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Viral suppression among adults with HIV receiving routine dolutegravir-based antiretroviral therapy and 3HP

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Abstract

Objective: We aimed to evaluate safety of 3 months weekly isoniazid-rifapentine (3HP) for tuberculosis (TB) prevention when co-administered with dolutegravir-based antiretroviral therapy (TLD), and compare viral suppression among those initiating TLD+3HP vs. TLD alone.

Design/Methods: We analyzed data from an ongoing Phase 3 randomized trial comparing TB screening strategies among adults with CD4≤350 cells/μL initiating routine antiretroviral therapy (ART) in Kampala, Uganda. TB screen-negative participants without contraindications are referred for self-administered 3HP. HIV viral load is routinely measured at six- and twelve-months. Here, we included TB-negative participants who initiated TLD with or without 3HP. We determined the number who discontinued 3HP due to drug toxicity. In addition, we assessed viral suppression

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

at 6- and 12-months and used log-binomial regression to assess risk of viremia at 6-months for participants who initiated TLD+3HP vs. TLD alone.

Results: Of 453 participants initiating TLD (287 [63.4%] female, median age 30 years [IQR 25-37], median pre-ART CD4 count 188 cells/μL [IQR 86-271]), 163 (36.0%) initiated 3HP. Of these, 154 (94.5%) completed 3HP and one (0.6%) had treatment permanently discontinued due to a possible 3HP-related adverse event. At 6-months, for participants who received TLD+3HP, risk of viremia >50 copies/mL was 1.51 (95% CI 1.07-2.14) times that of participants who received TLD alone. There was no difference in viral suppression between those who received TLD+3HP vs. TLD alone at 12-months.

Conclusions: Co-administration of TLD+3HP was well-tolerated. However, those who received TLD+3HP were less likely to achieve viral suppression within six-months compared to those who received TLD alone.

Keywords

rifapentine; dolutegravir; drug interactions; viral suppression

BACKGROUND

Tuberculosis preventive therapy (TPT) significantly reduces tuberculosis (TB) incidence and mortality among people with HIV (PWH), however global implementation of the established TPT regimen (6-9 months daily isoniazid) has been poor and effectiveness hampered by low completion rates [1–4]. Novel short course rifamycin-based TPT regimens such as 3HP (3 months weekly isoniazid-rifapentine) are equally efficacious as traditional TPT but have lower rates of serious adverse events and higher completion rates [5–7]. In 2018, the World Health Organization (WHO) recommended both 3HP for TPT [8] and dolutegravir (DTG)-based treatment as the preferred first-line antiretroviral therapy (ART) regimen for PWH [9]. DTG and 3HP have since been scaled-up in several high burden settings [10,11].

Potential drug-drug interactions between rifapentine and DTG present a concern given the concurrent expansion of DTG-based ART and 3HP [12,13]. The phase 1/2 DOLPHIN trial showed that rifapentine, when administered as part of 3HP, decreased DTG concentrations in PWH with undetectable HIV viral loads (VL). Nevertheless, DTG concentrations remained sufficiently high to maintain HIV viral suppression throughout co-treatment [13]. However, data on safety and viral suppression among ART-naïve PWH initiating both DTG-based ART and 3HP in routine care are lacking. We therefore aimed to assess safety and tolerability of DTG-based ART co-administered with 3HP, and HIV viral suppression among adults initiating DTG-based ART with or without 3HP, in routine care.

METHODS

Study design and participants

We performed an analysis of participants enrolled in an ongoing phase 3 individual randomized controlled trial comparing two TB screening strategies among ART-naïve outpatient adults presenting to four HIV clinics in Kampala, Uganda (NCT04557176) [14].

On November 16, 2020, we began enrolling ART-naïve adults with CD4 counts ≤350 cells/μL, excluding patients who had recently taken any anti-TB drugs (including as TPT). All participants provide written informed consent. The trial was approved by the institutional review boards of the University of California San Francisco, Makerere University, and the Ugandan National Council for Science and Technology.

Study procedures

At enrollment, participants were randomized to receive pre-ART TB screening via point-of-care C-reactive protein (POC-CRP, intervention arm) or the WHO four-part symptom screen (control arm). Those who screened positive for TB by their randomization assignment (either POC-CRP ≥8 mg/L; or presence of cough, fever, night sweats or weight loss) underwent intensified case finding via urine LAM ± sputum Xpert Ultra MTB/RIF. Participants who screened negative for TB by their randomization assignment were assessed for 3HP eligibility [14]; eligible participants initiated 3HP two weeks after ART initiation. 3HP was dispensed as self-administered fixed-dose combination tablets, with doses 1, 6, and 11 administered via directly observed therapy during in-person visits following checklist-based side effect monitoring and active TB screening. Demographic and clinical data were collected at enrollment and follow-up (every 6 months for 2 years) using standardized forms. At every visit, trained study staff extracted relevant clinical data from participants' charts including current ART regimen and HIV VL test results (routinely measured at 6 and 12 months).

Statistical analysis

For this analysis, we included participants enrolled from November 2020-December 2021 who initiated TDF/3TC/DTG (TLD) [15]. We excluded participants diagnosed with TB at baseline and participants receiving 3HP but missing side effects or adherence monitoring. We compared characteristics of participants who initiated TLD+3HP vs. TLD alone using Chi-squared or Wilcoxon rank-sum tests.

To assess safety of TLD+3HP, we measured the type and frequency of 3HP side effects, the proportion who completed 3HP (defined as completing at least 11 of 12 doses within 16 weeks), and the proportion who discontinued 3HP due to drug toxicity.

For our analysis of viral suppression, we excluded participants diagnosed with active TB before their follow-up VL measurement. We used Chi-squared or Fisher's exact tests to compare viral suppression (≤50 and ≤200 copies/mL) at 6- and 12-months, and Wilcoxon rank-sum tests to compare median 6-month and 12-month VL among participants who received TLD+3HP vs. TLD alone. We performed unadjusted and adjusted log-binomial regression analyses to compare risk of 6-month viremia (>50 copies/mL) between participants who received TLD+3HP vs. TLD alone. All analyses used data aggregated across study arms, to maintain the integrity of the ongoing trial.

RESULTS

We enrolled 623 participants, of whom 561 (90.0%) initiated TLD. We excluded 103 (18.4%) with active TB diagnosed at baseline and 5 (0.9%) who initiated 3HP without

documented side effect/adherence assessment. Of 453 participants included, 287 (63.4%) were female, median age was 30 years (IQR 25-37), median pre-ART CD4 count was 188 cells/μL (IQR 86-271), and median body mass index (BMI) was 22.7 kg/m^2 (IQR 20.7-25.1, Table 1). Overall, 409 (90.3%) initiated TLD within one day. One-hundred-sixty-three (36.0%) initiated 3HP, after a median of 14 days (IQR 14-15). Participants who received TLD+3HP had higher CD4 counts (p<0.01) and BMI (p=0.02) than those who received TLD alone.

3HP completion and safety

Of 163 participants who initiated TLD+3HP, 154 (94.5%) completed 3HP. Of the nine who did not complete 3HP, only one (0.6%) had treatment permanently discontinued due to a possible 3HP-related adverse event (rash after 10 doses). Suspected side effects that did not result in treatment discontinuation occurred in 32 (19.6%) participants (Supplementary Table). Three (1.8%) participants had treatment discontinued due to presumptive TB diagnosis, one (0.6%) stopped therapy after becoming pregnant, and four (2.5%) self-discontinued therapy.

Viral suppression

We excluded 16 (3.5%) participants diagnosed with active TB before 6-month VL was measured (3/163 [1.8%] who received TLD+3HP and 13/289 [4.5%] who received TLD alone) and 93 (20.5%) with missing (n=71) or indeterminate (n=22) VL results. Of the remaining 344 participants with 6-month VL results, 136 (39.5%) received TLD+3HP and 208 (60.5%) received TLD alone. Compared to those who received TLD alone, a lower proportion who received TLD+3HP achieved viral suppression at ≤50 copies/mL (77.4% vs. 66.9%, p=0.03) and ≤200 copies/mL (93.3% vs. 89.0%, p=0.16, Table 1). For participants who received TLD+3HP, the risk of viremia >50 copies/mL was 1.51 (95% CI 1.07-2.14) times that of participants who received TLD alone, after adjusting for sex, age, pre-ART CD4 count, and BMI (Table 2).

Of 198/437 (45.3%) participants with 12-month VL results, none of whom were diagnosed with active TB, 61 (30.8%) received TLD+3HP and 137 (69.2%) received TLD alone. There was no difference in viral suppression at ≤50 copies/mL (75.4% vs. 81.0%, p=0.37) or ≤200 copies/mL (93.4% vs. 93.4%, p=1.00) between those who received TLD+3HP vs. TLD alone.

DISCUSSION

In this ongoing pragmatic trial comparing TB screening strategies among ART-naïve PWH, we found that 3HP co-administered with DTG-based ART was safe and well tolerated, with <1% discontinuing 3HP due to a possible adverse event and >95% completing treatment. However, participants who received TLD+3HP were less likely to be virally suppressed at ≤50 copies/mL by 6-months than participants who received TLD alone, despite having higher median pre-ART CD4 counts. Our finding of lower viral suppression at VL ≤50 at 6 months emphasize the importance of further studies to assess the impact of 3HP on early efficacy in treatment-naïve persons initiating DTG based ART.

Despite WHO recommendations supporting the global scale-up of 3HP and DTG, there have been some safety concerns stemming from a small study of 3HP and DTG conducted among HIV-negative healthy volunteers that was stopped early after two of four participants experienced adverse events [12]. Our results differ from this study and are consistent with subsequent studies demonstrating the safety of 3HP co-administered with DTG-based ART among PWH [13,16]. As these latter studies were conducted among treatment-experienced PWH with high CD4 counts (median >683 cells/uL), our trial extends their findings by demonstrating the safety and tolerability of 3HP among ART-naïve PWH with low CD4 counts (median 188 cells/μL) initiating DTG-based ART, thus supporting its continued global scale-up.

Our trial found that those receiving co-treatment with 3HP+TLD had a lower risk of viral suppression at ≤50 copies/mL at 6-months compared to those receiving TLD alone, despite having higher median pre-ART CD4 counts. Although rifamycins are known to be potent inducers of enzymes involved in DTG metabolism, differences in 6-month VL (approximately 3 months after 3HP completion) were unexpected and raise the possibility of potential acquired DTG or NNRTI resistance. However, given we did not see differences in the proportion of PWH achieving viral suppression at ≤200 copies/mL and differences in the proportion achieving viral suppression at ≤50 copies/mL waned by 12 months, this may be less likely. Notably, gender-based differences in ART adherence may have contributed to differences in viral suppression. In our trial, the proportion of men receiving 3HP+TLD was substantially higher than the proportion of men receiving TLD alone; poorer ART adherence among men may have contributed to differences in 6-month VL. Indeed, our multivariable analyses found that women had an approximately 20% lower risk of viremia >50 copies/mL at 6-months compared to men, though the finding was not statistically significant. Overall, our results suggest the need for pharmacokinetic studies to evaluate this combination therapy among PWH initiating ART.

The primary limitations of our study are the lack of VL measurements prior to ART initiation and during prescribed 3HP, and that approximately 20% of TB-negative participants did not have a 6-month VL available. TB SCRIPT is a pragmatic trial with VL assessments performed as part of routine care; as such, the proportion with missing VL is higher than optimal. Importantly, characteristics of participants with and without 6-month VL were similar. An additional limitation is that neither 3HP nor DTG drug levels were measured. Despite these limitations, our findings represent the first published data on viral suppression among PWH receiving TLD+3HP in routine care, with important insights for TB and HIV programmes scaling-up 3HP and DTG-based ART.

In conclusion, we found that TLD+3HP was safe and well-tolerated among ART-naïve PWH, but that a higher proportion of participants who received TLD+3HP remained viremic at >50 copies/mL at six months compared to those who received TLD alone. Additional research to assess the clinical impact of drug-drug interactions between rifapentine and DTG will be important for the ongoing scale-up of both DTG-based ART and rifapentine-based TPT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author roles:

CY, FCS, DWD, and PPJP designed the study. FCS, FN, and BO oversaw the local collection of data. FN was responsible for obtaining clinical measurements and data collection. LHC and CY analyzed and interpreted the data. LHC and CY drafted the manuscript. All authors reviewed and approved the final manuscript.

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Conflicts of Interest and Source of Funding:

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REFERENCES

1. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. Int J Tuberc Lung Dis 2003; 7:S384–390. [PubMed: 14677827]
2. Horsburgh CRJ, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest 2010; 137:401–409. [PubMed: 19793865]
3. Melgar M, Nichols C, Cavanaugh JS, Kirking HL, Surie D, Date A, et al. Tuberculosis Preventive Treatment Scale-Up Among Antiretroviral Therapy Patients - 16 Countries Supported by the U.S. President's Emergency Plan for AIDS Relief, 2017-2019. MMWR Morb Mortal Wkly Rep 2020; 69:329–334. [PubMed: 32214084]
4. 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]
5. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011; 365:11–20. [PubMed: 21732833]
6. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365:2155–2166. [PubMed: 22150035]
7. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS 2016; 30:1607–1615. [PubMed: 27243774]
8. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva, Switzerland: World Health Organization; 2018.
9. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. Geneva, Switzerland: ; 2018.
10. Harris EL, Blumer K, Perez Casas C, Ferris D, Amole C, Doherty M, et al. Accelerating access and scale-up of optimized antiretroviral therapy in low-income and middle-income countries: results of a coordinated end-to-end approach. AIDS 2021; 35:S165–S171. [PubMed: 34848583]

11. IMPAACT4TB. Increasing market and public health outcomes through scaling up affordable access models of short course preventive therapy for TB. Johannesburg, South Africa: The Aurum Institute; 2020.
12. Brooks KM, George JM, Pau AK, Rupert A, Mehaffy C, De P, et al. Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug-Drug Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifapentine. Clin Infect Dis 2018; 67:193–201. [PubMed: 29415190]
13. Dooley KE, Savic R, Gupte A, Marzinke MA, Zhang N, Edward VA, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. Lancet HIV 2020; 7:e401–e409. [PubMed: 32240629]
14. Semitala FC, Chaisson LH, Dowdy DW, Armstrong DT, Opira B, Aman K, et al. Tuberculosis screening improves preventive therapy uptake (TB SCRIPT) trial among people living with HIV in Uganda: a study protocol of an individual randomized controlled trial. Trials 2022; 23:399. [PubMed: 35550621]
15. Uganda Ministry of Health. Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda. Kampala, Uganda: ; 2020.
16. Semitala FC, Kadota JL, Musinguzi A, Nabunje J, Welishe F, Nakitende A, et al. Completion of isoniazid-rifapentine (3HP) for tuberculosis prevention among people living with HIV: Interim analysis of a hybrid type 3 effectiveness-implementation randomized trial. PLoS Med 2021; 18:e1003875. [PubMed: 34914696]

Table 1.

Baseline characteristics and 6-month and 12-month viral suppression among participants initiating dolutegravir-based ART (TDF/3TC/DTG [TLD]) with or without 3HP; Table shows N (%) unless otherwise specified.

	Total	TLD+3HP	TLD	p-value[1]
Baseline characteristics	**N=453**	**N=163**	**N=290**	
Female sex	287 (63.4%)	95 (58.3%)	192 (66.2%)	0.09
Median age, years (IQR)	30 (25-37)	31 (25-37)	30 (25-37)	0.75
Median pre-ART CD4 count, cells/μL (IQR)	188 (86-271)	222 (118-295)	174 (74-249)	<0.01
Median BMI, kg/m^2 (IQR)	22.7 (20.7-25.1)	23.0 (21.3-25.8)	22.4 (20.3-25.0)	0.02
6-month follow-up	**N=344**	**N=136**	**N=208**	
Median $\log_{10}$ viral load (IQR)[2]	1.70 (1.79-1.76)	1.70 (1.70-1.88)	1.70 (1.70-1.70)	0.07
Viral load ≤50 copies/mL	252 (73.3%)	91 (66.9%)	161 (77.4%)	0.03
Viral load ≤200 copies/mL	315 (91.6%)	121 (89.0%)	194 (93.3%)	0.16
12-month follow-up	**N=198**	**N=61**	**N=137**	
Median $\log_{10}$ viral load (IQR) [2]	1.70 (1.70-1.70)	1.70 (1.70-1.70)	1.70 (1.70-1.70)	0.41
Viral load ≤50 copies/mL	157 (79.3%)	46 (75.4%)	111 (81.0%)	0.37
Viral load ≤200 copies/mL	185 (93.4%)	57 (93.4%)	128 (93.4%)	1.00

Abbreviations: 3HP, 3 months of weekly isoniazid and rifapentine; ART, antiretroviral therapy; IQR, interquartile range

[1]Based on Chi-squared, Fisher's exact, or Wilcoxon ranksum tests

[2]Viral loads below the lower limit of detection set to 50 copies/mL

Table 2.

Unadjusted and adjusted risk of viremia >50 copies/mL at 6-months among participants initiating TLD.

Characteristic	Risk Ratio (95% CI)	p-value	Adjusted Risk Ratio[1] (95% CI)	p-value
3HP	1.46 (1.04-2.07)	0.03	1.51 (1.07-2.14)	0.02
Female sex	0.72 (0.51-1.02)	0.07	0.81 (0.54-1.19)	0.28
Age	1.01 (0.99-1.03)	0.13	1.00 (0.98-1.03)	0.64
Pre-ART CD4 count, cells/μL	1.00 (0.99-1.00)	0.04	0.99 (0.99-0.99)	0.04
BMI, kg/m^2	0.99 (0.95-1.04)	0.89	1.01 (0.97-1.05)	0.62

[1]Adjusted for all other factors