariates based on sample size, we verified that alternative choices did not meaningfully affect results.

Covariates that were measured in only one country were not included in the primary model, but their associations with negative urine test results were estimated within single-country models with adjustment for sex, age, time on isoniazid, ART use, and reported adherence.

Significance was evaluated at alpha of 0.05, and regression coefficients are reported with 95% confidence intervals. Analyses were performed using R version 3.5.2 [18] and the 'sandwich' [19] and 'mice' [20] packages.

Results

Patient characteristics

Two hundred ninety-six patients (203 from Brazil and 93 from South Africa) were included in analyses. Ten additional eligible patients were excluded because they did not provide consent (n=3; South Africa), were unable or unwilling to provide urine (n=6; 5 in Brazil and 1 in South Africa), or had newly started isoniazid on the day of enrollment (n=1; South Africa).

Compared to patients enrolled in Brazil, South African patients were younger (median 42 years in Brazil, 34 in South Africa), more likely to be female (40% [81/203] female in Brazil, 68% [63/93] in South Africa), diagnosed with HIV more recently (median 62 months since diagnosis in Brazil versus 6 months in South Africa), more severely immunocompromised (median $CD4^+$ T-cell count 573 per mm^3 in Brazil, 165 per mm^3 in South Africa), and more likely to be on ART (67% [135/203] in Brazil prior to guidelines recommending universal ART, 100% in the more recent South African cohort) (Table 1). Isoniazid preventive therapy was typically prescribed for 6 months in Brazil and for 12 months in South Africa at the time of evaluation; the median time from isoniazid initiation to study enrollment was 3 months in Brazil and 4 months in South Africa (with 29% on isoniazid for more than 6 months). In Brazil, 28% of enrolled patients (56/203) smoked tobacco. South African participants were largely unemployed (54/92, 59%), had completed at least some secondary education (92% [86/93], with 38% [35/93] having completed grade 12 or above), and reported moderate alcohol use (53% [49/93] reporting some alcohol use, but 92% [45/49] of those averaging less than one drink per day).

Self-reported isoniazid adherence

Patient-reported isoniazid adherence was high in both populations. Although only 69% of Brazilian patients (140/203) and 50% of South African patients (46/93) reported having already taken isoniazid on the day of enrollment (with many others mentioning that they followed an evening dosing schedule and had taken a dose the night before), 90% in each setting (183/203 in Brazil, 84/93 in South Africa) reported taking a dose on the current or

prior calendar day. In addition, 93% (182/196) of Brazilian patients and 86% (80/93) of South African patients reported good adherence (missing no more than five doses in the past 30 days in Brazil, or an average of no more than one dose per week in South Africa).

Among patients who reported missed doses and provided a reason, the most common reasons in both settings were forgetting (36/100 in Brazil, 10/24 in South Africa), scheduling difficulties (13/100 in Brazil and 9/24 in South Africa), or being out of pills (21/100 in Brazil and 5/24 in South Africa, including 2 instances in each country of medication unavailability at a clinic).

In Brazil, where subsequent chart review was performed after the planned end of therapy, 79% of patients (160/203) had been documented by their clinic as completing TPT.

Urine-based adherence assessment

Overall, the isoniazid metabolite urine assay was positive for any color change in 192 (65%) patients (138/203 [68%] in Brazil, 54/93 [58%] in South Africa), including 165 (55%) with strongly-positive results (Figure 2).

For the 93 patients with known hourly timing of urine collection and self-reported last dose (documented only in South Africa), same-day doses were reported to have been taken a median of 5 hours before urine collection (with 98% taken within 12 hours), and previous-day doses were reported to have been taken a median of 18 hours before urine collection (with 100% taken within 36 hours of urine collection) -- supporting our expectation of positive urine testing results in adherent patients.

Risk factors for negative urine testing result

In univariable unadjusted analysis, nonadherence as indicated by a negative urine result was positively associated with a longer time on isoniazid (prevalence ratio [PR] 1.10, 95% CI 1.06–1.15 per additional month) and negatively associated with time since HIV diagnosis (PR=0.88, 95% CI 0.77–0.98 per quintile of time since diagnosis).

We constructed a multivariable model which included country, age, sex, time on isoniazid, reported isoniazid adherence, time since HIV diagnosis, CD4 count, and the interaction of CD4 cell count with time since HIV diagnosis (Table 2). In this model, nonadherence as indicated by a negative urine result was significantly associated with longer time on isoniazid (adjusted prevalence ratio [aPR]=1.11 per month, 95% CI 1.05–1.18). Near their median values, CD4 cell count and time since HIV diagnosis were not associated with adherence as measured by urine test, but a lower CD4 cell count was associated with lower prevalence of nonadherence among recently-diagnosed HIV patients (aPR for negative urine result = 1.42, 95% CI 0.87–2.33, per increase in CD4 count quintile within the most recently-diagnosed HIV quintile [0–6 months]), while a lower CD4 count was significantly associated with a higher prevalence of nonadherence among patients with more longstanding HIV diagnoses (aPR for negative urine result =0.67, 95% CI 0.45–0.98 per increase in CD4 count quintile for patients in the upper quintile [>7.8 years] of time since HIV diagnosis).

These effects were similar when analysis was limited to patients who reported an isoniazid dose on the current or preceding day, and when the outcome considered was a urine result unsupportive of self-reported adherence (Table 3).

Among additional variables that were collected in only one setting, neither smoking (aPR= 0.76, 95% CI 0.42–1.37) nor documented TPT completion (aPR=0.65, 95% CI 0.35–1.18) was significantly associated with nonadherence as indicated by negative urine testing in Brazil. In South Africa, employment, grade 12 completion, alcohol use, and isoniazid side effects were not independently and significantly associated with nonadherence, but grade 12 completion was associated with less nonadherence (aPR=0.57, 95% CI 0.33–0.98), and an association between alcohol use and more nonadherence (aPR=1.53, 95% CI 0.97–2.40) also approached statistical significance.

Consistency between reported and measured adherence

Of the 90% of patients (267/296) who reported taking isoniazid on either the day of or the day before urine testing, 184/267 (69%) had a positive urine result. Urine results were strongly positive in 59% (158/267) of these patients overall, and in 69% (129/186) of the 63% of patients who reported a dose on the day of urine testing (Figure 2).

Thus, among the 267 patients who reported taking a dose on the current or preceding day, urine results supported the self-reported timing of patients' most recent dose for 171 (64%) patients. Among all 296 patients in the study, 96 (32%) were estimated to have taken their last dose of isoniazid at an earlier time than was self-reported (53/203 [26%] in Brazil and 43/93 [46%] in South Africa).

As in the primary analysis, risk factors for over-reported recent isoniazid adherence compared to urine testing evidence included longer time on isoniazid (aPR=1.12 per month, 95% CI 1.05–1.18) and, among patients with longstanding HIV diagnoses, lower CD4 count (aPR=0.57 per increase in CD4 quintile, 95% CI 0.37–0.90, in the highest quintile of time since HIV diagnosis) (Table 3).

Among patients who reported that their most recent dose was at least two days prior to testing, urine tests remained positive in 2/20 (10%) Brazilian patients and 3/9 (67%) South African patients.

Discussion

Although 90% of HIV-seropositive patients reported good adherence with rare missed isoniazid doses in both Brazil and South Africa, one third of patients who were attending HIV clinics and had active prescriptions for isoniazid had no detectable isoniazid metabolites in their urine. Nonadherence as measured by urine testing increased with longer time on isoniazid. Although nonadherence is difficult to measure and therefore often omitted from cascades of care, these findings suggest that adherence to TB preventive therapy is a substantial gap among people with HIV.

Negative biological measures of adherence among patients who reported good adherence are consistent with other studies in TB and HIV prevention and emphasize the importance of

broad programs to improve TPT adherence. Among injection drug users with latent tuberculosis in the United States, over-reporting of adherence to isoniazid was reported by more than one-third of participants in a study using both urine metabolite testing and electronic bottle caps [21]. In studies of HIV pre-exposure prophylaxis (PrEP) in Africa, over half who said they were adherent had undetectable plasma drug levels [22], and reported adherence did not correlate with effect as would be expected [23]. In a study of weekly self-administered isoniazid and rifapentine as TPT, some patients in South Africa (but not at sites in the United States, Hong Kong, or Spain) claimed adherence when electronic medication event monitoring pill-bottle caps reported their bottles had not been opened. Because patients are unlikely to self-identify as not taking TPT consistently, adherence support needs to be provided regardless of self-reported adherence, although some risk factors (such as alcohol use, or under-response to long-term ART as assessed by CD4 count) may help in identifying those at highest risk. In addition, given how frequently our study participants reported missing doses due to lack of medication, attention should be paid to ensuring that pharmacies are adequately stocked and that patients are supplied with sufficient pills between visits and able to return for refills in a timely fashion.

We measured adherence at only a single time point, but our finding that nonadherence was substantial and increased over time has important implications for the selection of TPT regimens. Three-month and one-month regimens of isoniazid and rifapentine have demonstrated efficacy similar to nine months of isoniazid in the context of clinical trials where patient selection and close monitoring were likely to maximize patient adherence [11,12], and shorter regimens have been observed to improve preventive therapy completion in both clinical trial and health department settings [24,25]. If the poor adherence we observed is more common in programmatic contexts and worsens over time, shorter preventive regimens might lead to greater gains in effectiveness than seen in clinical trials. Long-acting forms of TPT that do not require daily administration (for example, monthly injections for patients receiving monthly HIV clinical care) could also be advantageous [26].

Our results also highlight questions about how to monitor the success of TPT roll-out. WHO currently collects country-level data on the “coverage” of TPT among people newly diagnosed with HIV, but actual initiation and successful completion are not assessed. In South Africa, TPT initiation was recently reported to be 53% [7], but our data suggest that completion of TPT may be substantially lower. There is also evidence that the number of patients on TPT may be overestimated [27]. Adherence is difficult to measure, and fortunately, historical data suggest that a partial or intermittent TPT course has some preventive efficacy [28]. However, as TB programs worldwide pursue the recently-established goal of providing TPT to 30 million people by 2022, it will be important to consider assessing completion as opposed to mere initiation of TPT – perhaps by monitoring prescription renewals or drug dispensation at the programmatic level, or performing surveillance of adherence at the individual level by self-report, pill count [29], or a test such as Isoscreen.

Potential limitations of our study include imperfect sensitivity of the Isoscreen urine assay. We did find that, due to daytime study enrollment, most urine was collected within 12 hours of reported same-day doses and within 24 hours of doses reportedly taken the previous day,

leading to expected >95% sensitivity for the color-change criteria we used [15,16]. Still, some patients were likely misclassified as nonadherent in our analysis based on false-negative urine results, and we could have underestimated adherence by up to 5% (although the assay's false-positive rate of 2%[15] would counteract this to some extent). If we assume 95% sensitivity for our adherence-confirmation criteria, our estimates of nonadherence change minimally, from 44% to 43% of patients. Another potential limitation of urine testing is the uncertain effect of variable isoniazid acetylation on urine metabolite excretion; however, the sensitivity of Isoscreen was not found to depend on ethnicity or NAT2 polymorphism in an earlier study [16].

There are also limitations to our study design. The patients included were a convenience sample, because to be recruited, patients had to be attending regular HIV clinic visits and had to be willing to speak with study staff. To the extent that IPT adherence is likely to be associated with HIV treatment adherence and engagement, the potential selection bias introduced by this recruitment strategy is likely to lead to under-estimation of nonadherence in the overall IPT patient population. We also combined data from studies in two different sites which were conducted at different times and measured some different variables. Our definitions of self-reported general adherence differed slightly between sites, and some other covariates were assessed only at one site and could be included only in secondary, single-country analyses. However, the urine assay used, the primary measure of self-reported adherence, and most covariates were consistent across both sites, and the consistency of our primary findings across very different settings is an important strength of the study that speaks to external validity not often evaluable in single-site studies. Another limitation is that we made only a single, cross-sectional assessment of adherence. Longitudinal assessment would provide a clearer picture of patients' adherence over time, including the extent to which the same patients were persistently nonadherent (which could allow them to be targeted for additional support if identified) and what proportion of patients had sufficient cumulative adherence to receive preventive benefits. Finally, because we were not able to review pharmacy logs or patients' prescription bottles, we are unable to assess whether other more easily-observed data, such as refill records or pill counts [30], could have helped in identifying patients with suboptimal adherence.

In summary, we observed urine metabolite evidence of >30% recent nonadherence to isoniazid preventive therapy among patients with HIV in two high-burden countries. Among patients who reported good adherence, adherence was overreported by nearly one-third. Nonadherence increased with increasing time on TPT even among patients who maintained active prescriptions and reported continued adherence, highlighting a potential under-recognized benefit of shorter preventive therapy regimens. Promotion and support of adherence have an important role in achieving the expected benefits of ongoing global scale-up of TPT for high-risk individuals including people with HIV.

Acknowledgments

This work was supported by funding from the Bill & Melinda Gates Foundation (grant number 19790.01 to the Consortium to Respond Effectively to the AIDS-Tuberculosis Epidemic) and from the US National Institutes of Health Institute of Allergy and Infectious Diseases (grant numbers K01 AI066994 to JEG, R01 AI131796 to JEG, and K08 AI127908 to EAK).

The authors also thank all members of the THRio and TEKO study teams and the participating patients for their contributions to this research.

References

1. UNAIDS. AIDSinfo http://aidsinfo.unaids.org./ (accessed 14 May 2019).
2. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med 2015; 373:808–822. [PubMed: 26193126]
3. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. The Lancet 2014; 384:682–690.
4. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé J-B, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. The Lancet Global Health 2017; 5:e1080–e1089. [PubMed: 29025631]
5. World Health Organization. Latent TB Infection: Updated and consolidated guidelines for programmatic management World Health Organization; 2019 https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/
6. United Nations General Assembly. Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis ; 2018 https://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3 (accessed 14 May 2019).
7. World Health Organization. Global tuberculosis report 2018 Geneva: World Health Organization; 2018 https://www.who.int/tb/publications/global_report/en/
8. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2016; 16:1269–1278. [PubMed: 27522233]
9. Matteelli Alberto. Monitoring and evaluating LTBI management: standard indicators and system 2016https://www.who.int/tb/areas-of-work/preventive-care/matteelli_m_and_e.pdf (accessed 14 May 2019).
10. President's Emergency Plan for AIDS Relief. PEPFAR Monitoring, Evaluation, and Reporting (MER 2.0) Indicator Reference Guide ; 2017 https://www.pepfar.gov/documents/organization/263233.pdf (accessed 26 Jun 2019).
11. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine plus isoniazid for treatment of M. tuberculosis infection in HIV co-infected persons. AIDS Published Online First: 17 3 2016. doi:10.1097/QAD.0000000000001098
12. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. New England Journal of Medicine 2019; 380:1001–1011. [PubMed: 30865794]
13. Golub JE, Cohn S, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis 2015; 60:639–645. [PubMed: 25365974]
14. Schraufnagel DE, Stoner R, Whiting E, Snukst-Torbeck G, Werhane MJ. Testing for Isoniazid: An Evaluation of the Arkansas Method. Chest 1990; 98:314–316. [PubMed: 2376164]
15. Guerra RL, Conde MB, Efron A, Loredo C, Bastos G, Chaisson RE, et al. Point-of-care Arkansas method for measuring adherence to treatment with isoniazid. Respiratory Medicine 2010; 104:754–757. [PubMed: 20202806]
16. Soobratty MR, Whitfield R, Subramaniam K, Grove G, Carver A, O'Donovan GV, et al. Point-of-care urine test for assessing adherence to isoniazid treatment for tuberculosis. Eur Respir J 2014; 43:1519–1522. [PubMed: 24435008]
17. Zou G A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004; 159:702–706. [PubMed: 15033648]

18. R Core Team. R: A Language and Environment for Statistical Computing Vienna, Austria: R Foundation for Statistical Computing; 2014 http://www.R-project.org/

19. Zeileis A Econometric Computing with HC and HAC Covariance Matrix Estimators. Journal of Statistical Software 2004; 11:1–17.

20. Buuren S van, Groothuis-Oudshoorn K mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011; 45:1–67.

21. Chaisson RE, Barnes GL, Hackman J, Watkinson L, Kimbrough L, Metha S, et al. A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. Am J Med 2001; 110:610–615. [PubMed: 11382368]

22. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. N Engl J Med 2015; 372:509–518. [PubMed: 25651245]

23. MacQueen KM, Weaver MA, van Loggerenberg F, Succop S, Majola N, Taylor D, et al. Assessing Adherence in the CAPRISA 004 Tenofovir Gel HIV Prevention Trial: Results of a Nested Case–Control Study. AIDS Behav 2014; 18:826–832. [PubMed: 24647763]

24. Pease C, Hutton B, Yazdi F, Wolfe D, Hamel C, Quach P, et al. Efficacy and completion rates of rifapentine and isoniazid (3HP) compared to other treatment regimens for latent tuberculosis infection: a systematic review with network meta-analyses. BMC Infect Dis 2017; 17:265. [PubMed: 28399802]

25. Stennis NL, Burzynski JN, Herbert C, Nilsen D, Macaraig M. Treatment for Tuberculosis Infection With 3 Months of Isoniazid and Rifapentine in New York City Health Department Clinics. Clin Infect Dis 2016; 62:53–59. [PubMed: 26338781]

26. Kaushik A, Ammerman NC, Tyagi S, Saini V, Vervoort I, Lachau-Durand S, et al. Activity of a Long-Acting Injectable Bedaquiline Formulation in a Paucibacillary Mouse Model of Latent Tuberculosis Infection. Antimicrob Agents Chemother 2019; 63. doi:10.1128/AAC.00007-19

27. Martinson NA, McLeod KE, Milovanovic M, Msandiwa R, Lebina L. Implementation of isoniazid preventive therapy for HIV-infected adults: overstatement of district reports 2014. doi:info:doi/10.5588/ijtld.13.0855

28. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis 1999; 3:847–850. [PubMed: 10524579]

29. Egere U, Sillah A, Togun T, Kandeh S, Cole F, Jallow A, et al. Isoniazid preventive treatment among child contacts of adults with smear-positive tuberculosis in The Gambia. Public Health Action 2016; 6:226–231. [PubMed: 28123958]

30. Raymond JF, Bucek A, Dolezal C, Warne P, Benson S, Abrams EJ, et al. Use of Unannounced Telephone Pill Counts to Measure Medication Adherence Among Adolescents and Young Adults Living With Perinatal HIV Infection. J Pediatr Psychol 2017; 42:1006–1015. [PubMed: 28369465]

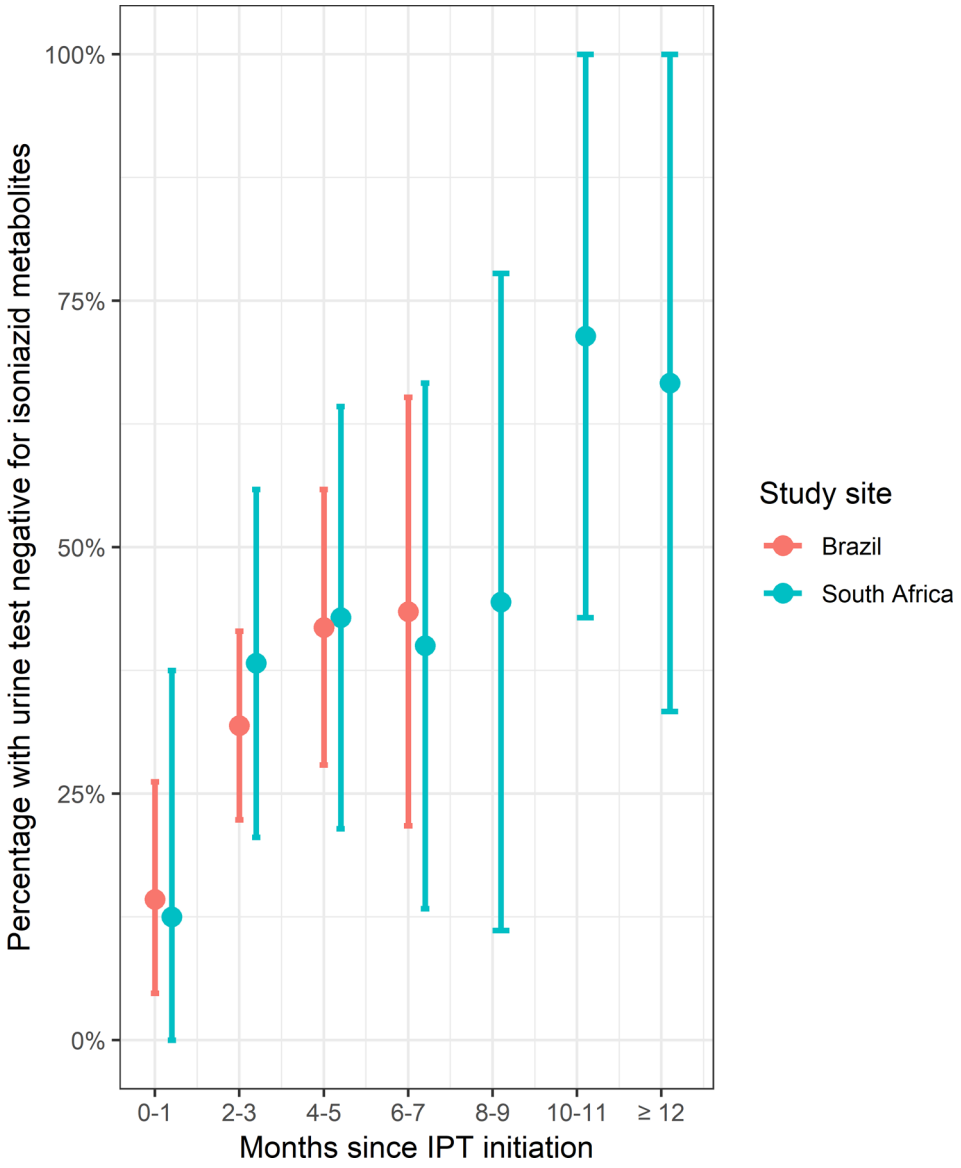

Figure 1: Relationship between time since isoniazid initiation and percent of patients with undetectable urine isoniazid metabolites.

Error bars indicate a 95% bootstrapped confidence interval.

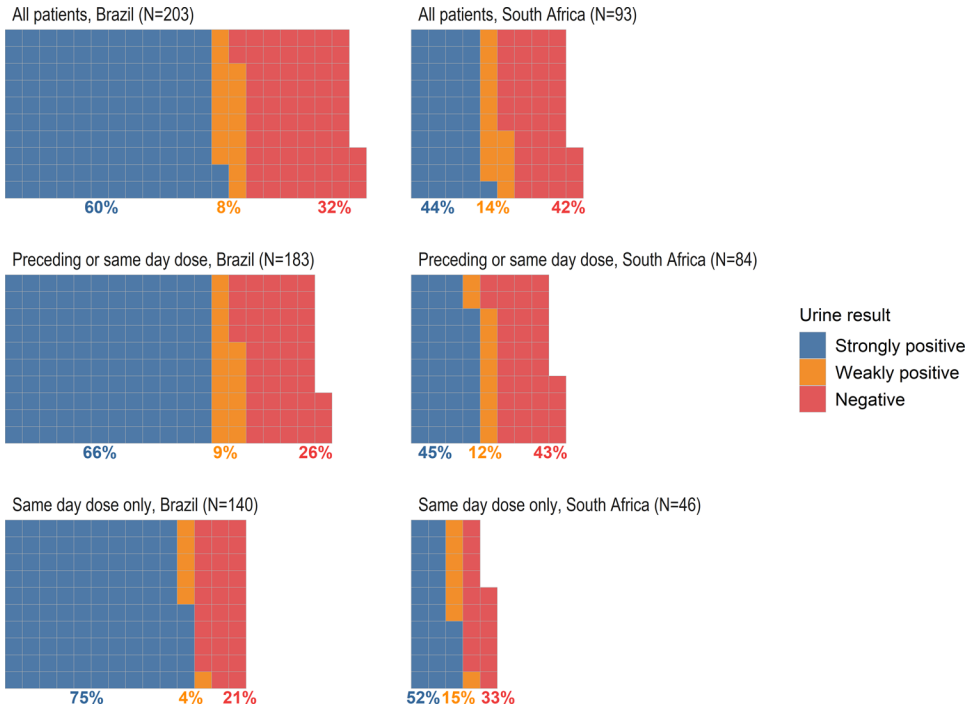

Figure 2:

Prevalence of positive and negative Isoscreen urine results, overall and among patients reporting recent and same-day isoniazid adherence

Table 1:

Patient characteristics

	Brazil (N=203)	**South Africa (N=93)**
Age in years (Median, IQR)	42 (35 – 49)	34 (28 – 45)
Female (N, %)	81 (39.9%)	63 (67.7%)
Months since HIV diagnosis (Median, IQR)	62 (27 – 103)	6 (3 – 10)
On ART (N, %)	135 (66.5%)	93 (100%)
Months on ART (Median, IQR)	48 (24 – 79)	5 (3 – 9)
Last known CD4 (Median, IQR)	573 (423 – 737)	165 (99 – 389)
Time on isoniazid**: 0–3 months (N, %)**	136 (67.3%)	42 (45.2%)
Time on isoniazid**: 4–6 months (N, %)**	65 (32.2%)	24 (25.8%)
Time on isoniazid**: >6 months (N, %)**	1 (0.5%)	27 (29%)
Smoke tobacco (N, %)	56 (27.6%)	Not measured
Use alcohol (N, %)	Not measured	49 (52.7%)
Education >= 12th grade (N, %)	Not measured	35 (37.6%)
Unemployed (N, %)	Not measured	54 (58.1%)

Table 2:

Risk factors for nonadherence as indicated by a negative urine isoniazid result (primary analysis, all 296 patients, 104 events)

Independent variable	PR, unadjusted	aPR
Country (South Africa)	1.3 (1.0, 1.8)	0.7 (0.3, 1.3)
Female sex	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)
Age: <34	1.3 (0.9, 1.9)	1.0 (0.7, 1.5)
34–45	Reference	Reference
>45	1.3 (0.9, 1.8)	1.4 (1.0, 2.0)
Months of isoniazid received (per month)	**1.1 (1.1, 1.2)**	**1.1 (1.1,1.2)**
Time since HIV diagnosis (per quintile)	**0.9 (0.8, 1.0)**	0.8 (0.7, 1.0) [1]
CD4 count (per quintile)	0.9 (0.8, 1.0)	1.0 (0.9, 1.2) [1]
Interaction of (time since HIV diagnosis) and (CD4 count) [1]		**0.9 (0.7, 1.0)**
On ART	1.2 (0.8, 1.7)	1.5 (0.9, 2.5)
Reports good general isoniazid adherence	**0.5 (0.3, 0.6)**	**0.5 (0.4, 0.7)**

Bold indicates statistical significance at P<0.05

PR = prevalence ratio, aPR = adjusted prevalence ratio (adjusted for the other variables listed)

[1]Multivariable models with interaction term included measure the effect of CD4 count at the middle quintile of time since HIV diagnosis (1–4 years), and measure the effect of time since HIV diagnosis at the middle quintile of CD4 count (400–550 cells/mm3).

Table 3:

Sensitivity analyses: consistency between reported and measured recent adherence

	Outcome: Negative urine result, among patients reporting a recent dose (267 patients, 83 events)		Outcome: Reported last dose not supported by urine result, among all patients (296 patients, 96 events)	
Independent variable	**PR, unadjusted**	**aPR**	**PR, unadjusted**	**aPR**
Country (South Africa)	**1.7 (1.2, 2.4)**	0.8 (0.3, 1.7)	**1.8 (1.3, 2.4)**	0.9 (0.4, 1.8)
Female sex	1.2 (0.9, 1.6)	0.9 (0.7, 1.4)	**1.3 (1.0, 1.7)**	1.0 (0.7, 1.4)
Age: <34	1.2 (0.8, 1.9)	1.0 (0.6, 1.6)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)
34–45	Reference	Reference	Reference	Reference
>45	1.3 (0.8, 1.9)	1.3 (0.8, 2.0)	1.2 (0.8, 1.8)	1.2 (0.9, 1.8)
Months of isoniazid received (per month)	**1.1 (1.1, 1.2)**	**1.1 (1.1, 1.2)**	**1.1 (1.1, 1.2)**	**1.1 (1.1, 1.2)**
Time since HIV diagnosis (per quintile)	**0.8 (0.7, 1.0)**	0.8 (0.7, 1.1) [1]	**0.8 (0.7, 0.9)**	0.8 (0.7, 1.1) [1]
CD4 count (per quintile)	**0.8 (0.7, 1.0)**	1.0 (0.8, 1.2) [1]	**0.8 (0.7, 0.9)**	1.0 (0.8, 1.1) [1]
Interaction of (time since HIV diagnosis) and (CD4 count) [1]		**0.8 (0.7, 1.0)**		**0.8 (0.7, 0.9)**
On ART	1.3 (0.8, 2.0)	1.5 (0.8, 2.6)	1.2 (0.8, 1.8)	1.3 (0.7, 2.3)
Reports good general isoniazid adherence	**0.5 (0.3, 0.9)**	0.6 (0.4, 1.1)	1.3 (0.7, 2.5)	1.5 (0.8, 2.9)

Bold indicates statistical significance at P<0.05

PR = prevalence ratio, aPR = adjusted prevalence ratio (adjusted for the other variables listed)

[1]Multivariable models with interaction term included measure the effect of CD4 count at the middle quintile of time since HIV diagnosis (1–4 years), and measure the effect of time since HIV diagnosis at the middle quintile of CD4 count (400–550 cells/mm3).