Successful Multidrug-Resistant Tuberculosis Treatment Without HIV Viral Suppression: A Missed Opportunity

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Background: Coinfection with multidrug-resistant tuberculosis (MDR-TB) and HIV is common, but few published studies examine how undergoing MDR-TB treatment affects HIV disease indicators.

Methods: Using data from a nested, retrospective cohort of people with HIV (PWH) and successful MDR-TB treatment outcomes, we built multivariable regression models to explore correlates of HIV viral suppression at MDR-TB treatment completion.

Results: Among 531 PWH successfully treated for MDR-TB, mean age was 37.4 years (SD 10.2, interquartile range 30–43), 270 (50.8%) were male, 395 (74.4%) were virally suppressed at MDR-TB outcome, and 259 (48.8%) took bedaquiline. Older age (adjusted odds ratio [aOR] 1.04, 95% confidence interval [CI]: 1.01 to 1.06) increased odds of viral suppression, while having a prior TB episode (aOR 0.45, 95% CI: 0.31 to 0.64), having a detectable viral load at MDR-TB treatment initiation (aOR 0.17, 95% CI: 0.09 to 0.30), living in a township (aOR 0.49, 95% CI: 0.28 to 0.87), and being changed from efavirenz-based antiretroviral therapy (ART) to a protease inhibitor due to bedaquiline usage (aOR 0.19, 95% CI: 0.04 to 0.82) or not having an ART change while on bedaquiline (aOR 0.29, 95% CI: 0.11 to 0.75) lowered odds of viral suppression. Changing from efavirenz to nevirapine due to bedaquiline usage did not significantly affect odds of viral suppression (aOR 0.41, 95% CI: 0.16 to 1.04).

Conclusions: Increased pill burden and adverse treatment effects did not significantly affect HIV viral suppression while switching ART to a protease inhibitor to accommodate bedaquiline or not changing ART while taking bedaquiline did, suggesting that PWH and MDR-TB may benefit from additional support if they must switch ART.

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INTRODUCTION

South Africa has a high burden of tuberculosis (TB), HIV, and TB/HIV coinfection.[1,2] Multidrug-resistant TB (MDR-TB), defined as TB resistant to the first-line drugs isoniazid and rifampicin, complicates TB treatment and worsens outcomes.[2,3] Although historically worldwide less than 60% of people diagnosed with MDR-TB completed their treatment or were cured,[2] South Africa has recently demonstrated considerable improvement in MDR-TB treatment outcomes for both people with and without HIV with newer oral MDR-TB regimens which use the novel antitubercular agent bedaquiline.[3] Although the effects of living with HIV on MDR-TB outcomes have been investigated, HIV treatment outcomes among people cotreated for MDR-TB and HIV are relatively unexplored.[4]

HIV viral load (VL) is widely considered the most important indicator of HIV treatment efficacy because of its sensitivity to detect changes in viral replication rapidly. Achieving viral suppression is the goal for all people with HIV (PWH) to prevent disease progression, ensure that PWH live without complications, and prevent new HIV infections.[5] Yearly HIV VL testing has been recommended by the World Health Organization for all PWH since 2013, and South African MDR-TB treatment guidelines add recommendations to repeat HIV VL at the time of MDR-TB diagnosis and routinely throughout MDR-TB treatment.[6–8] Given the intensity of clinical monitoring during MDR-TB treatment in the context of hospitalization for treatment initiation and monthly follow-up visits for 9 to 24 months, there is ample opportunity to support PWH to achieve virologic suppression. Virologic nonsuppression raises significant concerns about adherence, unidentified antiretroviral resistance, suboptimal clinical management, or a combination of these.[6]

Several factors could affect the ability of PWH to achieve and maintain HIV viral suppression during MDR-TB treatment, including increased pill burden and higher risk for adverse effects of medications from either antiretroviral therapy (ART) or MDR-TB regimens. In people with drug-sensitive TB and HIV, increased pill burden with twice-daily dosing of ART was significantly associated with poorer ART adherence and lack of HIV viral suppression at 48 weeks after treatment initiation.[9,10]

The type of MDR-TB regimen used may also affect HIV outcomes. Older MDR-TB regimens that included injectable medications had significant adverse effects such as hearing loss and required painful daily injections during the intensive phase of treatment, yet they rarely required adjusting ART regimens. Newer, all-oral MDR-TB treatment regimens with bedaquiline increase cure rates, reduce mortality, and eliminate the need for daily injections and aminoglycoside-associated toxicities.[11–13] However, the newer all-oral regimen complicates management of people with MDR-TB/HIV coinfection who are taking efavirenz (EFV). EFV, previously used as a first-line drug and available in a fixed-dose combination, reduces bedaquiline exposure by increasing the rate of bedaquiline metabolism.[14] To avoid the risk of under-treatment of MDR-TB related to subtherapeutic bedaquiline concentrations, treatment guidelines recommend an ART substitution for PWH taking EFV.[15] This ART substitution could affect pill burden, tolerability, adherence, and virologic outcomes.[16] As the new, all-oral MDR-TB regimen has only been implemented at a large scale in South Africa since September 2018, the effects of this regimen change on HIV indicators such as VL have not been well-documented.[16] As ART substitution could affect a person's likelihood of achieving or maintaining viral suppression, it may be an important predictor of viral suppression at MDR-TB outcome.

This study explores how factors related to the cotreatment of HIV and MDR-TB affect HIV viral suppression among a cohort of PWH who successfully completed MDR-TB treatment.

METHODS

Parent Study

The parent study for this nested, retrospective cohort analysis was a cluster-randomized trial of an intensive nurse case management intervention for people with MDR-TB in South Africa.[17] A total of 2847 participants from 13 tuberculosis treatment hospitals in KwaZulu-Natal and Eastern Cape, South Africa, were enrolled between 2014 and 2020. One nurse case manager was assigned to each of the 5 intervention sites. The nurse case manager assisted the treating clinicians with client management including adherence counseling, identification of adverse effects of treatment, tracing participants who missed appointments, and ensuring that appropriate laboratory values were obtained and participants were taking the appropriate treatment regimen. At the 5 control hospitals, participants received standard, clinician-guided care and data were abstracted from the client's hospital chart. In this analysis, the presence of the nurse case manager was controlled statistically by including the study arm as a covariate in multivariable models. Parent study inclusion criteria were at least 13 years of age and having microbiologically confirmed rifampicin-resistant tuberculosis at the time of enrollment. For adolescents aged 13 to 17 years, participants provided assent to participate in this study in addition to the parent's or guardian's informed consent. Adolescent participants received similar care to other participants, with the clinical team, including the nurse case manager for the intervention arm, working with the adolescent and caregivers according to clinical judgment and knowledge of the individual participant's needs.

Sample

To examine correlates of HIV viral suppression at the time of MDR-TB treatment completion, we included all parent study participants with extracted and validated data who were living with HIV, were successfully treated for MDR-TB, and had an available HIV VL result at the time of MDR-TB treatment completion. An additional 14 parent study participants were excluded from this analysis because of the lack of documentation indicating that they were prescribed ART during MDR-TB treatment. This substudy was conducted after all parent study participants had completed treatment and all data were collected, but before the final validation of the files for 302 participants. The study sample is shown in Figure 1.

All participants were treated programmatically according to South African national MDR-TB treatment guidelines.[5] In brief, participants taking injectable regimens took either a short-course (9–11 months) or long-course (18–20 months) injectable MDR-TB regimen including an intensive phase of daily injections with an aminoglycoside and oral medications, which included moxifloxacin, ethionamide, terizidone, and pyrazinamide, although clofazimine, high-dose isoniazid, ethambutol, and para-aminosalicylate sodium could be added. Those taking all-oral treatment regimens were prescribed bedaquiline, linezolid, levofloxacin, clofazimine, and either terizidone or high-dose isoniazid, ethambutol, and/or pyrazinamide, but treatment could include additional medications according to clinical judgment and individual client factors.[5] South African treatment guidelines allow for variation in MDR-TB medication regimen depending on drug sensitivity testing, resistance conferring-mutations, clinical and laboratory progression, and clinical judgment.[5]

Statistical Analyses

We descriptively examined the relationship between demographic, health system, and clinical factors and viral suppression status at MDR-TB treatment outcome. Next, we modeled the odds of HIV viral suppression based on these factors. We performed bivariate analyses using simple logistic regression before combining all factors into a multivariable logistic regression model. We considered multiple models using backward selection. Beginning with all covariates, factors were removed from the model if the P value was >0.20 with the largest P values removed first. Factors known to affect MDR-TB treatment outcomes including age, arm of the parent study, TB history, ART changes, and length of time of MDR-TB treatment were not allowed to be removed from the model. AIC was compared among the various models, and the model with the lowest AIC was remained. For all logistic regression models, we accounted for clustering in the parent study data set using cluster robust estimates of variance.[18,19] All tests were performed using Stata version 16.[20]

Variable Definitions

HIV Viral Suppression

Viral suppression was defined as an HIV VL below the detectable limit of the available assay or <400 copies per

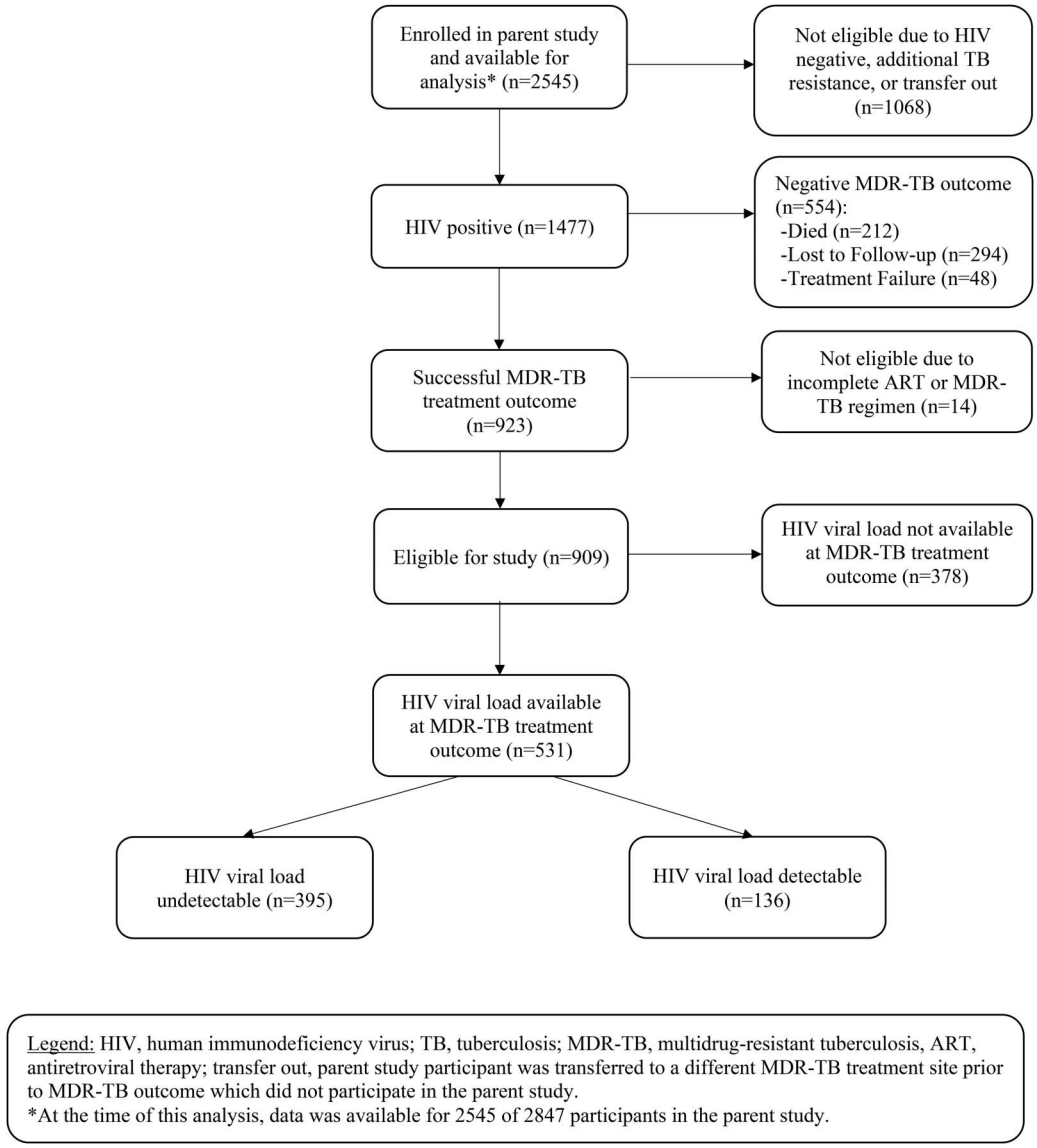

FIGURE 1. Study sample. Transfer out, the parent study participant was transferred to a different MDR-TB treatment site before MDR-TB outcome which did not participate in the parent study. *At the time of this analysis, data were available for 2545 of 2847 participants in the parent study.

milliliter, in accordance with South African national guidelines.[7] HIV VL results taken between 3 months before and 6 months after the date of MDR-TB treatment outcome were included in this analysis as outcome results, and HIV VL results taken within 12 month before or 4 weeks after the first antitubercular medication were included as results at the time of MDR-TB treatment initiation.

Pill Burden

The pill burden was defined as the number of pills used to treat MDR-TB and HIV taken daily during the intensive phase of treatment. If there were changes to the MDR-TB or HIV treatment regimen during this period, then the regimen used for the longest period was used to calculate pill burden. Pill burden was extracted from the parent study medication logs.

Treatment-Related Symptoms

The parent study systematically collected information related to the experience of symptoms during MDR-TB treatment. The nurse case manager completed symptom logs at intervention sites during or after their interviews with study participants. At control sites, research assistants extracted symptom information from the chart. Symptom logs underwent quality assurance evaluations by a senior member of the study team during site visits by comparing the completed logs to the hospital chart and pharmacy record. The total number of symptoms of each grade was abstracted from the parent study symptom logs. Symptoms were graded as mild if no

additional medications were used to treat the symptom, moderate if an additional medication was added to treat the symptom, and severe if treating the symptom required stopping or changing the MDR-TB or HIV treatment regimens.[16] We further categorized participants based on their experience of grade 3 symptoms into none, 1, or 2 or more grade 3 adverse effects during MDR-TB treatment.

ART Regimen Considerations

Participants were categorized based on whether they experienced a change to their ART regimen because of receiving a bedaquiline-based MDR-TB treatment regimen. Participants were categorized as never taking bedaquiline, changing ART from EFV to nevirapine (NVP), changing ART from EFV to a boosted protease inhibitor regimen (i.e., lopinavir, atazanavir, and darunavir), or not experiencing an ART substitution while taking bedaquiline which included those who started or were previously taking a bedaquiline-compatible regimen, those who remained on EFV while taking bedaquiline, and those who took a nonstandard ART regimen. Except when taking a nonstandard ART regimen, participants were using one of the standardized, three-drug ART regimens available in South Africa during the study period. In addition to EFV, NVP, or protease inhibitors, participants also took a nucleoside reverse transcriptase inhibitor backbone of tenofovir disoproxil fumarate, zidovudine, or abacavir with either lamivudine or emtricitabine. Integrase strand transferase inhibitors (INSTIs) such as dolutegravir were not widely available in South Africa during the parent study, and no participants used these regimens.

Additional covariates evaluated for inclusion in the analysis were the total length of MDR-TB treatment in days; age in years at MDR-TB treatment initiation; sex; baseline CD4 count, included if the result was obtained within 1 year before or 4 weeks after the date on which the first MDR-TB medication was taken and categorized as <50 cells per microliter (c/μL), 50 to 199 c/μL, 200 to 499 c/μL, and 500 or greater c/μL; baseline HIV VL, included if the result was obtained within 1 year before or 4 weeks after the date on which the first MDR-TB medication was taken; baseline body mass index (BMI), calculated from baseline height in meters and weight in kilograms; parent study arm, defined as intervention or control arm; baseline ART status, defined as taking or not taking ART at the time of MDR-TB treatment initiation; and history of TB treatment, defined as having received treatment for a prior episode of TB of any type, regardless of prior treatment outcome.

Missing Data

Before identifying a VL as missing, we searched for all missing results in the National Health Laboratory Services (NHLS) electronic database.[21] The NHLS database is a reliable and complete source of laboratory data from every public health facility in South Africa, including primary care and community clinics as well as hospitals, and inclusion in this database has been used as a marker for engagement in care among PWH in South Africa.[22,23] Database searches were conducted using a combination of patient identifiers, including first name, surname, date of birth, national ID number, and medical record number when available. Multiple searches were ran using different combinations of identifiers and a feature of the database that facilitates searching on similar sounding names until either all expected results were found or no other results were returned. If, after the search was completed, there were no HIV VL results returned, then HIV VL was considered clinically unavailable; that is, never obtained. No VL data were imputed. For all other variables, the amount and pattern of missingness was examined, and multiple imputation procedures were used to impute missing values for the covariates (percentage of participants missing values): housing location (0.2%), baseline ART status (0.6%), baseline CD4 count (11.5%), average pill burden (0.2%), and baseline BMI (13.9%).

Ethical Approval

The parent nurse case management study was approved by the Johns Hopkins School of Medicine Institutional Review Board (Application # NA_00078899), the province-level research committees in Eastern Cape and KwaZulu-Natal, and the IRB at the University of KwaZulu-Natal. This substudy was approved as a change in research protocol to the original parent study.

RESULTS

A total of 531 parent study participants were eligible for inclusion in this study (Fig. 1). Mean age at baseline was 37.4 years (interquartile range [IQR] 30–43), 270 (50.8%) were male, 259 (48.8%) took bedaquiline during MDR-TB treatment, and 395 (74.4%) were virally suppressed at MDR-TB treatment completion. Additional demographic and clinical characteristics of included participants are presented in Table 1. All participants who were not taking ART at the time of MDR-TB diagnosis were started on ART regimens during MDR-TB treatment.

When controlling for arm of the parent study and length of MDR-TB treatment, older age increased odds of HIV viral suppression (adjusted odds ratio [aOR] 1.04, 95% confidence interval [CI]: 1.01 to 1.06) while having a prior episode of TB of any type (aOR 0.45, 95% CI: 0.31 to 0.64) and living in a township (aOR 0.49, 95% CI: 0.28 to 0.87) decreased odds of HIV viral suppression (Table 2).

We also analyzed the effects of ART regimen changes related to bedaquiline use on odds of viral suppression compared with PWH who did not take bedaquiline as part of their MDR-TB regimen; that is, they used an older MDR-TB treatment regimen containing injectable aminoglycosides. Of the 259 participants who took bedaquiline, 145 (56.0%) were taking EFV at the time that bedaquiline was started. NVP was substituted for EFV in 110 (42.5%), boosted protease inhibitors were substituted for EFV in 22 (8.5%), and 13 (5.0%) stayed on EFV. Some participants (n = 110 or 48.2% of those who took bedaquiline) did not require an ART substitution because they were already taking a bedaquiline-compatible regimen (NVP or protease inhibitor) or started on one of these ART regimens after initiating bedaquiline-based

TABLE 1. Demographic and Treatment Characteristics of PWH With a Successful MDR-TB Outcome and an Available HIV VL Result at MDR-TB Treatment Outcome (N = 531)

	Total	HIV VL Undetectable	HIV VL Detectable
Total, n (%)	531	395 (74.4)	136 (25.6)
Age, mean (SD, IQR)	37.4 (10.2, 30–43)	37.9 (10.2, 31–43)	35.8 (9.8, 29–41)
Sex, n (%)			
Male	270	197 (73.0)	73 (27.0)
Female	261	198 (75.9)	63 (24.1)
Arm of the parent study			
Nurse case manager	254	186 (73.2)	68 (26.8)
Control	277	209 (75.5)	68 (24.5)
Baseline BMI, mean (SD, IQR)	21.3 (4.9, 18.0–23.8)	21.6 (4.9, 18.2–24.5)	20.5 (5.6, 17.3–22.5)
Prior TB episodes, n (%)			
Yes	293	204 (69.6)	89 (30.4)
No	238	191 (80.3)	47 (19.8)
Housing location, n (%)			
Rural or farm	334	265 (79.3)	69 (20.7)
Township	177	116 (65.5)	61 (34.5)
Urban/CBD or suburban	19	13 (68.4)	6 (31.6)
Unknown	1	1 (100.0)	0 (0.0)
Baseline ART status, n (%)			
Taking ART	357	265 (74.2)	92 (25.8)
Not taking ART	170	127 (74.7)	43 (25.3)
Unknown	4	3 (75.0)	1 (25.0)
Baseline viral load, n (%)			
Suppressed	201	174 (86.6)	27 (13.4)
Not suppressed	179	95 (53.1)	84 (46.9)
Unknown	151	126 (83.4)	25 (16.6)
MDR-TB regimen, n (%)			
Short injectable	234	192 (82.1)	42 (18.0)
Long injectable	38	32 (84.2)	6 (15.8)
Oral	155	96 (61.9)	59 (38.1)
Both regimens	104	75 (72.1)	29 (27.9)
Average pill burden, mean (SD, IQR)	15.5 (3.0, 13.5–17.5)	15.3 (3.1, 13–17.5)	16.0 (2.8, 14–18)
Number of grade 3 adverse events, n (%)			
None	244	174 (71.3)	70 (28.7)
One	162	125 (77.2)	37 (22.8)
Two or more	125	96	29
Baseline CD4, n (%)			
Less than 50 cells/mm^3	68	35 (51.5)	33 (48.5)
50–199 cells/mm^3	155	110 (71.0)	45 (29.0)
200–499 cells/mm^3	165	135	30
Greater than 499 cells/mm^3	82	68 (82.9)	14 (17.1)
Unknown	61	47 (77.0)	14 (23.0)
Total days in MDR-TB treatment, mean (SD, IQR)	495.3 (168.8, 317–622)	505.7 (168.8, 321–636)	464.9 (165.9, 315–617)
ART changes related to MDR-TB regimen, n (%)			
Did not take BDQ	272	224 (82.4)	48 (17.6)
EFV changed to NVP for BDQ	110	83 (75.5)	27 (24.6)
EFV changed to PI for BDQ	22	14 (63.6)	8 (36.4)
No ART substitutions	127	74 (58.3)	53 (41.7)

Some proportions do not add to 100.0% due to rounding.
mm^3, cubic millimeters; CBD, central business district; CD4, CD4 T-cell count; n, number; PI, protease inhibitor.

MDR-TB treatment. Thirteen participants (5.0% of those who took bedaquiline) remained on EFV, and 4 (1.5% of those who took bedaquiline) took individualized nonstandard ART regimens. Our results show that changing EFV to NVP reduced odds of HIV viral suppression at MDR-TB treatment outcome compared with those who never took bedaquiline, although this result did not achieve statistical significance (aOR 0.41, 95% CI 0.16-1.04), while changing to a protease

TABLE 2. Predictors of Viral Suppression Among PWH Successfully Treated for MDR-TB With an HIV VL Result (n = 531)

	Single Variable Model		Multivariable Model, All Covariates		Multivariable Model, Selected Covariates	
	OR	95% CI	aOR	95% CI	aOR	95% CI
Arm	0.89	0.60 to 1.31	1.59	0.96 to 2.61	1.63	0.96 to 2.77
Age	1.02*	1.00 to 1.04	1.04†	1.01 to 1.06	1.04†	1.01 to 1.06
Female (ref. Male)	1.16	0.79 to 1.72	0.81	0.50 to 1.30		
Prior TB Episode(s), (ref. no)						
Yes	0.53†	0.35 to 0.80	0.49†	0.31 to 0.77	0.45‡	0.31 to 0.64
Housing location (ref. rural or farm)						
Township	0.50†	0.33 to 0.75	0.48†	0.31 to 0.76	0.49*	0.28 to 0.87
City/CBD or suburban	0.57	0.21 to 1.57	0.36*	0.14 to 0.93	0.42	0.15 to 1.18
Taking ART at baseline (ref. No)						
Yes	0.98	0.64 to 1.48	0.55*	0.35 to 0.88		
Baseline CD4 category (ref. ≥500)						
<50	0.28†	0.14 to 0.58	0.63	0.19 to 2.03		
50-199	0.60	0.31 to 1.17	1.14	0.52 to 2.50		
200-499	1.01	0.51 to 2.01	1.40	0.70 to 2.77		
Pill burden	0.92*	0.86 to 0.98	0.94	0.83 to 1.06		
Number of grade 3 symptoms (ref. none)						
One	1.36	0.86 to 2.16	1.24	0.69 to 2.20	1.16	0.63 to 2.12
Two or more	1.35	0.81 to 2.22	1.26	0.64 to 2.50	1.14	0.62 to 2.10
Baseline BMI	1.04	0.99 to 1.09	1.03	0.99 to 1.07		
Baseline HIV viral load (ref. undetectable)						
Detectable	0.18‡	0.11 to 0.29	0.15‡	0.08 to 0.29	0.17‡	0.09 to 0.30
Unknown	0.78	0.43 to 1.41	0.66	0.31 to 1.42	0.75	0.39 to 1.44
ART changes related to BDQ (ref. did not take BDQ)						
EFV to NVP	0.66	0.389 to 1.12	0.50	0.23 to 1.05	0.41	0.16 to 1.04
EFV to PI	0.38*	0.15 to 0.94	0.25	0.06 to 1.00	0.19*	0.04 to 0.82
No ART substitutions	0.30‡	0.19 to 0.48	0.34*	0.15 to 0.80	0.29*	0.11 to 0.75
Total days in MDR-TB treatment	1.01*	1.01 to 1.01	1.00	1.00 to 1.00	1.00	1.00 to 1.00

n, number; OR, odds ratio; PI, protease inhibitor; ref., reference category.
*$P < 0.05$;
†$P < 0.01$;
‡$P < 0.001$.

inhibitor (aOR 0.19, 95% CI: 0.04 to 0.81) or not having an ART substitution while taking bedaquiline [BDQ] (aOR 0.29, 95% CI: 0.11 to 0.75) significantly lowered odds of HIV viral suppression.

In Table 3, we describe prescribing practices after MDR-TB treatment, specifically whether PWH initially switched were switched back or remained on the ART they received during MDR-TB treatment.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate HIV VL at the time of MDR-TB treatment completion and the first to document the impact of ART substitutions on HIV viral suppression among PWH receiving all-oral, bedaquiline-containing MDR-TB treatment regimens. South African MDR-TB treatment guidelines recommend VL testing at MDR-TB diagnosis, after 6 months of MDR-TB treatment, and then yearly for the duration of MDR-TB treatment if the results remain undetectable while a detectable VL requires rapid action including intensive counseling, adherence support, and repeat testing within 2 months.[6] However, we found that 378 (41.6%) of 909 eligible parent study participants did not have an HIV VL collected within a few months of MDR-TB treatment completion. After MDR-TB treatment completion, these PWH will experience a care transition back to primary care for ART management. Much of the care the client received during MDR-TB treatment will be unknown to the HIV clinician, including the ART substitutions. Thus, a post–MDR-TB treatment VL should be made routine, along with documentation of all ART changes made during treatment.

Although the new, all-oral MDR-TB treatment regimens containing bedaquiline are clearly effective in treating MDR-TB and have been successfully rolled out in many settings, there has been little published research investigating the impact of these regimens on HIV outcomes. Among our participants, people receiving a bedaquiline-based MDR-TB regimen had significantly lower odds of viral suppression at the time of treatment outcome if their ART regimen was switched from EFV to a boosted protease inhibitor–based regimen or not switched at all. Bedaquiline does not inhibit or

TABLE 3. ART Substitutions Among Participants Prescribed Bedaquiline for MDR-TB by HIV Viral Suppression Status at Treatment Outcome (N = 259)

	Total	HIV Viral Suppression, n (%)	Detectable HIV VL, n (%)
Total	259	171 (66.0)	88 (34.0)
Substituted NVP for EFV due to Bedaquiline and…	110	83 (75.5)	27 (24.5)
… returned to EFV after Bedaquiline completion	53	44 (83.0)	9 (17.0)
… remained on NVP	49	34 (69.4)	15 (33.6)
… to second-line regimen	8	5 (62.5)	3 (37.5)
Substituted PI regimen for EFV due to bedaquiline and…	22	14 (63.6)	8 (36.4)
… returned to EFV after bedaquiline completion	9	7 (77.8)	2 (22.2)
… remained on PI	13	7 (53.8)	6 (46.2)
No ART substitution due to…	127	74 (56.7)	53 (41.7)
… previously taking or initiated on NVP	62	38 (61.3)	24 (38.7)
… previously taking or initiated on PI	48	27 (58.3)	21 (43.8)
… clinician maintained EFV during BDQ	13	6 (46.2)	7 (53.8)
... Nonstandard ART regimen	4	3 (75.0)	1 (25.0)

Some proportions do not add to 100.0% due to rounding.
N, number; PI, protease inhibitor.

induce CYP isoenzymes, nor does it affect transporters, so it would not be expected to affect the pharmacokinetics of protease inhibitors, as confirmed in a single-dose study that showed no meaningful drug interaction.[24,25] Therefore, the lower odds of viral suppression should not be due to lowering of protease inhibitor exposures. Other possible explanations for the decreased odds of viral suppression among participants switching to protease inhibitors could include tolerability differences, ART adherence, underlying HIV viral resistance, or other factors. Others have recently linked twice-daily dosing of ART to lower adherence and reduced viral suppression rates during treatment for drug-sensitive TB.[9,10] This could be a mechanism underlying the association seen in this sample; however, we are unable to confirm this with the data at hand. For those not switching ART regimens while taking bedaquiline, the reasons underpinning the association are also unclear. However, many of these participants did not require an ART regimen substitution because they were already taking boosted protease inhibitors when bedaquiline was prescribed, which in South Africa is a marker of prior nonadherence and first-line ART failure.

Among our sample of PWH who successfully completed MDR-TB treatment, took ART, and had an available HIV VL, some of the factors that add complexity to MDR-TB treatment such as additional pill burden and higher risk of adverse effects of medication did not significantly affect HIV viral suppression at the time of MDR-TB treatment completion. These findings, along with the high overall proportion of PWH who had HIV viral suppression, should reassure clinicians that viral suppression among PWH with MDR-TB is achievable and should be the goal. Our finding that older age is associated with HIV viral suppression is consistent with other studies.[26,27] When controlling for age, however, living in a township and having a prior TB episode lowered odds of HIV viral suppression. Living in a township has been associated with lack of viral suppression at the time of MDR-TB treatment initiation, and it is likely that the issues that could drive this association such as poverty, poor access to services, crowded conditions, and generational poverty would continue to have an impact during MDR-TB treatment.[28] Having a prior TB episode also decreased odds of HIV viral suppression. This association could be due to clinical factors such as the well-established association between a detectable HIV VL and TB reinfection.[29]

In settings outside South Africa where HIV genotyping is widely available, determining the pattern of ART resistance should be prioritized in PWH undergoing treatment for MDR-TB to ensure the best choice of ART and the best odds of achieving HIV viral suppression. Clinicians may wish to capitalize on the risk factors identified in this study (township living, having had a prior TB episode, taking second-line ART, or younger age) to help determine which PWH to prioritize for more frequent VL testing and genotyping. We recommend that clinicians choose alternate first-line regimens such as NVP when drug–drug interactions necessitate an ART regimen change during MDR-TB treatment. Second, we recommend that clinicians prioritize PWH taking ART regimens containing protease inhibitors for intensive adherence counseling and monitoring during MDR-TB treatment.

After the conclusion of the parent study, South Africa began large scale roll out of a new first-line ART regimen consisting of a once-daily fixed-dose combination containing the INSTI dolutegravir. Because no participants in our substudy were taking INSTIs, we are unable to comment on how this newer regimen affects HIV viral suppression during MDR-TB treatment. However, given the general tolerability of INSTIs, smaller pill size, once-daily dosing in a fixed-dose combination, rapid suppression of viral replication, and a lack of anticipated drug–drug interactions with MDR-TB medications, we expect that taking an INSTI regimen would increase the likelihood of viral suppression at the time of MDR-TB treatment completion. This study should be repeated once sufficient data from South Africa and other settings with high MDR-TB/HIV burdens are available. In the meantime, we recommend clinicians prioritize PWH and MDR-TB for switching to newer ART regimens containing

INSTIs and closely monitor individual HIV VLs during this period. Specifically, ensuring an undetectable VL before switching ART regimens and then repeating VL measurements within 3 months of switching is indicated.

There are several limitations to this study. First, we did not include any indicator of ART adherence because data were collected by self-report and programmatic VL monitoring was conducted as part of the parent study. Given the importance of ART adherence to achieving HIV viral suppression, we must consider that preferential adherence to certain ART regimens may have driven some of our results because many PWH in South Africa are familiar with EFV-based regimens and may have adhered to daily treatment more closely on this regimen than to new regimens. We also excluded 377 parent study participants because they did not have an available HIV VL result within 3 months before to 6 months after MDR-TB outcome. A likely explanation is electronic gatekeeping at NHLS that prevents repeat HIV VL measures more frequently than yearly as a cost-containing measure. Finally, the decision to include only PWH who were successfully treated for MDR-TB introduces a survivor bias that limits the ability to generalize these results to PWH whose MDR-TB treatment was not successful.

CONCLUSIONS

Being diagnosed with and treated for MDR-TB is challenging for PWH because treatment is long, complex, and requires a considerable amount of effort from the client, clinician, and health system to be successful. Newer MDR-TB regimens are shortening treatment lengths and improving outcomes.[30,31] Now that we have greater confidence in our ability to treat MDR-TB successfully among PWH and MDR-TB, we must turn our attention to the treatment of HIV. Viral suppression can be achieved when guideline-based care, including regular HIV VL monitoring and guideline-based ART substitutions, as well as close monitoring for clients changing ART regimens, is implemented systematically for PWH and MDR-TB.

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