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Effectiveness of Double-Dose Dolutegravir in People Receiving Rifampin-based Tuberculosis Treatment: An Observational, Cohort Study of People With HIV From 6 Countries

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Background. Tenofovir-lamivudine-dolutegravir (TLD) is the preferred first-line antiretroviral therapy (ART) regimen. An additional 50-mg dose of dolutegravir (TLD+50) is required with rifampin-containing tuberculosis (TB) co-treatment. There are limited data on the effectiveness of TLD+50 in individuals with TB/human immunodeficiency virus (HIV).

Methods. We performed a prospective, observational cohort study at 12 sites in Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. Participants starting TLD and rifampin-containing TB treatment were eligible. The primary outcome was HIV-1 RNA ≤1000 copies/mL at end of TB treatment.

Results. We enrolled 91 participants with TB/HIV: 75 (82%) ART-naive participants starting TLD after a median 15 days on TB treatment, 10 (11%) ART-naive participants starting TLD and TB treatment, 5 (5%) starting TB treatment after a median 3.3 years on TLD, and 1 (1%) starting TB treatment and TLD after changing from efavirenz-lamivudine-tenofovir. Median age was 37 years, 35% were female, the median CD4 count was 120 cells/mm^3 (interquartile range, 50–295), and 87% had HIV-1 RNA >1000 copies/mL. Among 89 surviving participants, 80 were followed to TB treatment completion, including 7 who had no HIV-1 RNA result due to missed visits. The primary virologic outcome was assessed in 73 participants, 69 of whom (95%; 95% confidence interval, 89%–100%) had HIV-1 RNA ≤1000 copies/mL. No dolutegravir resistance mutations were detected among 4 participants with HIV-1 RNA >1000 copies/mL.

Conclusions. In programmatic settings, concurrent rifampin-containing TB treatment and TLD+50 was feasible, well tolerated, and achieved high viral suppression rates in a cohort of predominantly ART-naive people with TB/HIV.

Keywords. tuberculosis; HIV; antiretroviral treatment; drug–drug interactions.

The World Health Organization recommends the fixed-dose combination of tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD) as the preferred first-line regimen for adults and adolescents with human immunodeficiency virus (HIV) [1]. HIV programs have rapidly transitioned to TLD while also evaluating safety and efficacy in various populations and clinical situations [2, 3].

For people with HIV (PWH) who also have tuberculosis (TB), early initiation of TB treatment concurrent with antiretroviral therapy (ART) is recommended as the global standard of care, except in complicated cases such as TB meningitis [4]. However, a major challenge with concurrent treatment of TB and HIV is drug–drug interactions caused by rifampin, a critical drug in first-line treatment for drug-susceptible TB. Rifampin induces drug metabolizing enzymes and efflux transporters that can reduce concentrations of many antiretrovirals, including

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dolutegravir [5]. In healthy volunteers, rifampin reduced dolutegravir exposure by 56% [6]. The reduction in dolutegravir exposure can be overcome by giving an additional 50-mg dose of dolutegravir 12 hours after TLD (TLD+50), which has been shown to be safe and effective in clinical trials [7, 8].

As TLD has become the global standard of care in low- and middle-income countries with an additional 50 mg dolutegravir for all patients receiving rifampin-containing TB treatment, there is a need to evaluate its effectiveness in patients with TB/HIV in real-world settings. We conducted a prospective observational study of patients initiating TLD+50 and rifampin-containing TB treatment in routine HIV care settings to evaluate virologic success, dolutegravir resistance, and safety.

METHODS

Study Design and Participants

ACTG study A5381 (the Hakim Study) was a prospective multicohort study of the efficacy of TLD in programmatic settings. The focus of this article is on the cohort enrolled to assess therapeutic efficacy and emergence of HIV drug resistance following initiation of TLD+50 in PWH who were receiving rifampin-containing TB treatment.

Participants were recruited and followed at 12 clinical sites in 6 countries: South Africa, Malawi, Zimbabwe, Uganda, Kenya, and Haiti. Participants were adults aged ≥18 years with documented HIV-1 and receiving care at a US President's Emergency Plan For AIDS Relief (PEPFAR)-supported site. Key inclusion criteria for timing of TB treatment initiation and TLD+50 included the following: for participants already on rifampin-containing TB treatment but not on TLD at study entry, expected initiation of TLD +50 within 7 days after study entry and within 56 days after the start of rifampin-containing TB treatment; for participants not on rifampin-containing TB treatment but already on TLD at study entry, receipt of TLD for at least 6 consecutive calendar months prior to study entry and expected initiation of rifampin-containing TB treatment within 7 days after study entry; and for participants not on rifampin-containing TB treatment nor TLD at study entry, expected initiation of TLD+50 and rifampin-containing TB treatment within 7 days after study entry. Participants not already on TLD could have been ART-naive or switched from first- or second-line ART.

Participants who weighed ≤30 kg or were already taking TLD and rifampin-containing TB treatment prior to study entry were excluded.

All local ethics committees and national regulatory agencies in the respective countries approved the study. All participants provided written informed consent.

Study Procedures

A5381 was an observational study, and no treatment was provided through the study. TLD was provided as a fixed-dose combination single tablet taken once daily with an additional daily dose of 50 mg dolutegravir 12 hours later during rifampin-containing TB treatment. Participants received standard TB therapy as prescribed by the routine program clinical services (daily weight-based, oral, 6-month regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months). TB treatment was by directly observed therapy or per national TB program guidance. Any changes in dosing or duration of TB treatment were determined by the local TB clinic.

Enrollment occurred between November 2019 and June 2021 but was paused from March 2020 to July 2020 because of the coronavirus disease 2019 (COVID-19) pandemic. Although study visits and data collection were permitted to be done remotely based on site and/or participant preference, no participants had remote collection during this period.

Participants had visits at study entry and end of TB treatment, which included measurement of plasma HIV-1 RNA. There was longer-term follow-up after the end of TB treatment (on standard daily TLD), but data from that follow-up are not included here except when participants had missing information at the end of TB treatment. For participants with virologic failure (defined as HIV-1 RNA >1000 copies/mL) at the end of TB treatment, genotypic resistance testing was performed on a plasma sample obtained at the end of TB treatment and on a sample obtained at study entry if the participant also had HIV-1 RNA >1000 copies/mL at that time (for those with HIV-1 RNA ≤1000 copies/mL at entry, no resistance testing was performed on the entry sample, and any mutations identified during follow-up were considered to be new). Genotypic resistance testing was performed in College of American Pathologists (CAP)-accredited specialty laboratories (Bio analytical research corporation-South Africa and Lancet Laboratories and Pittsburg Clinical Trials Unit (CTU) Laboratories). Drug-resistance mutations were identified using the Stanford Algorithm (version 8.8). Dried blood spot (DBS) samples for tenofovir (TFV)-DP were collected at the time of virologic failure confirmation to perform intracellular tenofovir-diphosphate (TFV-DP) concentration measurements.

Adverse events (AEs) were defined and graded according to standard criteria [9].

Outcomes

The primary outcomes were suppression of HIV-1 RNA to ≤1000 copies/mL at the end of TB treatment and, for participants with HIV-1 RNA >1000 copies/mL at the end of TB treatment visit, new dolutegravir resistance mutations detected at that visit that were not present at study entry (ie, at the start of concurrent TLD+50 and rifampin-containing TB treatment). Secondary outcomes included suppression of plasma HIV-1 RNA to ≤200 and <50 copies/mL at the end of TB treatment, toxicities leading to discontinuation of the TLD regimen,

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and AEs relevant to TLD. TB treatment outcomes and medication adherence were not measured.

Statistical Analyses

A sample size of approximately 90 participants with TB/HIV was chosen to provide good precision in estimating the proportion with HIV-1 RNA ≤1000 copies/mL at the end of TB treatment. For example, with 90 participants, the width of a 95% confidence interval (CI) would be approximately ±7.4% if the success rate was 85% and would be ±10.4% if the success rate was 50%.

Analysis of the primary outcome was performed among participants who were still on TLD+50 at the end of TB treatment. The proportion of participants with HIV-1 RNA ≤1000 copies/mL at the end of TB treatment was estimated together with the associated 2-sided exact 95% CI. We also estimated the proportion of participants with new dolutegravir resistance mutations among those on TLD at the end of TB treatment, together with the associated 2-sided exact 95% CI based on the binomial distribution. For this outcome, an exact CI was planned since the proportion experiencing virologic failure with new dolutegravir resistance mutations was expected to be low.

Analyses were performed using SAS version 9.4.

RESULTS

From November 2019 to June 2021, 94 participants with TB/HIV were enrolled. Three participants who did not start TLD were excluded from this analysis (Figure 1). The baseline characteristics of the participants are shown in Table 1. Of the 91 participants who started TLD+50 and rifampin-containing TB treatment, 32 (35%) were female and the median age was 37 years (interquartile range [IQR], 32–43 years). At start of treatment, median HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (IQR, 4.1–5.6 $\log_{10}$ copies/mL) and median CD4+ cell count was 120 cells/mm^3 (IQR, 50–295 cells/mm^3). Of the 91 participants, 75 (82%) were ART-naive and had been on TB treatment for a median of 15 days (IQR, 13–17 days) prior to starting TLD+50, 10 (11%) were ART-naive and started TLD+50 and rifampin-containing TB treatment together, and 6 (7%) had been on ART for a median of 3.1 years (IQR, 2.7–3.8 years) when they started concomitant TLD+50 and rifampin-containing TB treatment. Among the 6 participants already on ART when they started TB treatment, 5 were already taking TLD and 1 switched from efavirenz-lamivudine-tenofovir.

Follow-up Achieved, Treatment Status, and Treatment-Limiting AEs

Eight (9%) of the 91 participants were lost to follow-up with no contact after the study entry visit. One other participant withdrew 24 weeks after study entry, prior to having a study visit at the end of TB treatment. Two participants (2%) died while on TLD+50 and TB treatment: 1 from disseminated TB 4 weeks after study entry and 1 from suspected COVID-19 infection 12 weeks after study entry. Therefore, 80 participants had follow-up through to planned end of TB treatment. Concurrent TLD+50 and TB treatment lasted for a median of 23.9 weeks (IQR, 22.0–25.9 weeks).

One participant had a change in their TB treatment regimen due to a grade 3 AE (drug-induced liver injury). The participant was only off TB treatment for 2 days and only off all treatment for 1 week. This participant had a viral load of <40 copies/mL at the end of TB treatment. Another participant interrupted both TLD+50 and TB treatment due to jaundice at study week 19. This participant resumed TB treatment at week 34 for 6 weeks and resumed TLD treatment 3 weeks later. The participant was not evaluated for HIV-1 RNA until 48 weeks after study entry, at which time it was <40 copies/mL.

Primary Outcomes

Among the 80 participants who survived and remained in follow-up to the end of TB treatment, 73 had an available HIV-1 RNA result at that time and were included in the analysis of the primary outcome (Figure 1). For the other 7, there was contact with the participant after the end of TB treatment but no study visit to measure HIV-1 RNA within the study defined window. The end of TB treatment study visit generally occurred soon after the end of rifampin-containing TB treatment (median: 5 days; quartiles: 2, 16 days). The last day of the additional 50 mg of dolutegravir was typically before but very close to the study visit (median: 3 days before; quartiles: 1 to 13 days before). Of the 73 participants, 69 (95%) had HIV-1 RNA ≤1000 copies/mL (exact 95% CI: 87%–98%; Figure 2). No sex-specific difference in viral suppression was observed (96% for females versus 94% for males). Of the 7 participants in follow-up at the end of TB treatment who had no study visit at that time, 4 had subsequent follow-up with HIV-1 RNA measurement (all were on TLD at that time); 3 of the 4 had values <40 copies/mL and 1 had a value of 1352 copies/mL.

We explored viral suppression using lower thresholds (Figure 2). The proportion with HIV-1 RNA ≤200 copies/mL at end of TB treatment was 93% (n = 68 of 73; exact 95% CI: 85%–98%); the proportion with HIV-1 RNA <50 copies/mL was 88% (n = 64 of 73; exact 95% CI: 78%–94%).

All 4 participants with HIV-1 RNA >1000 copies/mL at end of TB treatment were ART-naive at start of TLD and had HIV-1 RNA >1000 copies/mL at study entry. HIV-1 RNA levels at end of TB treatment for these 4 participants ranged from 83 139 to 158 428 copies/mL. All 4 had TFV-DP concentrations on DBS samples that were low (range: below limit of detection to 405 fmol/sample), suggesting poor adherence or improper timing of doses. None of these 4 participants developed new dolutegravir resistance mutations (also, none had dolutegravir resistance mutations identified in the baseline sample). There were also no nucleoside reverse transcriptase inhibitor (NRTI) mutations identified at end of TB treatment (or at study entry) for these 4 participants.

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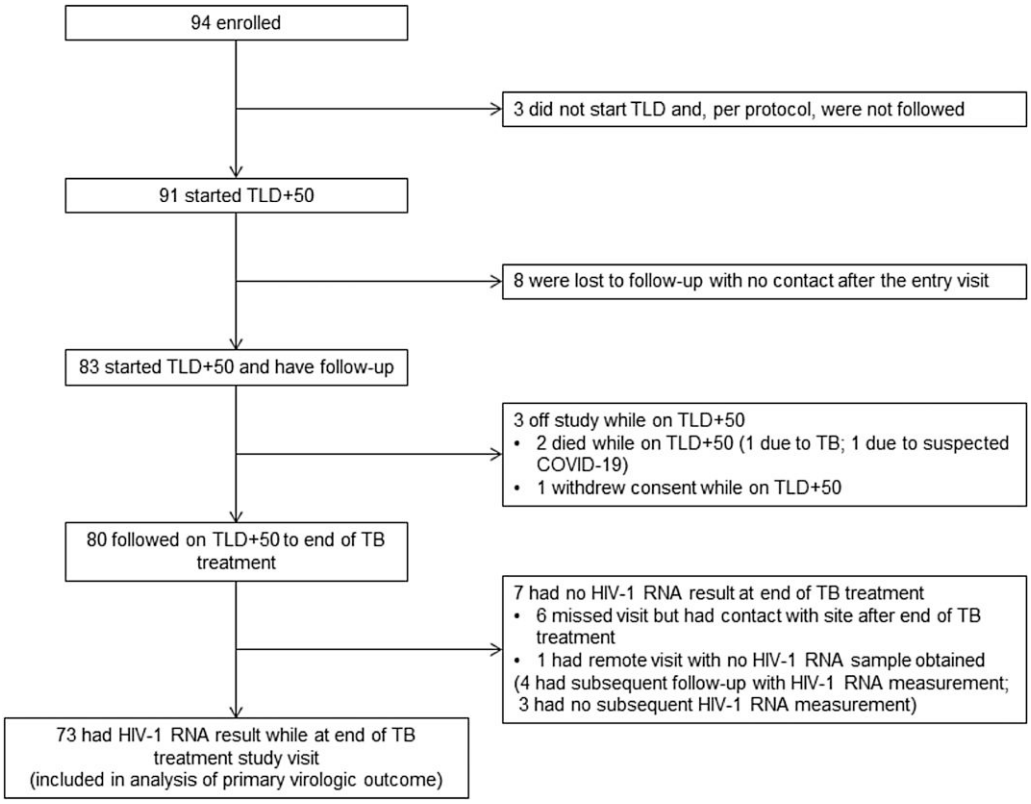

Figure 1. Strengthening Reporting of Observational Studies in Epidemiology (STROBE) diagram of participant enrollment and study cohort. Abbreviations: COVID-19, coronavirus disease 2019; HIV-1, human immunodeficiency virus type 1; TB, tuberculosis; TLD, tenofovir-lamivudine-dolutegravir.

DISCUSSION

As ART continues to evolve with newer regimens offering substantial benefits, identifying safe and effective ways to deliver concurrent TB treatment remains a global priority. In this multicountry study, we found high rates of virologic suppression among patients with TB/HIV co-infection receiving TLD with an extra 50 mg dolutegravir given 12 hours later. Co-treatment with TLD+50 and rifampin-containing TB treatment was well tolerated, and there were no treatment-emergent resistance mutations among the participants with virologic failure. These findings support the feasibility, safety, and effectiveness of the currently recommended treatment of HIV/TB co-infection using TLD+50 in routine programmatic settings.

The majority of patients in our study were ART-naive (93%), and nearly half of the study population had a baseline viral load >100 000 copies/mL. Despite the challenging dual management of TB and HIV, 95% of patients achieved viral suppression to ≤1000 copies/mL, and 88% achieved ≤50 copies/mL, similar to rates observed in clinical trials [7, 8]. These viral suppression rates are comparable to those observed for PWH who do not have TB, further evidence that TLD+50 while on TB treatment does not impact outcomes. Data from HIV/TB patients in programmatic settings are limited. In a survey of 86 HIV clinics in sub-Saharan Africa that provided dolutegravir and rifampin-containing TB treatment, more than 90% of sites providing dolutegravir reported using twice-daily dosing and more than 95% reported an adequate supply of 50-mg dolutegravir tablets [10]. Using routine clinical data obtained from health records, the same study reported viral suppression among patients receiving dolutegravir was high (91%) and similar for those who received efavirenz during TB treatment. Our findings are consistent with these data and offer a more robust assessment of viral suppression, resistance, and safety.

Suboptimal dosing of dolutegravir can increase the risk for virologic failure and emergence of HIV drug resistance due to low plasma trough concentrations. The data to support once-daily dosing of dolutegravir with rifampin are currently limited to a small, noncomparative, single-site phase 2b study that excluded people with a baseline CD4 count <100 cells/mm^3 and a single-site, retrospective observational cohort study that used registry data on TB and HIV [8, 11]. Virologic suppression in these studies ranged from 83% to 95%. While compelling, additional data from larger cohort studies designed to evaluate once-daily versus twice-daily dosing of dolutegravir during co-treatment for TB are needed to inform clinical practice and treatment guidelines, and such studies are underway.

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Table 1. Baseline Characteristics of Participants in the Overall Study Population (N = 91) and in the Subpopulation With Human Immunodeficiency Virus Type 1 RNA Measurements at the End of Concomitant Rifampin/Tenofovir-Lamivudine-Dolutegravir Plus 50-mg Dose of Dolutegravir Treatment Included in the Primary Analysis (N = 73)

Characteristic	Total (N = 91)	Subpopulation for Primary Analysis (N = 73)
Demographics		
Sex: Female	32 (35%)	25 (34%)
Gender: Cisgender	91 (100%)	73 (100%)
Age, median (IQR), y	37 (32–43)	37 (32–43)
18–19	1 (1%)	1 (1%)
20–29	13 (14%)	11 (15%)
30–39	47 (52%)	38 (52%)
40–49	23 (25%)	18 (25%)
50–59	5 (5%)	4 (5%)
≥60	2 (2%)	1 (1%)
Race: Black	91 (100%)	73 (100%)
Country		
Haiti	5 (5%)	5 (7%)
Kenya	15 (16%)	9 (12%)
Malawi	38 (42%)	36 (49%)
South Africa	24 (26%)	16 (22%)
Uganda	1 (1%)	1 (1%)
Zimbabwe	8 (9%)	6 (8%)
Body mass index, median (IQR), kg/m^2	19.8 (18.0–22.5)	20.2 (18.2–22.9)
Underweight (<18.5)	31 (34%)	22 (30%)
Normal (18.5 to <25)	48 (53%)	40 (55%)
Overweight (25 to <30)	10 (11%)	9 (12%)
Obese (≥30)	2 (2%)	2 (3%)
HIV characteristics		
HIV-1 RNA, median (IQR), log_{10} copies/mL	4.9 (4.1–5.6)	4.9 (4.1–5.6)
<50 copies/mL	9 (10%)	7 (10%)
201–1000 copies/mL	3 (3%)	3 (4%)
1001–10 000 copies/mL	8 (9%)	6 (8%)
10 001–100 000 copies/mL	27 (30%)	21 (29%)
>100 000 copies/mL	44 (48%)	36 (49%)
CD4 count, median (IQR), $cells/mm^3$	120 (50–295)	150 (47–302)
HIV/TB treatment characteristics		
ART/TB treatment at screening		
On RIF-containing TB treatment but not on ART	75 (82%)	60 (82%)
Not on RIF-containing TB treatment or ART	10 (11%)	8 (11%)
Not on RIF-containing TB treatment but on TLD	5 (5%)	4 (5%)
Not on RIF-containing TB treatment or TLD but on RT)	1 (1%)	1 (1%)

For participants already on ART at start of TLD/TB treatment, years on ART was calculated as time from start of ART to start of concomitant TLD and RIF-containing TB treatment. None of the 6 already on ART had gaps in ART reported, and HIV-1 RNA was <50 copies/mL for 5 of the 6. For the remaining 85 participants not already on ART, the median HIV-1 RNA was 5.0 log_{10} copies/mL (Q1, Q3: 4.3, 5.7).

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; RIF, rifampin; TB, tuberculosis; TLD, tenofovir-lamivudine-dolutegravir.

A critical question remains as to whether a phase 3 study that is powered to compare once-daily versus twice-daily dolutegravir dosing is needed to guide policy [12]. Experience from the phase 3 trial of raltegravir that was designed to answer a similar question about dosing during TB treatment (Reflate TB 2) provides a cautionary tale of unexpected conflicting results between phase 2 and phase 3 studies. Standard-dose raltegravir failed to meet noninferiority criteria compared with efavirenz, despite showing similar results to twice-daily raltegravir in the phase 2 study. Dolutegravir is more potent and has a higher genetic barrier to resistance than raltegravir. However, the current data are insufficient to support once-daily dosing. Instead, this may provide impetus to undertake a prospective phase 3 trial that includes people with lower CD4 cell counts.

A major strength of our study is the enrollment and follow-up in routine HIV care clinics, which increases the generalizability of our findings. Nonetheless, our findings are subject to limitations. The majority of the study was conducted during the height of the COVID-19 pandemic and severe health service disruptions. Despite this, patients and facilities did extremely well with the TLD+50 regimen, suggesting that concurrent TLD and TB treatment under routine clinical conditions is feasible and that even better viral suppression is achievable as conditions normalize. We did not measure

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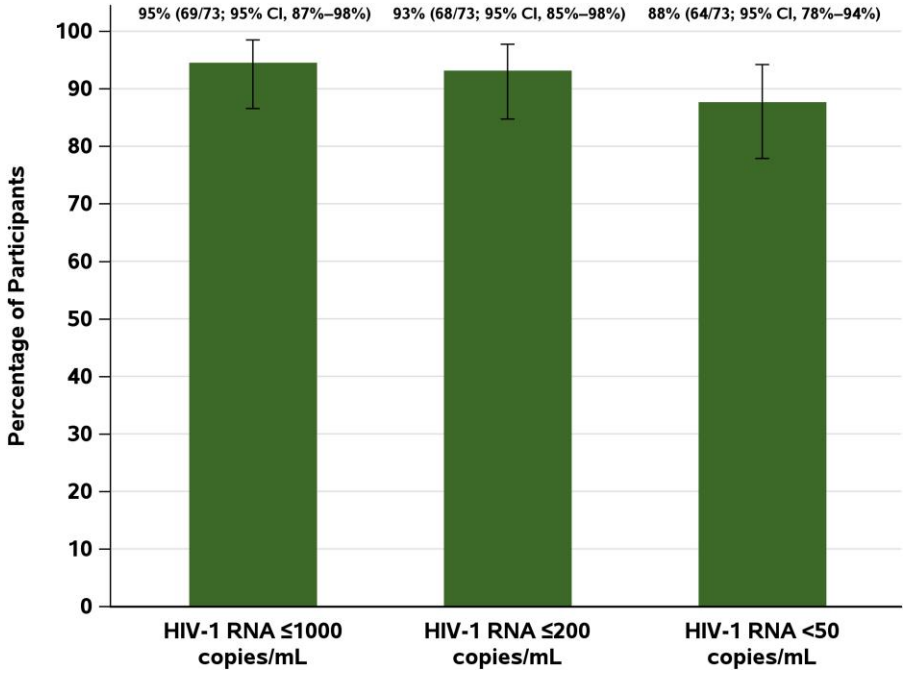

Figure 2. HIV-1 RNA at end of tuberculosis treatment among those with viral load measured within window (N = 73). Vertical bars represent exact 95% CIs. Abbreviations: CI, confidence interval; HIV-1, human immunodeficiency virus type 1. Tenofovir-lamivudine-dolutegravir (TLD) is the preferred first-line antiretroviral therapy (ART) regimen. An additional 50-mg dose of dolutegravir.

dolutegravir drug concentrations to assess whether patients took the additional 50 mg dose. HIV-1 RNA measurements were missing for 18 patients (19.8%), largely due to losses to follow-up and missed visits at the end of TB treatment, potentially reflecting the challenges of research during the COVID-19 pandemic. Globally, the number of deaths from TB increased during the COVID-19 pandemic, largely due to health system disruptions; however, this observed rate of loss to follow-up was higher than expected. Overall, the proportion of participants suppressed to ≤1000 copies/mL was very high (95%), and based on the lower bound of the 95% confidence rate, we can reasonably rule out a true rate below 87%. There were no participants who had new dolutegravir resistance mutations. Last, our study was conducted at PEPFAR-supported sites with steady access to the additional 50-mg dolutegravir dose and may not be generalizable to sites where drug supply is inconsistent.

In conclusion, we found a high rate of virologic suppression and no treatment-emergent dolutegravir resistance among TB/HIV patients receiving an extra 50 mg dolutegravir with TLD and rifampin-containing TB treatment in routine clinical settings. These findings, from a period of severe health service and societal disruptions due to the COVID-19 pandemic, suggest this regimen is highly feasible for patients and facilities. Until further phase 3 studies demonstrate noninferiority of once-daily dolutegravir during TB treatment, our study supports the use of TLD+50 as a safe, effective, feasible regimen in programmatic settings.

Notes

Author Contributions. N. S. S., C. K., M. D. H., C. M., C. L. W., M. C. H., D. L., M. N., M. R., R. D., Y. J., F. S., R. M., P. G. M., E. W., C. G., Y. C. M., J. W. M., C. F., and G. M. designed, carried out, and supervised study implementation, analysis, and interpretation. All authors reviewed and provided critical feedback on the manuscript.

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