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Treatment Adherence Among Persons Receiving Concurrent MDR TB and HIV Treatment in KwaZulu-Natal, South Africa

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Abstract

Treatment Adherence Among Persons Receiving Concurrent MDR TB and HIV Treatment in KwaZulu-Natal, South Africa

By Fay Stephens

Background
Concurrent multidrug-resistant tuberculosis (MDR-TB) and human immunodeficiency virus (HIV) treatment entails high pill burden, frequent adverse events and long therapy duration. KwaZulu-Natal province, South Africa, has approximately 5,000 MDR-TB cases annually (80% HIV-infected). We evaluated adherence to MDR-TB and antiretroviral therapy (ART) and its association with treatment outcomes.

Methods
We prospectively followed MDR-TB patients for 24 months. Adherence was assessed monthly using 3-day recall, 30-day recall and visual analog scale (VAS). MDR-TB treatment success was defined as cure or completion; failure, death or loss-to-follow-up were unsuccessful outcomes. We determined the proportion of fully adherent participants by each adherence measure, stratified by HIV status. We assessed the association with MDR-TB treatment success and 60-day culture conversion using unadjusted risk ratios. Among HIV-positive participants, we examined differential adherence to MDR-TB vs. HIV treatment using McNemar's test.

Results
Among 200 MDR-TB patients, 63% were female, median age was 33 years, and 144 (72%) were HIV-positive, of whom 81% were receiving ART at baseline. Adherence to MDR-TB and HIV treatment was high across all measures (82-96% fully adherent) and did not differ by HIV status (Figure). Among HIV-positive participants, ART adherence was significantly higher than MDR-TB treatment adherence by all measures (Figure). Using a composite measure of 3-day recall and VAS, MDR-TB treatment success and 60-day culture conversion were higher among participants who were fully adherent, but this difference was not statistically significant (RR: 1.11, 95%CI: 0.87-1.41; RR: 1.29, 95% CI: 0.70-2.43).

Conclusions
Self-reported MDR-TB treatment adherence was high and did not differ by HIV status, suggesting co-treated persons can achieve high adherence. Reported adherence to ART was higher than to MDR-TB treatment by all study measures. More objective adherence measures and a better understanding of preferential ART adherence are needed to inform interventions that improve outcomes for MDR-TB and HIV co-infected persons.

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CHAPTER I: LITERATURE REVIEW

Global TB and HIV Epidemics

Tuberculosis (TB) and human immunodeficiency virus (HIV) are leading infectious disease killers worldwide. According to the World Health Organization (WHO), an estimated 10.4 million new cases of TB occurred in 2015, with 1.4 million deaths among these incident cases [1]. At the end of 2015, there were an estimated 36.7 million people living with HIV worldwide and an estimated 1.1 million acquired immune deficiency syndrome (AIDS)-related deaths this same year [2].

The TB and HIV epidemics have converged into a global syndemic, magnifying the burden and consequences of both diseases [3]. In 2015, 11% (1.2 million) of the estimated 10.4 million incident TB cases were in people with HIV [1]. TB is a leading cause of mortality in people with HIV, with an estimated one in three HIV deaths due to TB in 2014 [4]. The treatment success rate for HIV-positive TB patients was lower than that of HIV-negative TB patients (73% vs. 88%) [1].

While co-infection of HIV and TB occurs across the globe, the burden is disproportionally high in Africa, where approximately 74% of co-infected cases occurred in 2014 [1]. Most of the countries that bear the greatest burden of the HIV and TB epidemics face these diseases without the necessary treatment and prevention resources. As the HIV/TB "syndemic" grows, prioritized research is critical to improve treatment outcomes and reduce the spread of TB and HIV, particularly in resource-limited settings.

Multidrug-Resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR TB), defined as resistance to at least two of the most potent anti-tuberculosis drugs, rifampin and isoniazid [5], is an increasingly prevalent global health issue. An 480,000 people developed MDR TB in 2015. Of these, only about one quarter, or 123,000 cases, were detected and reported [1]. Treatment success rates of drug-susceptible tuberculosis (DS-TB), using the standard 6-month regimen of four first-line drugs, are high, frequently reported as 85% or higher [1]. However, recommended regimens for treatment of MDR TB are more expensive, toxic, lengthy, and have lower treatment success rates [1]. Rates of treatment success for MDR TB vary, but the average success rate of 53% globally in 2013 i Extensively drug resistant TB (XDR TB) is a form of MDR TB that is resistant to both isoniazid and rifampin, as well as any fluoroquinoalone and at least one of three injectable second-line drugs (i.e., kanamycin, amikacin or capreomycin) [5]. Treatment for these two types of tuberculosis are substantially different and are often therefore considered separately in research and practice. Many incident cases of both MDR- and XDR-TB remain undetected and untreated, with approximately 23% of MDR TB cases and 8.7% of XDR TB cases reported as enrolled in treatment in 2014 worldwide [1]. Failure to detect and treat cases of drug-resistant TB (DR-TB) contributes to poor treatment outcomes for patients and ongoing transmission of the disease in communities [7]. In addition, DS-TB treatment completion rates are often below the World Health Organization (WHO) standard of 85% in many low-resource settings, further increasing the spread of drug-resistant strains [6,8]. Successful treatment of MDR TB relies on adherence to a much longer period of even more intense treatment lasting for 24 months, compared to 6-8 months for DS-TB treatment, with a substantial proportion of patients experiencing serious side effects, including hearing loss, kidney impairment, and depression [5].

MDR- and XDR-TB develop through inadequate therapy for DS-TB, caused by treatment misuse or mismanagement, including incorrect prescription of treatment by providers as well as lack of adherence to or availability of medication [5]. MDR TB can also occur through direct person-to-person spread and primary infection with a DR-TB strain [9]. It is estimated that

approximately 4% of new TB cases and about 20% of TB patients who previously received treatment have MDR TB worldwide [6], indicating the critical importance of efforts to improve treatment cure rates and stem transmission of this disease, especially in low-resource areas with high prevalence of TB.

MDR TB and HIV Co-infection

Prevalence

The increasing prevalence of MDR TB globally poses an even more complex and critical health threat in populations with high rates of HIV coinfection. The estimated 70% HIV co-infection rate for MDR TB patients in South Africa, the highest burden country for this syndemic, indicates the need for coordinated efforts to treat these diseases [10]. Prevalence estimates for co-infection rates in sub-Saharan Africa have been hindered in the past by limited health infrastructure resources and laboratories capable of performing drug-sensitivity testing (DST), suggesting that better surveillance could reveal higher prevalence rates than previously estimated [9]. South Africa has led efforts to improve laboratory capacity for DST, making it possible to have among the best estimates of MDR TB in sub-Saharan Africa. While South Africa currently bears the highest burden of MDR TB and HIV co-infection worldwide, other regions of the world are also likely to be impacted as the HIV epidemic continues and as MDR TB prevalence increases. Thus, studies aimed at improving health outcomes for MDR TB patients co-infected with HIV are critically important [1].

Treatment and Treatment Outcomes

MDR TB treatment involves 4-5 different drugs, including an injection with kanamycin or other injectable drug for the first six months of treatment followed by 12-18 months of four oral drugs, with many potential toxic side effects. Less than half (48%) of new MDR TB cases in South Africa were started on second-line treatment in 2015, and among rifampin-resistant TB

cases started on treatment in the country in 2013, 48% successfully completed treatment, roughly 18% were lost to follow-up, 20% died, and 2% failed treatment [11]. In a recent study conducted by Brust and colleagues, rates of culture conversion were found to be similar among MDR TB patients with and without HIV co-infection on ART in Tugela Ferry, South Africa (N=45) [12]. In fact, the results indicated a lower time to TB culture conversion for co-infected HIV-positive patients compared to those without HIV, suggesting the possibility for improved outcomes among co-infected patients when both diseases are managed effectively together [12]. The results of an additional study conducted by Brust et al in KwaZulu-Natal, South Africa, suggest out-patient, home-based treatment may improve treatment outcomes for patients co-infected with MDR TB and HIV in rural, low-resource settings. The home-based treatment model sought to improve rates of adherence through use of family member support, close monitoring of patients at home, and treatment literacy education for both patients and family members [13]. The challenges of treating MDR TB and HIV are amplified markedly in the context of co-infection with these two diseases. However, with proper treatment and patient-centered care, there is growing evidence for successful treatment outcomes in co-infected patients.

HIV infection has been associated with poorer treatment outcomes for MDR TB patients in multiple studies in a variety of global contexts [14]. However, a meta-analysis conducted by Orenstein and colleagues on MDR TB treatment outcomes indicated that fewer than half of the studies included in their review assessed the impact of HIV infection [15]. Among those studies that did include HIV status of MDR TB patients, the authors found a slightly higher MDR TB treatment success rate among cohorts without HIV co-infection (n=9) compared to cohorts with an HIV prevalence greater than 0% (68%, 95% CI (61-74) vs. 59%, 95% CI (49-69), respectively) [15]. Their findings indicate the potential gap in treatment success that can emerge in the context of HIV-coinfection, adding evidence to support to the importance of further research in the field of MDR TB and HIV co-infection.

The role of ART in improving MDR TB outcomes is further supported by data from Umanah et al's retrospective cohort study (N=1200) of MDR TB HIV-positive adult patients in South Africa. The study found that men who initiated ART before initiating MDR TB treatment were nearly twice as likely to achieve treatment cure for MDR TB compared with men who initiated ART after MDR TB treatment [16]. Patients with CD4 cell counts greater than 200 cells/mm^3 had better odds of cure compared with patients with CD4 count below 50 cells/mm^3, and cavitary changes on chest x-ray and a modified MDR-TB treatment regimen at baseline lowered the likelihood of cure [16]. These findings suggest early diagnosis of HIV (before severe immunocompromise) and early diagnosis of MDR TB (before extensive lung disease) are critical factors to improving treatment outcomes.

Collectively, the evidence supports the possibility for successful treatment of patients co-infected with MDR TB and HIV, even in rural and low-resource settings. However, these successful treatment outcomes rely on many factors, one of the most influential of which is administration of and adherence to effective treatment for both diseases. In order to stop the spread of MDR TB and reduce the burden of HIV co-infection, a multi-faceted approach must be taken. One key factor is patient adherence to treatment. However, a critical gap in knowledge exists regarding the association of adherence with treatment outcomes in patients with MDR TB and HIV co-infection.

Context of MDR TB and HIV in South Africa

South Africa has seen a collision of the TB and HIV epidemics over the past 2 decades. Among the 450,000 incident cases of TB in South Africa in 2013, approximately 270,000 (60%) were co-infected with HIV [17]. South Africa has among the highest burden of drug-resistant TB worldwide, with approximately 20,000 laboratory-confirmed cases of MDR-TB in 2015. Recent estimates indicate an approximate 70% HIV co-infection rate for MDR TB patients in South

Africa [10]. The intersection of the TB, HIV and drug-resistant TB epidemics further impedes control of these diseases in South Africa [18]. The maturing HIV epidemic in the country countered the successes of the introduction of short-course treatment and DOT for TB control in recent decades, setting the stage for the current challenges [18]. The establishment of HIV as an independent risk factor for MDR TB remains unclear; however, the high prevalence of HIV in South Africa created a large number of immunocompromised persons at increased risk of contracting and developing DR-TB [9]. Additionally, lack of appropriate airborne infection control measures and a high prevalence of HIV infection in hospital wards created dangerous conditions for the spread of DR-TB [9].

The province of KwaZulu-Natal, South Africa, has borne a disproportionally high burden of the HIV and TB syndemic in the country. This province had the highest percent of deaths due to TB in 2010 [17]. An estimated 80% of TB patients in KwaZulu-Natal province are co-infected with HIV [8]. Additionally, a retrospective study investigating the prevalence of DR-TB in this province from 2001-2007 indicated a 10-fold increase in MDR TB during this time period [19]. In a landmark study conducted in this province from 2005-2006, Gandhi and colleagues identified higher rates of MDR TB and XDR TB in the region than previously known (39% and 6%, respectively), and very high mortality rate (98%) and HIV-coinfection rate (100% among XDR TB patients tested for HIV) [8]. More than half of XDR TB patients had never previously been treated for TB, and about a third had completed treatment or been cured for previous TB. These data were the first report of XDR TB in a high HIV prevalence setting and raised global alarm about the high mortality and evidence of both nosocomial and community transmission of XDR-TB. Though initially considered an outbreak of XDR TB, further epidemiologic work in KwaZulu-Natal has revealed that it is a more wide-spread, evolving epidemic that warrants continued attention and intervention [9,18].

A substantial disparity in the effective delivery of treatment and achievement of desirable outcomes has been noted between HIV and TB treatment [18]. The historically separate functioning

of TB and HIV control programs within the public health system represents a missed opportunity and an area for future growth in the improvement of outcomes for both diseases [9]. Despite their length of establishment, TB treatment services have fallen behind those of HIV treatment in the country, allowing for poorer treatment outcomes and cure rates for TB as compared to HIV, in as much as these two diseases are comparable. As evidence of this gap, the cure rate for DS-TB was 71.9% in Western Cape province in 2005, but 90.6% of HIV patients treated with ART the same year achieved viral suppression at 6 months [18]. In 2014, 78% of new and relapse TB cases in South Africa were successfully treated [11], and 79% of HIV positive patients on ART were virally suppressed at 12 months, suggesting that this gap has narrowed in recent years [20]. One hypothesis for this disparity involves the lack of patient-centered care involving treatment literacy and empowerment of patients in TB treatment as compared to HIV treatment. The importance of this disparity is underscored by the move towards patient-centered care highlighted in the WHO's End TB Strategy [6]. Treatment adherence is critical to achieving global TB cure and control because full adherence minimizes the risk of treatment failure, TB relapse, and the development of DR-TB [21]. However, substantial challenges to adherence exist, especially in the context of DR-TB. Improving treatment adherence for HIV co-infected patients is a critical and even more challenging part of improving TB treatment success, particularly in highly burdened, low resource areas like KwaZulu-Natal.

The combination of increasing incidence of TB, emerging TB drug resistance, and the convergence with the HIV epidemic in South Africa have set the stage for a public health crisis in great need of attention and swift intervention [18]. Better understanding and improving patient adherence to treatment in this region is a critical component to tackling this crisis.

Adherence to Drug-Susceptible TB Treatment

Measuring Adherence to TB Treatment

Accurate knowledge of treatment adherence is essential to providing informed support of non-adherent patients as well as the protection of the public's health, in the case of infectious diseases [22]. Non-adherence to TB treatment poses a major threat to global TB control by increasing the risk of treatment failure, TB relapse, and the development of drug resistance [21]. Adherence to TB treatment is reduced by many factors, including the length of treatment (6 months), the side effects often experienced by patients on treatment, and the fact that patients often feel improvements to their symptoms before treatment is completed [23]. Measurement of adherence in TB treatment is made more complicated by the historically common approach to TB treatment of directly observed therapy (DOT), in which patients are observed as they take every dose of treatment. Because DOT was designed to improve and ensure complete patient adherence to treatment, adherence is assumed to be complete when this standard of care is in place [24]. However, the conflicting evidence for the effectiveness of DOT suggests the need for alternative methods of improving patient adherence to TB treatment in order to improve cure rates and limit the development of drug resistance. In addition, despite the acknowledgement of the importance of adherence to successfully treating TB, knowledge is limited regarding the effect of differing levels and patterns of non-adherence on TB treatment outcome [21]. This gap exists in DS-TB as well as in DR-TB treatment.

The Evolving Role of DOT

There is conflicting evidence regarding the effectiveness of DOT for treating TB. Since the WHO's declaration of TB as a global public health emergency in 1993, DOT has been the primary recommended strategy for TB treatment [6]. The WHO's Global Plan to Stop TB, in place from 2006-2015, was built upon DOT [1]. With the introduction of the WHO's new End TB Strategy moving forward from 2015, the updated recommendations involve a move towards more integrated, patient-centered care, and the strategy makes no specific mention of continuation of

the use of DOT [6]. However, DOT remains common in practice. The results of one systematic review of 11 randomized and quasi-randomized clinical trials (N=5609) indicated that neither cure nor treatment completion rates were statistically significantly different with DOT when compared to self-administered treatment [25]. The authors concluded that among randomized trials conducted in low-, middle-, and high-income countries, there is no conclusive evidence of an important effect of DOT on TB cure compared to self-administered treatment [25]. In a recently published article, McLaren et al. highlight the financial and psychosocial burden of DOT on patients and the lack of high-quality, quantitative evidence suggesting DOT is more effective than self-administration at achieving drug-susceptible TB cure [24].

In addition to the mixed evidence regarding DOT's effectiveness, this treatment strategy has several limitations. Constant supervision by a healthcare worker or family member through the long course of TB treatment, whether in the home or in a healthcare facility, can often lead to stigmatization in the community for the patient, adding social strife to their physical disease challenges [24]. Patients additionally face financial burdens in their compliance with DOT through visits to healthcare facilities in areas where home-based DOT is unavailable, and the DOT schedule can interfere with a patient's work schedule and home responsibilities [24]. The time intensive requirements of DOT often hinder patient's abilities to resume normal life and work and pose a daily burden that mandates orienting routines around the administration of drugs, especially in the more intensive and longer duration treatment of MDR TB [26]. Additionally, absence of a DOT provider has been cited as a commonly reported problem, enough so that some patients had a "contingency plan" to take their medication in the absence of a provider, yet no national TB program includes such contingency plans in its strategy [26].

The evolution from the Stop TB Strategy to the End TB Strategy called for by the WHO in 2015 marks a shift away from DOT towards patient-centered care, emphasizing context-specific treatment and care that is responsive to patients' diverse needs [1]. However, because DOT

is the widely-accepted standard of care for TB treatment, it will remain the comparison point for the acceptability and effectiveness of new adherence support strategies [22].

Challenges to TB Treatment Adherence

A systematic review of patient adherence to TB treatment conducted by Munro et al. identified four key categories of barriers to anti-TB medication adherence [27]. The first barrier to adherence was categorized as structural factors, including poverty and gender. The second barrier was identified as patient-level factors, such as variations in individual willingness and motivation, adverse effects of medication, and lack of understanding regarding the importance of treatment. The social context was identified as the third category of barriers to TB treatment adherence, including lack of support and knowledge of family members and stigmatization. The fourth category of barriers to TB treatment adherence identified by Munro et al. was health care service factors such as limited drug stocks, clinic wait times, and accessibility of care to individual patients (Figure 1) [27].

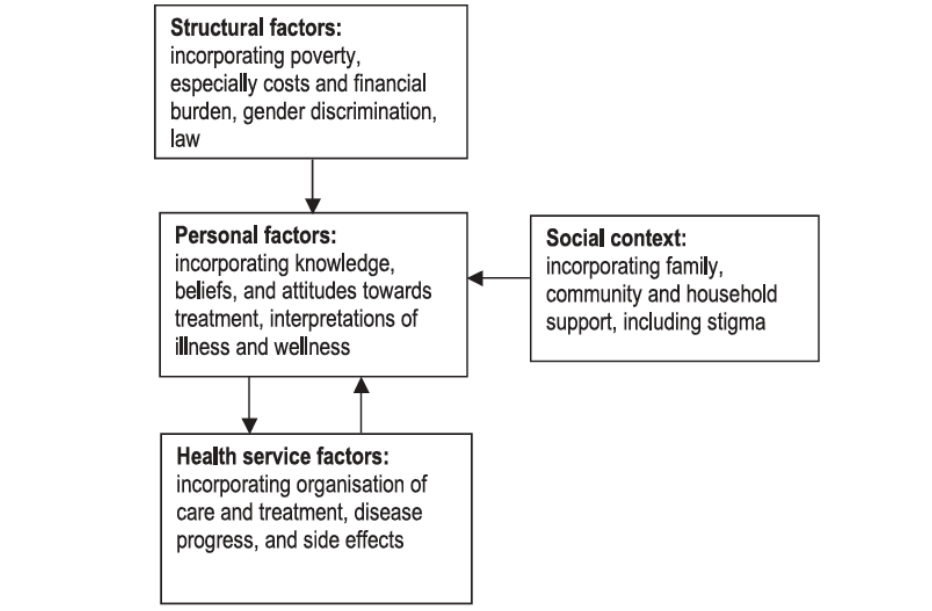

Figure 1. Model of Factors Affecting Adherence [27]

Patient-centered interventions could assist in overcoming these structural barriers to improve treatment adherence [27]. These findings are supported by a framework for improving adherence to TB treatment published by DiStefano et al., which emphasizes that adherence measures that draw undue attention to the patient should be avoided in order to reduce stigmatization [22]. DiStefano et al. additionally suggest that challenging life circumstances faced by patients, particularly present in low- and middle-income countries, can exacerbate the difficulty of complex daily medication regimens over long periods of time [22]. Present-biased perspective, or the tendency to prioritize short-term benefits over long-term treatment benefits, may additionally play a role in limiting patient adherence to medication, especially when adverse events, treatment stigma, and financial detriments of TB treatment force patients to make short-term sacrifices for the hope of cure in the long-term [28].

Gaps in Knowledge

The way adherence to TB treatment is defined and measured is inconsistent, and the association of different levels and patterns of non-adherence with TB treatment outcome remains unclear [21]. Van den Boogard and colleagues additionally identify the problematic nature of using treatment success as an indicator of adherence to treatment, citing four complicating factors that influence the path from adherence to treatment success [21]. These complicating factors include pathogenetic, immunological, pharmacokinetic, and pharmacodynamic factors, all of which can confound the association of adherence with treatment outcome, indicating the need for advances in research to better understand the direct association of adherence with treatment outcome for TB patients (Figure 2, [21]). The authors of this review suggest the need for both experimental studies that mimic different levels and patterns of non-adherence to study the effect on treatment response, as well as observational studies of patients with TB that validate adherence measurement instruments and markers of treatment response.

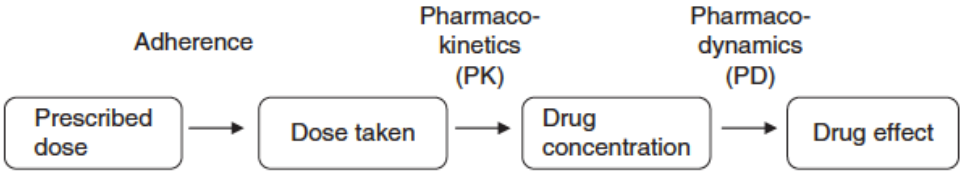

Figure 2. Clinical pharmacological view on antimicrobial therapy [21]

Adherence to MDR TB Treatment

Measuring Adherence to MDR TB Treatment

Adequate adherence is considered a critical component of successful treatment of both drug-susceptible and drug-resistant TB [29]. However, a critical gap in knowledge exists regarding the existence and extent of an association between adherence and treatment outcome for MDR TB. Despite the acknowledgement of the major challenge to global TB control posed by non-adherence, the impact of different levels and patterns of non-adherence on TB treatment outcome remains unknown [21]. Non-adherence impacts the spread of TB, in general, through prolonged infectious periods, and higher risk of treatment failure and relapse; its impact is heightened in the context of MDR TB, in which culture-conversion to negative (i.e., becoming non-infectious) is already prolonged and treatment failure rates are higher compared to DS-TB [30]. Data from a retrospective case-control study (N=1,109) conducted in Estonia, a country with one of the highest rates of MDR TB and XDR TB in the world, indicates that treatment success rates were substantially higher among MDR TB patients adherent to treatment as measured by completion of DOT, compared to those who were non-adherent (72.8% vs. 60.4%) [29]. However, "adherence" in this study was defined broadly as all participants who completed treatment under the DOT strategy, leaving a substantial remaining gap in knowledge regarding the quantified association of more nuanced adherence levels through treatment with MDR TB treatment outcomes in mono-

infected TB patients as well as in the context of HIV co-infection. An additional gap in understanding remains regarding the gold standard for measuring MDR TB adherence in the investigation of this association of adherence with treatment outcome.

A relatively large amount of the available literature relates to the effectiveness of DOT in the context of MDR TB. In a systematic review of 31 articles (N=7466 participants), authors Yin et al.'s findings suggest statistically significantly higher pooled treatment success rates among MDR TB patients on DOT for a full course of treatment compared with those on self-administered care [31]. It should be noted, however, that studies including exclusively HIV-positive patients were excluded from this meta-analysis, limiting the generalizability of this finding to patients co-infected with MDR TB and HIV. Additionally, this meta-analysis found no randomized controlled trials to include in the analysis, but used instead mostly retrospective cohort studies, highlighting the need for prospective studies.

In a study evaluating differing DOT delivery models, Yin et al. found no difference in treatment success rate between patients with DOT provided by healthcare workers compared with those receiving DOT from family members, nor between patients receiving health facility-based DOT compared with home-based DOT [31]. This indicates a possible area for improved treatment outcomes with home-based DOT, allowing for benefits of DOT to be felt without the stigma of health-care workers visiting the home by incorporating family member support instead, a component of treatment that has been cited as a barrier to successful adherence to MDR TB treatment [31]. This insight is supported by Gandhi et al.'s findings of improved treatment outcomes from home-based integration of TB and HIV therapies that used family members as treatment supporters [32].

In a systematic review and meta-analysis of strategies to reduce treatment default in MDR TB that included 78 studies and over 20,000 patients, Toczek and colleagues found a lower default rate in studies in which DOT was always provided compared with studies with no DOT provided [33]. This article additionally highlights the gap in available information regarding the

quantitative estimates of the association of adherence with treatment outcome for MDR TB. The authors indicated that treatment default was chosen as the outcome of interest, given the limited data available regarding actual patient adherence (i.e., number of doses taken correctly within a given time period) to treatment [33]. Their findings also suggest lower default rates when a community health worker (CHW) was the DOT provider compared with a health care worker in a facility or a nurse as the DOT provider. Counseling did not appear to impact default, while there was evidence of improved outcomes with increased patient education. Additionally, no combination of incentives or enablers were found to reduce treatment default rate [33]. These findings, in sum, emphasize the importance of patient education and community-level support to increase adherence and reduce treatment default for MDR TB treatment.

This idea of shifting the scope of the interpretation of DOT could provide insight as to the wide variability of evidence on its success as well as direction for designing future DOT programs that are more successful in improving adherence through community-level, individualized, and education-based patient support instead of de-personalized observation.

Barriers to Adherence to MDR TB Treatment

Additional barriers to adherence to MDR TB treatment, above and beyond drug-susceptible TB, exist. Treatment for MDR TB is longer than that of DS-TB, with more severe side effects. Lack of adherence to this challenging regimen has substantial consequences, including resistance amplification, failure to respond to treatment, and clinical deterioration [13]. Despite WHO support of more innovative approaches, DOT is still widely used as the cornerstone of TB care. Adherence is a critical determinant of patient outcomes, and a patient-centered, holistic approach to care focusing on team-based and decentralized care, patient education and counseling, and an emphasis on the human rights of patients has the potential to greatly improve adherence and DR-TB treatment outcomes [34].

What is known in MDR TB Treatment Adherence

Patients included in a qualitative study in India designed to understand loss to follow-up and improve retention-in-care for MDR TB patients indicated several key barriers to MDR TB treatment adherence, including difficulty with prolonged treatment, stigma and lack of support, and divergent perceptions and practices, such as addictions, use of traditional healers, and inadequate care at private facilities, such as use of first line drugs instead of effective DR-TB treatment [35]. Patients in the study indicated that daily injections, high pill burden, side effects, long duration of treatment, distance to the DOT clinic and long wait times were all barriers to adherence to treatment. Patients additionally expressed more likelihood to stop treatment once their symptoms resolved instead of completing the medication course, and cited frustration over failure of previous treatments as a barrier to continued adherence. Finally, patients indicated that stigma, a lack of family support, lack of adequate counseling, and unfriendly DOT providers made continued adherence to treatment even more challenging [35]. These findings highlight the need for accurate, thorough treatment education and counseling for both patients and family members for support from the beginning of treatment to help reduce loss to follow-up at the onset of adverse events or the improvement of symptoms [35].

Gaps in Knowledge

These challenges to MDR TB treatment adherence collectively indicate the need for improved patient education, more patient-centered care, and support for MDR TB patients through the course of treatment. In their updated MDR TB research agenda published in 2016, Mitnick et al. highlighted the consensus in the field of MDR TB for the need for effective and shorter treatment options, especially for special populations, like those co-infected with HIV [7]. Most of these findings, however, are qualitative in nature, and more starkly highlight the lack of quantitative data regarding the association of adherence with MDR TB treatment. This is a

critical area for future research, especially as this disease converges with HIV in low-resource contexts and creates an even more challenging treatment environment.

HIV Treatment Adherence

In contrast with the lack of published literature regarding the association of adherence with treatment outcome in MDR TB treatment, the association of adherence to antiretroviral therapy (ART) with treatment outcome is well-established in the HIV literature. There may be important lessons to learn from HIV that can be applied in the emerging field of TB treatment adherence. Compiled results of two large randomized clinical trials (N=1095) indicated adherence statistically significantly predicted HIV treatment outcomes of viral suppression and CD4 count [36]. Data from a prospective observational study of 99 HIV positive patients indicated the degree of adherence was statistically significantly associated with risk for virologic failure and suggested that adherence of 95% or greater is necessary to optimize virologic outcome [37]. Results of a pooled longitudinal analysis of 16 studies conducted in the United States between 1991-2009 (N=1088) indicated adherence was consistently strongly associated with response to ART across different regimens, providing evidence that incremental improvements in adherence may be associated with lower risk of virologic failure (Figure 3, Table 1) [38].

Table 1. Odds ratios and 95% confidence intervals of detectable HIV RNA by categories of covered time and the longest interruption, excluding less than 5% and more than 95% covered time.

Excluding less than 5% and more than 95% covered time	OR (95% CI)
Covered time	
93–100%	1.00
76–92%	1.47 (1.08, 2.04)
51–75%	1.56 (1.61, 3.50)
26–50%	2.38 (1.61, 3.50)
0–25%	4.23 (2.82, 6.34)
Length of longest interruption	
<48 h	1.00
>2 ≤ 7 days	1.21 (1.00, 1.46)
>7 ≤ 14 days	2.12 (1.62, 2.78)
>14 ≤ 21 days	2.62 (1.85, 3.72)
>21 ≤ 28 days	3.75 (2.46, 5.72)

CI, confidence interval; OR, odds ratio.

Measuring Adherence to ART

While the association of adherence to ART with treatment outcome is well-established, different methods for assessing treatment adherence exist, and the ideal method remains unclear [39]. Self-report recall questionnaires have been used to produce adherence measures with statistically significant associations with biologic HIV treatment outcomes [36]. Use of medication event monitoring system (MEMS) has also been used to measure more nuanced and precise adherence measurements, such as dose frequency and timing measures used to estimate the percent of time that ART drug levels were in the therapeutic range during the time period of interest [38]. Conclusions drawn from MEMS adherence measures were similar to those found by previous studies that used self-report measures of the strong association of adherence with treatment outcome, finding a dose-response relationship with increasing odds of detectable HIV-RNA with increasing length of treatment interruption [36,38]. The use of MEMS allowed the authors to measure the length and timing of treatment interruptions, and showed that consecutive

interruptions in treatment have a greater impact on HIV-RNA measurement than do sporadically-missed doses [38].

One prospective observational study (N=530) assessed an innovative adherence measurement technique, the SERAD (Self-Reported Adherence) questionnaire, and found this new questionnaire based on quantitative and qualitative self-report measures to be a valid measure of ART adherence when compared to pill count, electronic monitoring, and drug plasma monitoring [39]. The researchers found adequate agreement between all four measures when adherence was high. However, agreement between the measures fell as adherence levels decreased, highlighting the importance of improving adherence measurements for patients with lower adherence [39].

In a small, prospective cohort (N=34) of HIV positive patients in Kampala, Uganda, adherence data was collected and compared using 3-day self-report, 30-day visual analog scale (VAS), MEMS, and unannounced monthly pill count. The findings suggested a strong correlation between each of the adherence measures (pearson's correlation >0.75 between all measures) [40]. Both self-report measures accurately reflected objective adherence measures in this low-resource setting and indicated the potential benefit of using the VAS in particular, which is much simpler to administer but equally reflective of true patient adherence [40]. These findings, however, should be considered in light of the small sample size of the study.

In a prospective validation study of patients with HIV on ART (N=81), researchers validated a 3-item self-report of adherence against electronic drug monitoring (EDM) and found that the self-report, based on 30-day recall, minimally over-estimated adherence when compared to the EDM measure [41]. When the self-report adherence measures were calibrated to the EDM measures, however, the correlation was stronger. This study suggests that self-report adherence measures that assess recall over shorter periods of time may be a useful tool for measuring adherence to HIV medication, but the potential for overestimation of adherence should be considered and EDM measures might strengthen the validity of these self-report measures [41]. The

authors suggest this proposed three-item adherence self-report might be most appropriately used as a screening tool for non-adherence to help target interventions to improve compliance with treatment and in contexts where more expensive and complex methods cannot be used [41].

In contrast, a prospective study (N=78) of HIV-positive English-speaking patients in the United Kingdom designed to validate a new brief adherence assessment questionnaire, the Medication Adherence Self-Report Inventory (MASRI), measured adherence in both VAS and Likert scale (LS) form and used MEMS as the reference gold standard [42]. Subsequent results indicated that adherence recall improved when patients were asked to estimate adherence over a longer time period, in contrast with previously referenced findings of the greater validity of measures that involve shorter periods of recall. Adherence validity was measured through agreement of the MASRI self-report questionnaire with MEMS. The authors' findings also suggest that the VAS measure of adherence was the most strongly associated with MEMS cap data, supporting previous findings. The researchers concluded that despite the agreement of the tested self-report questionnaire with electronic drug monitoring in the study, multiple methods of measuring adherence should be employed in future studies, which mirrors the method in TB research of using multiple adherence measures to obtain the most valid estimate [42].

Gaps and Challenges to ART Adherence Measurement

Despite the breadth of studies of adherence in the treatment of HIV, a gap remains in understanding adherence in populations with lower overall levels of adherence, similar to that which exists in TB treatment [40]. This gap is problematic, as patients with low adherence are in the most need for adherence support in order to improve treatment outcome. In addition, the association of ART adherence and treatment outcome is well-established for the treatment of HIV, but methods to measure and improve adherence to DR-TB treatment are lacking. In addition, despite the establishment of the association of adherence with treatment outcome for HIV, the evidence remains controversial regarding a "gold-standard" for adherence measurement

in HIV treatment, as each method has strengths and weaknesses [43]. With the increasing prevalence of co-infection of HIV and MDR TB, for which much less in known regarding the association of adherence with treatment outcome, this is a critical area for future research in order to improve outcomes for co-infected patients.

TB/HIV Co-Infection Adherence

Adherence is a critical component to the successful treatment of TB and HIV, particularly in co-infected patients. Co-treatment of TB and HIV successfully reduces mortality rates for co-infected persons in a variety of contexts, particularly in patients with CD4 counts less than 50 cells/mL [32,44-46]. This successful reduction in mortality was cited in one study to be due in part to adherence support and training through strengthening the pre-existing TB DOT program in South Africa [32]. Data from this study additionally indicated nearly 80% of deaths in the study population were attributable to MDR or XDR TB [32]. After DR-TB cases were excluded from analysis, TB and HIV co-infection mortality declined substantially with integrated therapy and adherence support [32].

A cross-sectional study of TB/HIV co-infected patients in Uganda (N= 140) investigated the prevalence and factors associated with non-adherence to TB medication and found that the prevalence of non-adherence was high (25%), and that being on the continuation phase of treatment was significantly associated with non-adherence (OR: 6.24) [30]. Bivariate analysis indicated that alcohol consumption was associated with higher non-adherence, and knowledge of how TB is spread was associated with lower non-adherence [30]. These findings highlight the need for improving adherence during the continuation phase of treatment – after patients' symptoms improve but they still must remain on treatment – as well as the potential improvement in adherence with increasing awareness of how TB is spread and targeting interventions towards

patients who consume alcohol. However, the findings are generalizable only to patients with DS-TB, as the study did not include a population of patients with MDR TB. Because of the important differences in treatment of these two forms of TB, similar investigations regarding adherence in patients co-infected with HIV and MDR TB is critical.

MDR-TB/HIV Co-Treatment Adherence

Importance of and Measurements for Adherence to Treatment

Little to no evidence in the literature exists, to our knowledge, regarding the quantitative study of different adherence measures in patients with MDR-TB/HIV co-infection. The lack of publications on this topic has been cited, and no validated instruments to measure adherence to treatment for DR-TB exist [47].

However, one very relevant publication exists in the context of XDR TB, instead of MDR TB. In their prospective cohort study of patients with XDR TB and HIV co-infection in KwaZulu-Natal (N=104), O'Donnell and colleagues compared optimal treatment adherence to HIV and TB treatment and found that adherence to ART in this cohort was higher than adherence to anti-TB medication (88.2% optimal 6-month adherence to ART vs. 67.7% optimal six-month adherence to TB medication, $p<0.001$) [47]. The researchers measured adherence via self-report questionnaire which asked patients to recall adherence in the previous 7 days, and patients were classified as "sub-optimally adherent" if they reported any missed pills in the previous week. XDR TB patients co-infected with HIV were found to be less adherent to TB medications than HIV negative patients, but this difference was not statistically significant [47]. Male gender and low educational attainment were identified as risk factors for sub-optimal adherence in the study [47]. These findings support the potential usefulness of self-report adherence measures, as well as the classification of patients as non-adherent with any report of missed medication. However, this study of treatment outcomes for co-infected patients did not examine the association of adherence

with treatment outcomes, but focused instead on comparing adherence levels to ART and TB medications in the cohort.

O'Donnell and colleagues' finding that many sub-optimally adherent patients to TB treatment reported optimal adherence to ARV's suggests the possibility that with improved tolerability of DR-TB regimens and improved patient education and support, it may be possible to improve adherence to TB treatment for these patients [47]. This study also used a cumulative adherence measure over a six-month period, supporting the potential validity of collapsing adherence measurements from different time points.

Challenges to Adherence in the Context of MDR TB/HIV

A major challenge to measuring and improving MDR TB and HIV co-infected patient adherence is the historical use of DOT for TB treatment, causing it to be "so ingrained in the paradigm of DR-TB therapy" that very little "frank discussion of its utility" has occurred despite its wide-spread acceptance and use [26]. According to a cross-sectional analysis of 70 MDR TB patients, 65 DOT providers and 21 health center staff conducted in Mumbai, India, limited data exists regarding DOT's performance in MDR TB; DOT is often unrealistic and resource-draining in the context of the extended treatment regimen for MDR TB [26]. The strictness of DOT, but lack of patient-centered education and support have also been cited as key factors in loss to follow-up among MDR TB patients. Qualitative data suggests the stigma of DOT was reported to be even stronger in MDR TB patients co-infected with HIV who had already experienced stigma related to their HIV treatment [26]. In contrast, one study found the implementation of DOT through a full course of treatment was associated with higher treatment success rates for MDR TB patients, further highlighting the division in the field regarding the potential benefits and consequences of the use of DOT to improve MDR TB treatment adherence [31].

Umanah et el.'s retrospective review of MDR TB and HIV co-infected patients (N=1200) in South Africa found that mortality was higher among patients who began ART before initiating

MDR TB treatment, compared with patients who began ART after beginning MDR TB treatment [48]. These results are surprising and could be explained by several factors, including the overall poorer health of patients started on ART before MDR TB treatment as well as the impact of immune reconstitution inflammatory syndrome (IRIS). However, the researchers also hypothesized that the potential for drug-drug interactions with MDR TB and HIV co-treatment could impact adherence. [48].

Data from one qualitative study conducted in KwaZulu-Natal indicates that patients expressed a preference for ART over MDR- and XDR-TB medications [49]. These data additionally suggested that MDR- and XDR-TB treatment outcomes and social morbidity, including stigma and isolation, were perceived to be worse than those of HIV. These findings support the idea that non-adherence to DR-TB treatment regimens is complex and potentially associated in some way with poor perceived treatment outcomes, social isolation, stigmatization, and inadequate attention to patient education and support [49]. Additional cited challenges to adherence include high pill burden, worse adverse effects of DR-TB medications compared to those of ART, and better health education regarding HIV treatment [49]. Patients described feeling personally responsible for adhering to ART, whereas treatment for DR-TB was seen as the responsibility of nurses in this study [49]. These qualitative findings suggest areas for interventions and improved patient education to improve patient adherence.

Gaps in Knowledge

A systematic review conducted by O'Donnell and colleagues suggests that a lack of focus on medication adherence has played a role in contributing to poor treatment outcomes of HIV co-infected MDR TB patients [34]. Their findings also emphasize the importance of a move towards patient-centered care in order to improve treatment outcomes for this population [34]. This gap in knowledge regarding adherence in treating patients co-infected with MDR TB and HIV highlights

the potential for improved treatment outcomes with a renewed focus on understanding and improving adherence for these patients.

The available literature highlights the importance of individualized counseling and a flexible approach to improve adherence, as echoed by the WHO's End TB strategy shift from a uniform DOT strategy to individualized, patient-centered care that acknowledges the diverse needs of each patient [6]. The importance of individualized counseling was also a recurrent theme in key informant interviews of DOT experts in India [26]. Future research and work should also focus on improving the coordination of treatment for HIV and TB together [18,49]. It has also been suggested by Daftarty et al. that patient education and treatment literacy for MDR TB patients are less emphasized in drug-resistant TB treatment than in HIV treatment [49]. This gap could explain in part the higher rates of adherence to HIV medication found in their qualitative analysis of HIV and MDR TB co-infected patients [49]. Lack of treatment literacy, education, patient empowerment and ownership over treatment resulting from the need for constant observation of therapy in DR-TB may additionally be linked with lower rates of patient adherence to TB treatment compared with HIV treatment in South Africa [18].

Self-Report Adherence Measures

The SHOUT MDR (Survival and HIV OUTcomes in MDR TB) Study is an observational, prospective cohort study of MDR TB patients with and without HIV coinfection designed to examine survival and TB and HIV treatment outcomes. Adult male and female MDR TB patients with and without HIV co-infection were enrolled from three TB referral hospitals in KwaZulu-Natal Province, South Africa, from 2011 through 2013. The primary study objective was to compare treatment outcomes among patients with MDR TB/HIV coinfection to MDR TB patients without HIV coinfection.

Four adherence measures were additionally collected in the SHOUT MDR TB Study: a three-day self-report questionnaire, a thirty-day self-report questionnaire, a visual analog scale (VAS) on which patients marked their level of adherence to each medication type, on average, on a scale of 0-100% adherent, and pill counts. The first three measures were collected separately for TB and HIV medication, and pill counts were recorded for each individual medication type. Findings in the literature relating to the use of these four adherence measures specifically in the context of TB treatment were explored further. It should be noted that all of the studies cited here investigated adherence measures in other diseases or TB alone, but not in TB/HIV co-treatment or in drug-resistant TB.

Adherence Measures in Other Diseases

In a review of methods for measuring medication adherence, Farmer and colleagues compared direct adherence measurements, such as drug level in biologic fluids and biologic markers, to indirect adherence measures, including self-report, pill count, and electronic monitoring devices [50]. Indirect measures have strengths such as faster and lower-cost administration, as well as the potential to build provider-patient trust. However, indirect measures assume –- rather than directly measure --- patient adherence, and the authors cite several limitations to these measures. The large number of methods and questionnaires utilized to interview patients creates difficulty in determining the best method; the interviewers' skill and tone, as well as the wording of the questions can all impact the validity of the measures [50].

Pill count is also a commonly used indirect adherence measurement that is simple and inexpensive. However, its drawbacks include variable levels of accuracy, an inability to document patterns of non-adherence, potential for patient actions such as throwing pills away before study visits to alter measured adherence, and reasons for failure to comply [50]. Electronic drug monitoring, such as the widely used MEMS cap, which records time and date of obtaining a dose of medication, hold advantages over other indirect measures in its ability to provide more

continuous data. However, it is not without limitations, including the higher cost of implementation, especially in the context of MDR TB and HIV, which both require monitoring adherence for extended periods of time [50]. Farmer and colleagues conclude by suggesting none of the adherence measures in their review can be considered alone as the gold standard of medication adherence. They recommend a combination of adherence measures as the most effective method of accurately analyzing patient adherence, supporting the use of the four methods in the SHOUT study for measurement of MDR TB and HIV treatment adherence.

In a review of adherence to medication in the *New England Journal of Medicine*, Osterberg and colleagues echo the findings of Farmer, stating that indirect measures such as patient questionnaires are simple and inexpensive to administer, but may be subject to misinterpretation or misinformation by the patient and lead to overestimation of adherence levels [51]. This review additionally points out that pill counts, while commonly used, are subject to a number of problems, including changing medication type between measurements and discarding pills before clinic visits, and should therefore not be assumed to be an accurate indicators of adherence. It is also possible that the validity of adherence measures collected at study visits might be impacted by patient attempts to improve adherence with treatment in the days directly preceding a study visit, especially those that specifically measure adherence over a shorter period of recall in the three days to one week prior to the clinic visit [51]. The authors point out the benefit of physicians asking patients non-judgmentally about their adherence to medication, thereby encouraging honesty and enabling more accurate identification of non-adherence. Studies also show that despite the fact that adherence is often over-estimated by many measures, patients who admit to non-adherence are generally telling the truth [51,52]. However, even if a patient admits to non-adherence, they often underestimate their true level of compliance [52]. In addition to self-report measures, failure to attend clinic appointments might also serve as in indictor of non-adherence to treatment [52].

In a study (N=43) assessing the validity of a new medication adherence measurement tool, the Brief Medication Questionnaire (BMQ), researchers compared this self-report tool to MEMS [53]. The tool asked patients about their medication adherence in the past week, drug effects and bothersome features, and potential difficulties in remembering. The study found the sensitivity of the BMQ self-report tool was higher than many of the other published self-report measures at the time, suggesting that shortening the recall period may improve the validity of self-report measures. [50]. The researchers also found that the BMQ performed differently when measuring repeat non-adherence as compared to sporadic non-adherence [53]. These findings are relevant to the SHOUT study in that they identified the potential improvement in validity of self-reports over shorter periods of recall and that the sensitivity of the adherence measure varied by the type of non-adherence.

Serious concerns regarding the validity of self-reported adherence to treatment in general medicine have been cited, especially their poor sensitivity, or ability to detect true non-adherence [53]. However, there are merits to such tools, such as increased provider-patient trust and the ability to generally consider patients who admit non-adherence to be telling the truth. In addition, self-report adherence tools can be useful in low-resource settings and those which require long treatment times, as is the case in MDR TB patients co-infected with HIV, especially when they are measured over shorter periods of recall time.

Four Self-Report Adherence Measures in TB Treatment

In a cross-sectional validation study of adherence measures for TB treatment among new TB patients on home-based DOT in Tanzania (N=651), three adherence measures were validated against the gold standard of the direct adherence measurement of IsoScreen (isoniazid (INH)) intake in the previous day) [54]. The three indirect adherence tools assessed were the Morisky medication adherence scale (MMAS), which measures patient barriers to adherence; pill counts;

and a 2-day recall questionnaire. The study found high overall sensitivities of all three of the indirect adherence measures, but low specificities (all <50%). The 2-day adherence recall question performed best compared with the direct adherence measure [54], further supporting literature showing that self-reported adherence based on short periods of recall may be a valid measure of adherence. Such measures might also build patient-provider trust by communicating trust in the patient's honesty in reporting their adherence level [54]. However, the low specificities of all measures highlight the limitation of these measures' ability to detect non-adherent patients.

In a cross-sectional survey of new DS-TB patients in Kenya (N=212), researchers assessed the agreement of four adherence measures: urine testing for INH, pill count, 4-day recall questionnaire, and a VAS [55]. Patients were classified into three levels of adherence: unsatisfactory (more than 25% of pills missed), satisfactory (no more than 25% of pills missed in the last four days), and complete (no missed pills). While this tool is not exactly the same as the three-day recall measure used in the SHOUT study, it is similar in the type of questions and the period of recall. The study found fair agreement between the questionnaire and the biological marker of urine INH (k=0.43), as well as between the questionnaire and the VAS (k=0.40). Poor agreement was found between all of the other measures, suggesting that among the tested measures, a combination of self-report questionnaire and VAS could be used to best monitor adherence to TB treatment [55]. The study also indicated high overall levels of adherence using all measurement tools, measured as 92.5% complete adherence measured by the VAS, 95.2% complete adherence measured by the questionnaire, and 97.6% adherence measured by INH test. Pill count was the most incomplete measure. The low levels of agreement between all TB treatment adherence measures contradicted the researchers' expectations, as these measures have high levels of agreement in the context of HIV treatment [55]. This study population was composed of new, DS-TB patients, so similar study of adherence to DR-TB treatment is necessary and important, especially in the more complex context of HIV co-infection.

In a longitudinal pilot study of 50 TB patients in Tanzania, van den Boogard and colleagues measured and validated multiple self-report measures of TB treatment adherence against MEMS as the gold standard [56]. Their results indicated that MEMS detected a high overall level of adherence in the population (93.6%, SD: 7.7), and that an adapted version of the AIDS Clinical Trials Group (ACTG) adherence questionnaire and urine color test had the highest sensitivities. The adapted AIDS adherence questionnaire contained questions assessing adherence in the last thirty days, as well as questions that identified the time of the last estimated non-adherence over the past three months, so this measure could be considered to be the most similar to the 30-day recall questionnaires and VAS used in the SHOUT study. Recorded clinic visits for medication refills and the Morisky scale had the highest specificities, and pill counts combined with refill visits yielded moderate sensitivity and specificity. Their findings indicate that in settings without the resources to monitor adherence with MEMS, a combination of a self-reported adherence measure with pill counts and clinic visit attendance could serve as similarly valid indicators of non-adherence. However, the authors emphasized the need for further study in larger populations with a wider variety of adherence levels [56]. Van den Boogard and colleagues additionally found that the proportion of 100% adherent patients identified by the different adherence measures varied widely [56], supporting the use of multiple measures to obtain more valid assessments of treatment adherence.

Conclusion

In sum, the literature indicates that no one gold standard measure has been identified for measuring adherence to TB treatment. In lieu of this gold standard, multiple measures are recommended, and self-report based on a shorter period of recall as well as a VAS may be the most effective estimates of adherence, especially when used in combination. Reported levels of adherence are generally high in the reviewed literature. A critical gap remains in identifying measures that accurately detect non-adherence and are effective indicators of patients with the

lowest adherence. These patients are arguably the most important to detect with adherence measures, as they are in the greatest need of intensive adherence intervention [52].

The following investigation was designed to utilize adherence data collected in the SHOUT study to validate different adherence measures as markers of treatment response for MDR TB/HIV co-infected persons and shed light on the association of adherence with MDR TB treatment outcome through prospective study. The primary study objectives are to (1) investigate the level of adherence to MDR TB and HIV treatment among a cohort of MDR TB patients in KwaZulu-Natal, South Africa, and (2) determine the association of adherence with MDR TB treatment outcome. Secondary objectives of the study are to (1) investigate the performance of 3 adherence tools to predict MDR TB and HIV treatment outcomes, and (2) investigate differences in adherence to antiretroviral therapy (ART) and MDR TB treatment among persons with MDR TB and HIV co-infection.

CHAPTER II: MANUSCRIPT

Treatment Adherence Among Persons Receiving Concurrent MDR-TB and HIV Treatment in KwaZulu-Natal, South Africa

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ABSTRACT

Background. Concurrent multidrug-resistant tuberculosis (MDR-TB) and human immunodeficiency virus (HIV) treatment entails high pill burden, frequent adverse events and long therapy duration. KwaZulu-Natal province, South Africa, has approximately 5,000 MDR-TB cases annually (80% HIV-infected). We evaluated adherence to MDR-TB and antiretroviral therapy (ART) and its association with treatment outcomes.

Methods. We prospectively followed MDR-TB patients for 24 months. Adherence was assessed monthly using 3-day recall, 30-day recall and visual analog scale (VAS). MDR-TB treatment success was defined as cure or completion; failure, death or loss-to-follow-up were unsuccessful outcomes. We determined the proportion of fully adherent participants by each adherence measure, stratified by HIV status. We assessed the association with MDR-TB treatment success and 60-day culture conversion using unadjusted risk ratios. Among HIV-positive participants, we examined differential adherence to MDR-TB vs. HIV treatment using McNemar's test.

Results. Among 200 MDR-TB patients, 63% were female, median age was 33 years, and 144 (72%) were HIV-positive, of whom 81% were receiving ART at baseline. Adherence to MDR-

TB and HIV treatment was high across all measures (82-96% fully adherent) and did not differ by HIV status (Figure). Among HIV-positive participants, ART adherence was significantly higher than MDR-TB treatment adherence by all measures (Figure). Using a composite measure of 3-day recall and VAS, MDR-TB treatment success and 60-day culture conversion were higher among participants who were fully adherent, but this difference was not statistically significant (RR: 1.11, 95%CI: 0.87-1.41; RR: 1.29, 95% CI: 0.70-2.43).

Conclusions. Self-reported MDR-TB treatment adherence was high and did not differ by HIV status, suggesting co-treated persons can achieve high adherence. Reported adherence to ART was higher than to MDR-TB treatment by all study measures. More objective adherence measures and a better understanding of preferential ART adherence are needed to inform interventions that improve outcomes for MDR-TB and HIV co-infected persons.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR TB), defined as resistance to at least isoniazid and rifampin [5], is an increasing global health concern, with an estimated 480,000 cases in 2015. MDR TB treatment involves 4-5 different drugs, including an injection with kanamycin for the first six months of treatment, with many toxic side effects and treatment length of approximately two years. The global treatment success rate for MDR TB was 52% in 2013, compared to 83% treatment success for drug-susceptible TB globally in 2014, highlighting the need for improved treatment outcomes [1,6,11].

Worldwide, TB is a leading cause of mortality in patients with HIV [4]. Among patients with MDR TB and HIV, mortality rates are substantially higher, with one study citing a hazard ratio of 5.6 for HIV-infected vs. uninfected MDR TB patients [57,58]. Treatment for MDR TB/HIV co-infected patients requires complicated drug regimens that result in high pill burden and

potential for overlapping toxicities from antiretroviral therapy (ART) and MDR TB treatment, such as gastrointestinal symptoms, peripheral neuropathy, depression, and hearing and vision disturbances [14,59]. However, despite historically poor treatment outcomes for co-infected patients [14], concurrent MDR TB and HIV treatment is feasible and can yield good patient outcomes, even in low-resource settings [12].

Medication adherence is critical to successful treatment of both MDR TB and HIV [29]. Non-adherence poses a major threat to global TB control by increasing the risk of treatment failure, TB relapse, and the development of further drug resistance [13,21]. However, little quantitative evidence exists regarding adherence in MDR TB and HIV co-treatment, or the effect of non-adherence on treatment outcomes [21]. Studies have shown drug-susceptible TB treatment adherence is reduced by the length of treatment, medication side effects, and symptomatic improvement before treatment completion [23]. Qualitative studies of MDR TB treatment adherence have shown negative impacts of longer treatment time, serious adverse events, perception of poor treatment outcomes, stigma and lack of social support, and preferential adherence ART over MDR TB treatment all contribute to reduced adherence [35,49]. Successful treatment of MDR TB relies on adherence to a much longer period of treatment, with a substantial proportion of patients experiencing serious side effects [5], however there are limited data on the association between adherence and treatment outcomes for MDR TB patients co-infected with HIV.. Although directly-observed therapy (DOT) is recommended as the standard of care for TB to ensure patient adherence, implementation in high-burden settings is inconsistent due to logistical and human resource challenges. For MDR TB, provision of an injection generally ensures DOT during the 6-9 month intensive phase; however, lengthy treatment duration and twice daily dosing of certain drugs challenge successful DOT throughout MDR TB treatment.

South Africa has the highest burden of TB, MDR TB and HIV co-infection worldwide, harboring approximately 25% of the global TB/HIV burden [17]. South Africa had an estimated

20,000 (95% CI: 13,000-27,000) cases of MDR TB in 2014 [1,11], of whom 70-80% are HIV co-infected [10,12]. The high prevalence of MDR TB and HIV co-infection poses a complex and critical health threat for South Africa's population. We sought to investigate the association between adherence to MDR TB and HIV medication and MDR TB treatment outcome among MDR TB patients with and without HIV co-infection in KwaZulu-Natal, South Africa.

METHODS

Study Design and Population

The SHOUT MDR TB (Survival and HIV OUTcomes in MDR TB) Study is a prospective observational study of MDR TB patients with and without HIV coinfection designed to examine survival and TB and HIV treatment outcomes. Adult male and female MDR TB patients with and without HIV coinfection were referred for study enrollment from three TB referral hospitals in KwaZulu-Natal Province, South Africa, from 2011 through 2013.

Patients were screened for inclusion based on the following criteria: (1) culture-confirmed MDR TB (resistance to at least rifampicin and isoniazid), (2) age 18 years or older, (3) documented HIV status, either HIV-positive or HIV-negative, and (4) initiated on standard MDR TB treatment within 14 days of screening visit. All HIV-positive patients were on ART throughout the study according to standard of care guidelines. Exclusion criteria included: (1) history of previous MDR TB treatment, (2) resistance to fluoroquinolones or any injectable tuberculosis medications (i.e., extensively drug-resistant (XDR) or pre-XDR TB), (3) positive pregnancy test, (4) receipt of non-standard TB or HIV treatment, (5) abnormal baseline creatinine (>2x the upper limit of normal) or alanine aminotransferase (>5x the upper limit of normal), or (6) undocumented HIV status.

Treatment regimens for HIV and MDR TB were determined by participants' clinicians based on South African national guidelines; research staff were not involved in treatment decisions. The standard South African MDR TB regimen at the time of the study included

kanamycin, ofloxacin or moxifloxacin, ethionamide, terizidone, ethambutol, and pyrazinamide. Kanamycin was administered for at least 6 months or 4 months after culture conversion (whichever was longer), and oral medications without kanamycin were continued for 12-18 additional months following culture conversion. Most HIV-infected participants received efavirenz-based ART regimens with stavudine and lamivudine at the beginning of the study; stavudine was changed to tenofovir with a shift in national guidelines in 2013.

The cohort was followed monthly throughout the duration MDR TB treatment (typically 24 months). Patient demographics, TB exposure and treatment history, HIV exposure and treatment history, and other pertinent medical history information were obtained from the patient at the initial visit. Treatment response, adverse events, regimen changes, and patient adherence were assessed at each study visit. Sputum cultures and drug-susceptibility testing (DST) were conducted at each visit. Viral load and CD4 cell count was measured for HIV-positive patients every three months.

Adherence measurement

Three measures of adherence were collected separately for MDR TB and HIV treatment regimens at each study visit, yielding six adherence measures per participant per study visit. The three measures included: (1) a 3-day self-report questionnaire of the number of treatment pills missed over the last three days; (2) a 30-day self-report questionnaire of the number of pills lost, given away, not taken or additional pills taken from other sources since the previous study visit; and (3) a visual analog scale (VAS), ranging from 1 –100%, depicting the participant's overall self-reported level of adherence in the last 30 days. Full adherence to each individual measure was defined as no reported missed medication at any point in the study by that measure [51,52]. We created two composite adherence measures: (1) Full adherence reported by all three individual

measures; (2) Full adherence as reported by the 3-day recall measure and VAS. Separate composite measures were created for adherence to MDR TB and HIV treatment.

Outcomes of interest

The primary outcomes of interest were MDR TB treatment success, defined as either MDR TB cure or treatment completion, and TB culture conversion within 60 days of treatment initiation; participants with death, treatment failure or treatment interruption were categorized as having unsuccessful treatment (see Laserson et al [60] for details of treatment outcome definitions). MDR TB culture conversion was defined as two consecutive negative TB-cultures taken 30 days apart after MDR TB treatment initiation. The primary HIV outcome measure of interest was virologic failure, defined as a detectable viral load (>150 copies/mL) or failure to suppress by 6 months post ART initiation or viral suppression with two subsequent viral load values of greater than 1000 copies/mL during follow up.

Data Analysis

Data analysis was performed using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, USA). Demographic and clinical characteristics were described using medians and interquartile ranges (IQR) for continuous variables and frequencies for categorical variables. We used Wilcoxon Mann-Whitney test for continuous variables and the Fisher's exact and chi-squared tests for categorical variables to compare MDR TB patients with and without HIV coinfection. The proportion of fully adherent participants was calculated according to the three individual measures and both composite measures for HIV and MDR TB treatment, separately. Full adherence to MDR TB medication was compared among the HIV-positive and HIV-negative cohorts using chi-squared tests. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each individual and composite adherence measure for

predicting successful TB treatment outcome and virologic suppression were calculated for adherence to each regimen, respectively. Among HIV-positive participants, we compared adherence to MDR TB treatment and ART using McNemar's test.

Log-binomial regression was used to assess associations of the most valid composite measure with MDR TB and HIV treatment outcomes, as defined above. Variables were selected for inclusion in the final log-binomial models based on previously published literature and assessment of significant bivariate associations (two-sided p-value <0.2). We used backwards elimination to build the final models.

Ethical Considerations

All study participants provided written informed consent prior to screening for study enrollment. The study was approved by the institutional review boards of Emory University, Albert Einstein College of Medicine, the University of KwaZulu-Natal (UKZN) and by the KwaZulu-Natal Department of Health and the Centers for Disease Control and Prevention's (CDC) National Center for HIV, Hepatitis, STDs and Tuberculosis.

RESULTS

We screened 599 MDR TB persons who provided consent for study enrollment from 2011–2013, of whom 206 comprised the final study sample (Figure 1). Diagnosis of TB determined not MDR TB by DST (n=189) was the most common reason for exclusion after consent was obtained. Additional reasons for exclusion after consent included abnormal creatinine or alanine aminotransferase (ALT) levels, non-standard MDR TB or HIV treatment, and pregnancy (Figure 1). Six participants were excluded from adherence analysis because they withdrew from the study or died before adherence data could be collected. The final cohort for

the adherence analysis was 200 participants, which included 144 HIV co-infected MDR TB participants and 56 MDR TB HIV-negative participants.

Characteristics of the 200 MDR TB patients included in this analysis are described in Table 1. The mean age was 35 years, and 63% were women. Two-thirds (65%) reported previously receiving TB treatment. Of the 144 participants co-infected with HIV, 116 (81%) were receiving ART at the time of MDR TB treatment initiation. At baseline, participants' median CD4 count was 215 cells/mm^3 (IQR: 109–376) and 66% had an undetectable viral load (threshold of <150 copies/mL). HIV-positive MDR TB participants were more likely to be female than were HIV-negative participants (69% vs. 46%, p=0.0025), more likely to have previous TB treatment (72% vs. 46%, p<0.001), and less likely to be diabetic (0.69% vs. 11%, p<0.0021).

Overall, reported levels of adherence to both MDR TB and HIV treatment were high (Table 2). The 30-day recall questionnaire identified the highest proportion of participants reporting full adherence to MDR TB treatment (94% adherence) and to HIV treatment (94% adherence). As assessed by the three-day recall questionnaire and visual analog scale, adherence was substantially lower than by the 30-day questionnaire for both MDR TB treatment (85% vs 85% vs. 94%, respectively) and ART (92% vs 91% vs. 98%). According to both composite measures, reported adherence was slightly lower than indicated by the individual measures for both MDR TB treatment (81% for 3-part composite, 82% for 2-part composite) and ART (88% and 89%, respectively).

Bivariate analysis indicated no significant differences in adherence to MDR TB treatment between HIV-positive and HIV-negative participants (Table 2). However, among HIV and MDR TB co-infected patients, all three individual measures and both composite measures identified significantly higher adherence to ART than to MDR TB treatment (Figure 2). The three-day recall (84% to MDR TB treatment vs. 92% to ART, p=0.003) and composite measure of VAS and 3-day recall (82% vs. 89%, respectively, p=0.013) indicated the largest differences.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting favorable MDR TB and HIV outcomes were calculated for the three adherence measures (Appendix A). All had high sensitivities and most had fairly high positive predictive values for MDR TB treatment success, 60-day culture conversion, and HIV virologic suppression, based on medication adherence (all sensitivities >80%, all PPV's ≥74% except for 60-day culture conversion). The 30-day self-report questionnaire had the highest sensitivity for all three treatment outcomes, while either the 3-day recall, VAS, or composite measure based on both had the highest negative predictive values, except for the HIV outcome. The overall specificity and negative predictive values of all instruments was low (all ≤69%). The most valid adherence measure available was determined based on these calculations to be composite measure 2, which includes 3-day recall and visual analogue scale. This 2-part composite was therefore the adherence measure included in all analyses with treatment outcomes.

The unadjusted relative risk of MDR TB treatment success among fully adherent versus less than fully adherent participants to MDR TB treatment are shown in Table 3. All measures, except the 30-day questionnaire, showed a marginal, though non-significant, increased risk of TB treatment success among fully adherent vs. less than fully adherent participants. The composite measure of 3-day recall and VAS indicates the strongest association of adherence with MDR TB treatment success (RR: 1.11, 95% CI (0.87-1.41)). The unadjusted risk of culture conversion within 60 days of treatment initiation was also higher, though not statistically significant, for fully vs. not fully adherent participants (Table 3, RR: 1.29, 95% CI: 0.69 –2.43). The unadjusted relative risk of achieving sustained virologic suppression is shown in Table 3.

In multivariate analysis adjusted for age, HIV status, gender, and neurological symptoms reported at baseline, the risk of MDR TB treatment success was approximately 4% higher among participants who reported full adherence to TB treatment than among those less than fully adherent (aRR: 1.04, 95% CI: (0.82-1.32)). Adjusting for age, gender, and HIV status, the risk of

TB culture conversion within 60 days of treatment initiation was approximately 12% higher among fully vs. less than fully adherent participants (aRR: 1.12, 95% CI: (0.61-2.07)).

DISCUSSION

This is the first study to our knowledge to prospectively examine the association between medication adherence and treatment outcome in patients co-infected with MDR TB and HIV. To date, published studies have examined adherence to HIV or TB medication independently, but not together, and none examined adherence among MDR TB patients co-infected with HIV. We utilized three adherence measures in a prospective cohort of patients undergoing treatment for MDR TB in KwaZulu-Natal, South Africa. We found high adherence to both MDR TB treatment and to antiretroviral therapy (ART), with no difference in MDR TB adherence among HIV co-infected persons. Nonetheless, among co-infected persons, adherence to ART was higher than to MDR TB treatment. Together, these findings suggest that MDR TB and HIV co-treatment is feasible without substantial effect on medication adherence, despite the added pill burden and potential overlapping toxicities. In addition, a better understanding of preferential ART adherence can be used to inform interventions that improve MDR TB treatment adherence in co-infected populations.

Higher adherence to HIV medication than to TB medication in our study supports previously published findings of preferential adherence to ART over TB treatment in a qualitative study of co-infected MDR TB persons [49] and a prospective cohort of 104 persons with extensively drug-resistant TB (XDR TB) and HIV [47], both conducted in KwaZulu-Natal. Researchers found non-adherence to drug-resistant (DR) TB treatment is influenced by poor perceived treatment outcomes for DR TB, social isolation, stigmatization, and inadequate attention to patient education and support compared to HIV care, in addition to the clinical adherence barriers of higher pill burden and worse adverse effects of DR-TB medications [49]. Patients also expressed

feeling personally responsible for adhering to ART, whereas treatment for DR TB was seen as the responsibility of nurses [49]. The association of adherence to ART with treatment outcome is well-established in the HIV literature [36-38]. In contrast, TB treatment's historically standard use of directly observed therapy (DOT) to assume 100% medication adherence has limited critical examination of its effectiveness, despite conflicting evidence [26]. As the global TB community shifts towards more patient-centered TB care [6], this adherence gap is a critical opportunity to improve MDR TB adherence through application of lessons learned from higher ART adherence among co-infected persons, such as improved TB patient support and education [35].

None of the adherence measures used in this study were robust predictors of treatment outcomes, however, there was a trend towards a protective effect of adherence on successful MDR TB treatment outcome. Our finding of potentially higher risk of MDR TB treatment success and 60-day culture conversion among fully adherent participants is similar to the well-established association of higher HIV medication adherence with better treatment outcomes for HIV patients [37,38]. Of the three adherence instruments used in the study and two composite measures, a combination of the three-day recall questionnaire and VAS was found to be the most valid measure, as indicated by its negative predictive value and comparatively stronger association with the clinical measures of treatment success for MDR TB treatment. The association of self-reported adherence based on a shorter recall period (3-day) with an objective measure of treatment success is consistent with the findings of a small prospective study in a similar, resource-limited setting in Uganda, even though the findings in our study were not statistically significant [40]. However, very low specificities in our results for all measures suggest that indirect, or self-reported, non-adherence to MDR TB treatment is not a robust predictor of unsuccessful treatment outcomes.

The overall high levels of adherence found in our study were likely an over-estimation that resulted from the lower ability of indirect adherence measures to detect true non-adherence [21]. However, these high adherence levels are consistent with previous literature regarding adherence

measure validation in TB and HIV [40,54,55]. The higher specificity and NPV of the 3-day recall measure as compared with the 30-day recall measure is consistent with published literature that self-report of adherence over shorter periods of recall (2-4 days) tend to be more accurate than are more general recall questions referencing the last month and is often a more feasible option in contexts where more expensive and complex methods cannot be used [41]. An observational study of 530 HIV-infected persons in Spain compared adherence assessed via weekly and monthly self-report questionnaires and found that the shorter-recall adherence measure more closely matched the adherence levels indicated by drug plasma levels in the study [5]. A cross-sectional study of 651 TB patients in Tanzania found that shorter recall self-report identifies patient adherence more accurately than does recall of the previous month's overall adherence [54]. The low specificities of all adherence measures in our study are also consistent with those of this cross-sectional study of Tanzanian TB patients, which found that none of the investigated measures accurately identified non-adherent patients [54]. The highest validity of the composite measure in our analysis supports previous research that encourages future studies to employ multiple methods of measuring adherence to obtain the most valid adherence estimate in TB research [42].

This study had several limitations. First, the study's sample size was relatively small, and the analysis was limited by the number of participants defined as non-adherent because of the high reported levels of adherence in the study population. This reduced the heterogeneity of adherence categories and limited the power to conduct certain analyses, particularly for the ART measures which had higher levels of adherence. However, the strict cut-offs used to identify "non-adherence" in our study are supported by previous TB adherence literature [47,54]. Recall bias was a potential limitation to the accuracy of self-report questionnaires. However, the use of the 3-day recall questionnaire potentially minimized recall bias by using a measure based on shorter periods of recall that has been shown to more accurately predict adherence [41]. Additionally, this analysis was limited by its inability to include a more objective adherence measure than self-report, such as MEMs cap devices or urine drug levels. Pill count information was collected at

every study visit, but this analysis was also not able to examine the association of this data, nor that of adherence to clinic visits, as potentially more sensitive measures of adherence. Future data cleaning and analysis are planned for these additional adherence measures.

Despite these limitations, this was, to our knowledge, the first prospective cohort study to investigate the association of adherence with treatment outcome among MDR TB patients co-infected with HIV in a low-resource setting. Adherence in this study population was high, and did not differ significantly between MDR TB participants with and without HIV co-infection. This finding contradicted our hypothesis that increased pill burden and more severe adverse events from overlapping drug toxicities often experienced by co-infected participants might reduce their adherence levels. Even though self-reported adherence to both treatment regimens was high in the study, the data provide quantitative evidence of preferential adherence to ART over MDR TB treatment. This finding suggests the importance of efforts to investigate this preferential adherence and apply strengths of ART adherence support to improve MDR TB treatment adherence. Our findings also highlight the importance of developing adherence assessments that can more accurately identify non-adherent persons while also building provider-patient trust [54]. Building such trust provides a critical opportunity for moving towards a model of patient-centered care**,** which is believed to be a critical next step to improve adherence and outcomes for MDR-TB and HIV co-infected persons [34].

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TABLES

Table 1. Baseline characteristics of the SHOUT cohort (N=200).

	Total Cohort (N=200)	HIV+ (N=144)	HIV- (N=56)	
	N(%)	N(%)	N(%)	p-Value
Demographics				
Age (categories)				**<0.001[a]**
18-25	41 (21)	14 (10)	27 (48)	
26-35	72 (36)	66 (46)	6 (11)	
36-45	51 (26)	45 (31)	6 (11)	
46-55	21 (11)	13 (9)	8 (14)	
>55	15 (8)	6 (4)	9 (16)	
Gender (Female)	126 (63)	100 (69)	26 (46)	**0.003[b]**
Race				0.077[a]
Black	198 (99)	144 (100)	54 (96)	
Indian	1 (0.5)	0 (0)	1 (0.5)	
White	1 (0.5)	0 (0)	1 (0.5)	
Previous History of TB Treatment	130 (65)	104 (72)	26 (46)	**0.006[b]**
Smoking History	47 (24)	35 (24)	12 (21)	0.666[b]
Alcohol History	62 (31)	48 (33)	14 (25)	0.253[b]
Household Member with TB	35 (18)	22 (15)	13 (23)	0.185[b]
Healthcare Worker, past 12 months	13 (7)	7 (5)	6 (11)	0.197[a]
Work in the Mines, past 12 months	6 (3)	5 (4)	1 (2)	1.000[a]
Prison, past 12 months	5 (3)	4 (3)	1 (2)	1.000[a]
Hospitalized (any reason), past 2 years	38 (19)	30 (21)	8 (14)	0.323[a]
Medical History and Current Symptoms				
Past Medical History (% Yes)				
Vision Loss	27 (14)	23 (16)	4 (7)	0.113[a]
Hearing Loss	15 (8)	11 (8)	4 (7)	1.000[a]
Asthma/Recurrent Wheezing	13 (7)	8 (6)	5 (9)	0.360[a]
Hepatitis or Liver Disease	3 (2)	2 (1)	1 (2)	1.000[a]
Kidney Disease	2 (1)	1 (0.7)	1 (2)	0.483[a]
Diabetes	7 (4)	1 (0.7)	6 (11)	**0.002[a]**
Seizures	5 (3)	4 (3)	1 (2)	1.000[a]
Peripheral Neuropathy	43 (22)	36 (25)	7 (13)	0.057[a]
Depression or Psychiatric Condition	14 (7)	11 (8)	3 (5)	0.761[a]
Other	10 (5)	5 (4)	5 (9)	0.147[a]
Other Symptoms				
Respiratory	112 (56)	77 (54)	35 (63)	0.248[b]
Gastrointestinal	35 (8)	26 (18)	9 (16)	0.838[a]
Joint and Muscle Pain	51 (26)	36 (25)	15 (27)	0.795[b]
Neurological	87 (44)	69 (48)	18 (32)	**0.043[b]**
Psychological	35 (18)	29 (20)	6 (11)	0.148[a]
Other	33 (17)	23 (16)	10 (18)	0.832[a]
HIV Characteristics				
On ARV's		116 (81)		
CD4 Count (Median (IQR)), n = 139		215 (109-376)		
Virologically Suppressed at Baseline, n = 97		64 (66)		

[a]Fisher's exact test (2-sided p-value)
[b]Chi squared test

Table 2. Proportion of participants fully adherent[a] to MDR TB and HIV medication using three adherence measures, by HIV status.

	Medication Adherence				
	3-day Recall[b], n (%)	**30-day Questionnaire[c], n (%)**	**Visual Analog Scale[d], n (%)**	**Composite Adherence Measure 1[e], n (%)**	**Composite Adherence Measure 2[f], n (%)**
Combined Cohort					
MDR TB Tx (n = 200)	170 (85)	188 (94)	169 (85)	162 (81)	164 (82)
HIV+					
MDR TB Tx (n = 144)	121 (84)	134 (93)	122 (85)	116 (81)	118 (82)
ART (n=139)	128 (92)	136 (98)	126 (91)	123 (88)	124 (89)
P-value	0.003	0.031	0.039	0.007	0.013
HIV-					
MDR TB Tx (n = 56)	49 (88)	54 (96)	47 (84)	46 (82)	46 (82)
P-value[g]	0.35	0.30	0.65	0.84	0.97

MDR TB: Multidrug-resistant tuberculosis; **HIV**: Human immunodeficiency virus; **Tx**: Treatment; **ART**: Antiretroviral Therapy

[a]Full adherence defined as no reported missed medication at any point in the study

[b]Percent that did not report missing any pills in the last 3 days at any point in the study

[c]Percent that did not report missing any pills in the last 30 days at any point in the study

[d]Based on visual analog scale rating (from 0-100%) of percent of medication taken since last study visit

[e]Composite measure 1 indicates full adherence by all three individual measures (3-day, 30-day, and VAS) throughout the study

[f]Composite measure 2 indicates full adherence by both the 3-day recall measure and the visual analog scale throughout the study

[g]Based on Fisher's exact test for dichotomous variables comparing MDR TB treatment adherence among HIV+ and HIV- participants

Table 3. Relative risk of successful MDR TB and HIV treatment outcome among fully adherent[a] participants.

	TB Treatment Success[b] (N=188)	60-Day Culture Conversion[c] (N=139)	Sustained Virologic Suppression[d] (N=137)
Adherence Measure	**RR[e] (95% CI)**	**RR[e] (95% CI)**	**RR[f] (95% CI)**
3-day Recall	1.09 (0.84 - 1.15)	1.19 (0.61 - 2.31)	1.02 (0.77 - 1.36)
30-day Questionnaire	0.99 (0.71 - 1.39)	0.87 (0.38 - 1.98)	1.26 (0.56 - 2.81)
Visual Analog Scale	1.08 (0.84 - 1.38)	1.45 (0.69 - 3.09)	0.89 (0.75 - 1.07)
Composite Measure 1[g]	1.07 (0.86 - 1.35)	1.08 (0.63 - 1.86)	0.95 (0.77 - 1.16)
Composite Measure 2[h]	1.11 (0.87 - 1.41)	1.29 (0.69 - 2.43)	0.96 (0.77 - 1.19)

[a]Full adherence defined as no reported non-adherence to MDR TB drugs at any point in the study
[b]TB treatment success defined as cure or treatment completion; failure defined as any outcome besides cure or treatment completion (treatment failure, treatment default, moved, transfer, or withdrawal)
[c]TB culture conversion within 60 days of treatment initiation.
[d]No virologic failure during the study period.
[e]Risk ratio for participants fully adherent to MDR TB treatment vs. not fully adherent.
[f]Risk ratio for participants fully adherent to ART vs. not fully adherent.
[g]Composite measure 1 includes non-adherence indicated by any of the three individual measures.
[h]Composite measure 2 includes non-adherence indicated by either the 3-day recall measure or the visual analog scale.

FIGURES

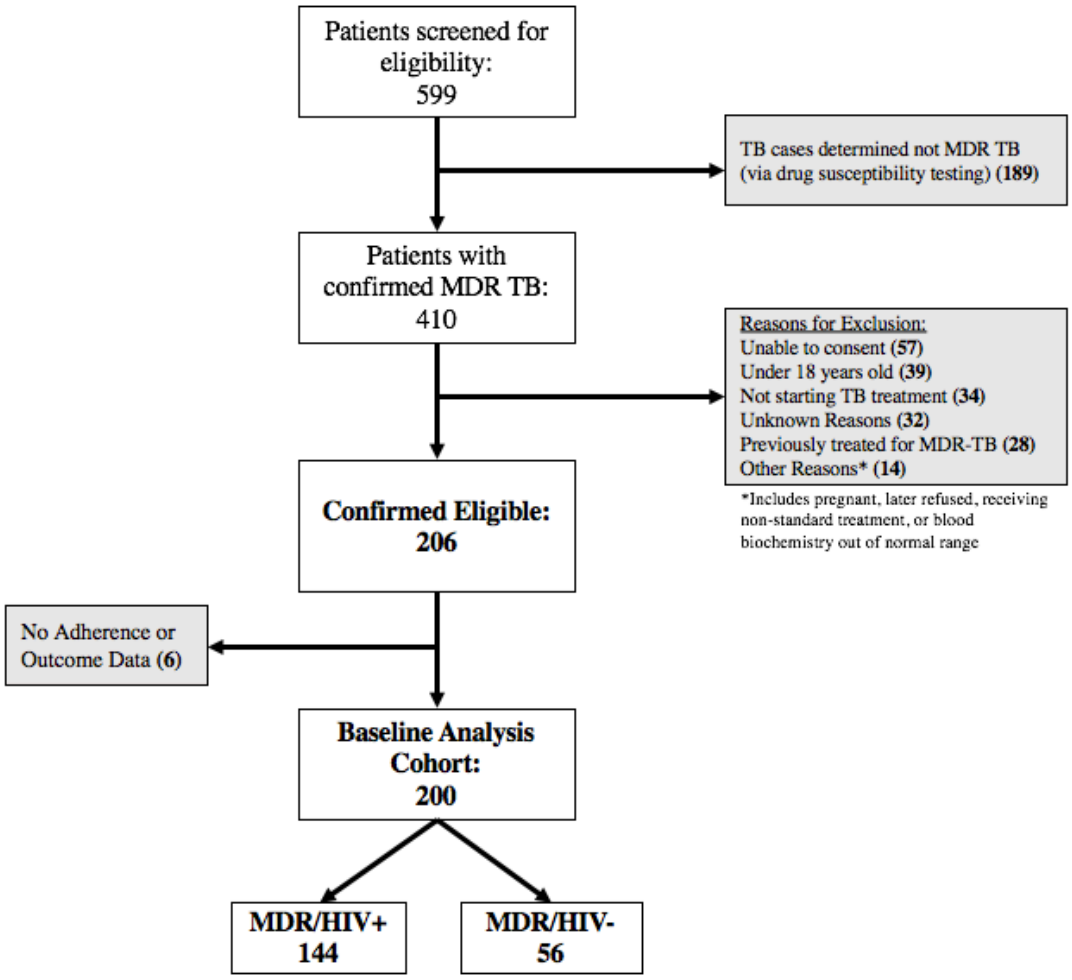

Figure 1. Enrollment flowchart of participants screened and enrolled.

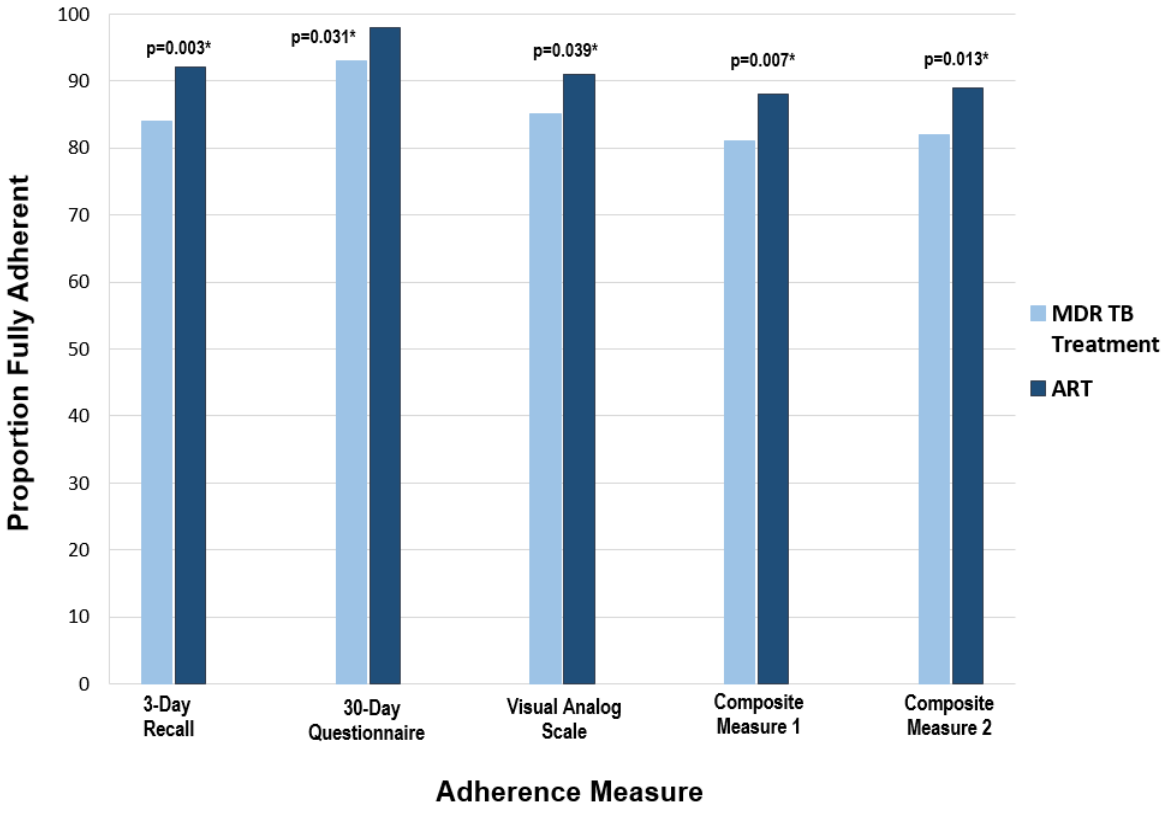

Figure 2. Proportion of MDR TB/HIV-positive participants fully adherent to MDR TB and HIV treatment regimens, by adherence measure (n=139).

CHAPTER III: PUBLIC HEALTH IMPLICATIONS AND FUTURE DIRECTIONS

This study indicated co-treatment for MDR TB and HIV can be administered successfully while maintaining high levels of adherence to treatment and that patients preferentially adhere to ART over MDR TB treatment, expanding upon this currently under-represented topic in the TB literature. As the global prevalence of drug-resistant TB rises and converges with HIV in high disease-burden areas such as South Africa, further research that builds on the findings of this study to identify and validate more objective adherence measures and better understand preferential adherence to ART is critical.

Our finding of preferential adherence to ART over MDR TB treatment reinforces previously published qualitative evidence of several patient-expressed factors that reduce their ability to adhere to MDR TB treatment compared to ART. This literature suggests increased social stigma, decreased levels of patient support and education, and more severe adverse effects and pill burden associated with DR TB treatment reduce patients' adherence to TB treatment compared to ART. Our findings provide quantitative support for these patient-expressed perspectives, and represent an opportunity to investigate with greater intentionality the reasons for this adherence gap. Despite recent improvements in treatment for MDR TB and HIV, including shorter regimens for TB, these treatments still entail a high pill burden and challenging regimen for a comparatively long amount of time. Patient support through this challenging treatment is critical, but it may be lacking in TB care as compared to support for patients on HIV treatment. However, once preferential ART adherence is better understood, practitioners can apply the strategies and support factors that have effectively created high ART adherence in this population to improving MDR TB treatment adherence.

The low ability of the adherence measures in our analysis to identify non-adherent participants highlights the importance of developing and validating more objective adherence

measures, with high specificities for detecting non-adherence. A number of more objective adherence measures exist, such as MEMs caps and urine TB drug level test, such as the IsoScreen INH test. Additionally, patient adherence to clinic visits might be able to serve as a proxy for adherence to treatment and warrants further study. However, rigorous investigation of these measures in the unique context of DR TB with and without HIV co-infection, has not been conducted, to our knowledge, despite its importance to these vulnerable patient populations.

Because of the subjective nature of the self-reported adherence measures in our investigation, the estimated proportion of fully adherent patients is likely an over-estimate of the true adherence level in the study population. Future efforts to quantify the association of adherence with treatment outcomes should be conducted with more objective adherence measures, robust to the potential for bias in self-reported measures. These measures will allow for more confident conclusions to be drawn regarding the impact of reduced adherence on MDR TB treatment outcomes for HIV-co-infected persons. In addition, the greatest validity of the composite measure in our analysis supports established evidence of the increased validity of combining multiple adherence measures. Future studies should employ multiple measures of adherence to obtain the most valid adherence estimates in the context of DR TB and HIV co-infection.

Though not statistically significant, our findings of increased risk of negative treatment outcomes with less than full adherence suggest that even a small amount of non-adherence may be association with treatment outcome. The overall low reported level of adherence in the study population limited our power to compare adherence levels with confidence, so future studies of larger size are important to validate the findings presented here. If adherence is truly associated with treatment outcome for MDR TB patients with HIV-co-infection, efforts to better understand this association will not only improve individual DR TB patient outcomes but also population-level health. As more MDR TB patients achieve cure, this minimizes transmission of DR TB and

magnification of drug resistance, moving the field closer to the ultimate goal of ending TB on a global scale.

Future investigations which utilize objective, validated adherence measures and of larger sample size will provide a clearer picture of the true impact of adherence on outcomes for people living with these two diseases. Prioritization of this topic is critically important not only to treat current MDR TB/HIV cases, but also to control and eventually eliminate the burden of these converging epidemics on vulnerable populations across the globe.

APPENDIX A: ADDITIONAL TABLES

Table A1. Performance of adherence measures for predicting MDR TB and HIV treatment outcomes in the SHOUT cohort.

	Sensitivity[c] % (95% CI)	Specificity[d] % (95% CI)	PPV[e] % (95% CI)	NPV[f] % (95% CI)
MDR TB TREATMENT				
Adherence Measure (MDR TB Treatment Success)[g], n=188				
3-day Recall	85.7 (79.9-91.5)	18.8 (7.7-29.8)	75.5 (68.8-82.2)	31.0 (14.2-47.9)
30-day Questionnaire	93.6 (89.5-97.6)	6.3 (0.0-13.1)	74.4 (68.0-80.9)	25.0 (0.5-49.5)
Visual Analog Scale	85 (79.1-90.9)	18.8 (7.7-29.8)	75.3 (68.6-82.0)	30.0 (13.6-46.4)
Composite 1[h]	81.4 (75.0-87.9)	22.9 (11.0-34.8)	75.5 (68.6-82.4)	29.7 (15.0-44.5)
Composite 2[i]	82.9 (76.6-89.1)	22.9 (11.0-34.8)	75.8 (69.0-82.6)	31.4 (16.1-46.8)
Adherence Measure (MDR TB 60-Day Culture Conversion)[j], n=137				
3-day Recall	90.0 (82.4-97.6)	13.0 (5.5-20.5)	44.6 (35.8-53.5)	62.5 (38.8-86.2)
30-day Questionnaire	95.0 (89.5-100.0)	3.9 (0.0-8.2)	43.5 (35.0-52.0)	50.0 (10.1-90.0)
Visual Analog Scale	91.7 (84.7-98.7)	14.3 (6.5-22.1)	45.5 (36.6-54.3)	68.8 (46.0-91.5)
Composite 1[h]	85.0 (76.0-94.0)	16.9 (8.5-25.3)	44.4 (35.3-53.4)	59.1 (38.6-79.6)
Composite 2[i]	88.3 (80.2-96.5)	16.9 (8.5-25.3)	45.3 (36.3-54.3)	65.0 (44.1-85.9)
HIV TREATMENT				
Adherence Measure (Sustained Virologic Suppression)[k], n=139				
3-day Recall	92.2 (85.8-96.4)	8.7 (1.1-8.0)	83.6 (76.1-89.6)	18.2 (2.3-51.8)
30-day Questionnaire	98.3 (93.9-99.8)	4.4 (0.1-22.0)	83.8 (76.5-89.9)	33.3 (0.8-90.6)
Visual Analog Scale	89.7 (82.6-94.5)	4.4 (0.1-22.0)	82.5 (74.8-88.7)	7.7 (0.2-36.0)
Composite 1[h]	87.9 (80.6-93.2)	8.7 (1.1-28.0)	82.9 (75.1-89.1)	12.5 (1.6-38.4)
Composite 2[i]	88.8 (83.1-94.5)	8.7 (0.0-20.2)	83.1 (76.5-89.7)	13.3 (0.0-30.5)

Notes for Table 1a.

[a]Multidrug-resistant tuberculosis
[b]Human immunodeficiency virus
[c]Proportion of adherent patients (as indicated by the adherence measure) among those who with an outcome of TB treatment success for MDR TB or lack of virologic failure for HIV
[d]Proportion of non-adherent patients (as indicated by the adherence measure) among those who with an outcome of TB treatment failure for MDR TB or virologic failure for HIV
[e]Positive Predictive Value: proportion of patients who were determined by the measure to be adherent who achieved treatment success for MDR TB and did not have virologic failure for HIV
[f]Negative Predictive Value: proportion of patients who were determined by the measure to be non-adherent who failed treatment for MDR TB or had virologic failure for HIV
[g]Primary TB Treatment Outcome of cure or treatment completion used as the gold standard for adherence to MDR TB treatment
[h]Composite measure 1 includes non-adherence indicated by any of the three individual measures
[i]Composite measure 2 includes non-adherence indicated by either the 3-day recall measure or the visual analog scale
[j]TB culture conversion within 60 days of treatment initiation used as the gold standard for adherence to MDR TB treatment
[k]Lack of virologic failure used as the gold standard for adherence to HIV treatment

Table A2a. Baseline demographic characteristics of the SHOUT cohort, by adherence[a] status throughout the study (N=200).

	Total Cohort		Less than Fully Adherent		Fully Adherent		
	N	n (%)	N	n (%)	N	n (%)	p-value
	200		36		164		
Age (years), median (IQR)		33.5 (15.1)		32.5 (17.3)		33.9 (14.8)	0.846[b]
Age (years by category)							0.832[c]
18-25		41 (20.5)		8 (22.22		33 (20.1)	
26-35		72 (36)		14 (38.89)		58 (35.4)	
36-45		51 (25.5)		7 (19.44)		44 (26.8)	
46-55		21 (10.5)		5 (13.89)		16 (9.8)	
>55		15 (7.5)		2 (5.56)		13 (7.9)	
Gender (female)		126 (63)		23 (63.89)		103 (62.8)	0.903[d]
Race							
Black		198 (99)		36 (100)		162 (98.8)	1.000[c]
Indian		1 (0.5)		0 (0)		1 (0.6)	
White		1 (0.5)		0 (0)		1 (0.6)	
Previous History of TB Treatment		130 (65)		22 (61.1)		108 (65.9)	0.589[c]
Smoking History		47 (62)		11 (30.6)		36 (22)	0.270[c]
Alcohol History		62 (31)		14 (38.9)		116 (70.7)	0.258[c]
Household Member with TB		35 (17.5)		4 (11.1)		31 (18.9)	0.338[d]
Healthcare Worker, past 12 months		13 (6.5)		2 (5.6)		11 (6.7)	1.000 [d]
Work in the Mines, past 12 months		6 (3)		1 (2.8)		5 (3.1)	1.000 [d]
Prison, past 12 months		5 (2.5)		0 (0)		5 (3.1)	0.588 [d]
Hospitalized, past 2 years		38 (19)		6 (16.7)		32 (19.6)	0.817 [d]

[a] Fully vs. less than fully adherent to MDR TB treatment

[b] Wilcoxon Mann-Whitney comparison of medians

[c] Fisher's exact test

[d] Chi squared test

Table A2b. Baseline medical history and symptoms characteristics of the SHOUT cohort, by adherence[a] status (N=200).

	Total Cohort		Less than Fully Adherent		Fully Adherent		
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
Past Medical History (% Yes)	200		36		164		
Vision Loss		27 (13.5)		5 (13.9)		22 (13.4)	1.000[b]
Hearing Loss		15 (7.5)		1 (2.8)		14 (8.5)	0.316[b]
Asthma/Recurrent Wheezing		13 (6.5)		5 (13.9)		8 (4.9)	**0.062**[b]
Hepatitis or Liver Disease		3 (1.5)		1 (2.8)		2 (1.2)	0.451[b]
Kidney Disease		2 (1.0)		1 (2.8)		1 (0.6)	0.328[b]
Diabetes		7 (3.5)		0 (0)		7 (4.3)	0.355[b]
Seizures		5 (2.5)		2 (5.6)		3 (1.8)	0.221[b]
Peripheral Neuropathy		43 (21.5)		9 (25)		34 (20.7)	0.654[b]
Thyroid Disease		0 (0)		0 (0)		0 (0)	n/a
Depression or Psychiatric Condition		14 (7)		4 (11.1)		10 (6.1)	0.285[b]
Drug Allergies		0 (0)		0 (0)		0 (0)	n/a
Other		10 (5)		2 (5.6)		8 (4.9)	1.000[b]
Other Symptoms- categorized (% Yes)	200		36		164		
Respiratory		112 (56)		17 (47.2)		95 (57.9)	0.241[c]
Gastrointestinal		43 (21.5)		8 (22.2)		35 (21.3)	1.000[b]
Joint and Muscle Pain		52 (26)		10 (27.8)		42 (25.6)	0.835[b]
Neurological		89 (44.5)		22 (61.1)		67 (40.9)	**0.027**[c]
Psychological		35 (17.5)		9 (25.0)		26 (15.9)	0.225[b]
Other		17 (8.5)		6 (16.7)		11 (6.7)	**0.09**[b]

[a] Fully vs. less than fully adherent to MDR TB treatment

[b] Fisher's exact test

[c] Chi squared test

Table A2c. Baseline HIV characteristics of the HIV positive SHOUT cohort, by adherence[a] status.

	Total Cohort		Less than Fully Adherent		Fully Adherent		
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
HIV (Positive)	200	144 (72.0)	36	26 (72.2)	164	118 (72)	1.000[b]
On ARV's	144	116 (80.6)	26	19 (73.1)	118	97 (82.2)	0.285[b]
CD4 Count, cells/mm3 - median(IQR)	139	215 (267)	15	248 (267)	119	206 (256)	0.767[c]
CD4 Count, cells/mm3 - categorized							0.597[b]
<=100		31 (22.3)		4 (26.7)		26 (21.9)	
>100-<=200		32 (23.0)		3 (20)		29 (24.4)	
>200-<=350		40 (28.8)		6 (40)		33 (27.7)	
>350		36 (25.9)		2 (13.3)		31 (26.1)	
Viral Load, copies/mL - median(IQR)	97	39 (411)	11	39 (271)	83	39 (481)	0.981[c]
Log(viral load) - median (IQR)		3.6 (2.5)		3.6 (3.4)		3.6 (2.6)	0.981[c]
Viral Load, copies/mL - categorized							0.710[b]
<=150		65 (67.0)		7 (63.6)		56 (67.5)	
>150 to <=1000		10 (10.3)		1 (9.1)		8 (9.6)	
>1000 to <=10000		4 (4.1)		1 (9.1)		3 (3.6)	
>10000		18 (18.6)		2 (18.2)		16 (19.3)	

[a] Fully vs. less than fully adherent to HIV treatment (ART)

[b] Fisher's Exact

[c] Wilcoxon Mann-Whitney comparison of medians

Table A3a. Baseline demographic characteristics of the SHOUT cohort, by MDR TB treatment outcome (N=200).

	Total Cohort		Not cured (Failed/Died/Default)		Cured/Treatment Completed		p-value
	N	n (%)	N	n (%)	N	n (%)	
	188		48		140		
Age (years), median (IQR)		34.1 (15.2)		31.3 (11.2)		34.7 (15.3)	0.207[a]
Age (years by category)							
18-25		36 (19.2)		8 (16.7)		28 (20)	0.207[b]
26-35		68 (36.2)		24 (50)		44 (31.4)	
36-45		48 (25.5)		9 (18.8)		39 (27.9)	
46-55		21 (11.2)		3 (6.3)		18 (12.9)	
>55		15 (8)		4 (8.3)		11 (7.9)	
Gender (female)		117 (62.2)		33 (68.8)		84 (60)	0.281[c]
Race							1.000[b]
Black		186 (98.9)		48 (100)		138 (98.6)	
Indian		1 (0.5)		0 (0)		1 (0.7)	
White		1 (0.5)		0 (0)		1 (0.7)	
Previous History of TB Treatment		119 (63.3)		29 (60.4)		90 (64.3)	0.631[c]
Smoking History		46 (24.5)		11 (22.9)		35 (25)	0.772[c]
Alcohol History		127 (67.6)		15 (31.3)		46 (32.9)	0.837[c]
Household Member with TB		32 (17.0)		13 (27.1)		19 (13.6)	**0.032**[c]
Healthcare Worker, past 12 months		12 (6.4)		3 (6.3)		9 (6.4)	1.000[b]
Work in the Mines, past 12 months		6 (3.2)		1 (2.1)		5 (3.6)	1.000[b]
Prison, past 12 months		5 (2.7)		1 (2.1)		4 (2.9)	1.000[b]
Hospitalized, past 2 years		33 (17.6)		9 (18.8)		24 (17.1)	0.827[b]

[a] Wilcoxon Mann-Whitney comparison of medians

[b] Fisher's Exact test

[c] Chi squared test

Table A3b. Baseline medical history and symptoms characteristics of the SHOUT cohort, by MDR TB treatment outcome (N=200).

	Total Cohort		Not cured (Failed/Died/ Default)		Cured/Treatment Completed		
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
Past Medical History (% Yes)	188		48		140		
Vision Loss		25 (13.3)		7 (14.6)		18 (12.9)	0.807 [a]
Hearing Loss		14 (7.5)		5 (10.4)		9 (6.4)	0.354 [a]
Asthma/Recurrent Wheezing		11 (5.9)		3 (6.3)		8 (5.7)	1.000 [a]
Hepatitis or Liver Disease		3 (1.6)		2 (4.2)		1 (0.7)	0.161 [a]
Kidney Disease		2 (1.1)		1 (2.1)		1 (0.7)	0.447 [a]
Diabetes		7 (3.7)		2 (4.2)		5 (3.6)	1.000 [a]
Seizures		5 (2.7)		3 (6.3)		2 (1.4)	0.106 [a]
Peripheral Neuropathy		41 (21.8)		14 (29.2)		27 (19.3)	0.153 [b]
Thyroid Disease		0 (0)		0 (0)		0 (0)	n/a
Depression or Psychiatric Condition		14 (7.5)		3 (6.3)		11 (7.9)	1.000 [a]
Drug Allergies		0 (0)		0 (0)		0 (0)	n/a
Other		10 (5)		2 (4.2)		8 (5.7)	1.000 [a]
Other Symptoms- categorized	188		48		140		
Respiratory		105 (55.9)		27 (56.3)		78 (55.7)	0.949 [b]
Gastrointestinal		40 (21.3)		16 (33.3)		24 (17.1)	**0.018** [b]
Joint and Muscle Pain		52 (27.7)		7 (35.4)		35 (25)	**0.164** [b]
Neurological		85 (45.2)		27 (56.3)		58 (41.4)	**0.075** [b]
Psychological		35 (18.6)		12 (25)		23 (16.4)	**0.188**[a]
Other		17 (9.0)		5 (10.4)		12 (8.6)	0.771[a]

[a] Fisher's exact test

[b] Chi squared test

Table A3c. Baseline HIV characteristics of the HIV positive SHOUT cohort, by MDR TB treatment outcome.

	Total Cohort		Not cured (Failed/Died/Default)		Cured/Treatment Completed		
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
HIV (Positive)	188	135 (71.8)	48	38 (79.2)	140	97 (69.3)	**0.189**[a]
On ARV's	135	110 (81.5)	38	29 (76.3)	97	81 (83.5)	0.335[b]
CD4 Count, cells/mm3 - median(IQR)	131	215 (267)	38	175 (220)	93	215 (255)	**0.124**[c]
CD4 Count, cells/mm3 - categorized							
<=100		30 (22.9)		13 (34.2)		17 (18.3)	0.273[b]
>100-<=200		31 (23.7)		7 (18.4)		24 (25.8)	
>200-<=350		37 (28.2)		10 (26.3)		27 (29.0)	
>350		33 (25.2)		8 (21.1)		25 (26.9)	
Viral Load, copies/mL - median(IQR)	90	39 (301)	27	150 (44,123)	63	39 (143)	**0.005**[c]
Log(viral load) - median (IQR)		3.6 (2.2)		5.0 (7.0)		3.6 (2.1)	**0.005**[c]
Viral Load, copies/mL - categorized							**0.012**[b]
<=150		61 (67.8)		14 (51.9)		47 (74.6)	
>150 to <=1000		10 (11.1)		2 (7.4)		8 (12.7)	
>1000 to <=10000		2 (2.2)		2 (7.4)		0 (0)	
>10000		17 (18.9)		9 (33.3)		8 (12.7)	

[a] Chi squared test

[b] Fisher's exact test

[c] Wilcoxon Mann-Whitney comparison of medians

APPENDIX B: SELECTED EXAMPLE SAS CODE

DATA MANAGEMENT:
Example code for use of arrays to create composite adherence variables collapsed across all visits

```
*Previously transposed dataset from long format to wide, with every row
of data representing one SID;

data a.adhrec;
      set a.adht;

      *Use an array to calculate number of visits for all participants
where missing tb pills yesterday was indicated;

*3-DAY TB;

*Number of people who missed tb pills yesterday;
a_mtby=0;

array mtby_{24} miss_tb_pills_yesterday2-miss_tb_pills_yesterday25;

      do i=1 to 24;
            if mtby_{i}=1 then a_mtby = a_mtby+1;
            else if mtby_{i}=0 then a_mtby= a_mtby+0;

      end;

      *account for missings- array above does not;
      if (miss_tb_pills_yesterday2=. and miss_tb_pills_yesterday3=.
      and miss_tb_pills_yesterday4=. and miss_tb_pills_yesterday5=.
      And miss_tb_pills_yesterday6=. and miss_tb_pills_yesterday7=.
      and miss_tb_pills_yesterday8=. and miss_tb_pills_yesterday9=.
      and miss_tb_pills_yesterday10=. and miss_tb_pills_yesterday11=.
      and miss_tb_pills_yesterday12=. and miss_tb_pills_yesterday13=.
      and miss_tb_pills_yesterday14=. and miss_tb_pills_yesterday15=.
      And miss_tb_pills_yesterday16=. and miss_tb_pills_yesterday17=.
      and miss_tb_pills_yesterday18=. and miss_tb_pills_yesterday19=.
      and miss_tb_pills_yesterday20=. and miss_tb_pills_yesterday21=.
      and miss_tb_pills_yesterday22=. and miss_tb_pills_yesterday23=.
      and miss_tb_pills_yesterday24=. and miss_tb_pills_yesterday25=.)
      then a_mtby=.;

      else if (miss_tb_pills_yesterday2=9 and
      miss_tb_pills_yesterday3=9 and miss_tb_pills_yesterday4=9 and
      miss_tb_pills_yesterday5=9 and miss_tb_pills_yesterday6=9 and
      miss_tb_pills_yesterday7=9)
      then a_mtby=.;

*Number of people who missed tb pills the day before yesterday;
a_mtb2d=0;

array mtb2d_{24} miss_tb_pills_day_b4_yest2-
miss_tb_pills_day_b4_yest25;
```

```
      do i=1 to 24;
            if mtb2d_{i}=1 then a_mtb2d = a_mtb2d+1;
            else if mtb2d_{i}=0 then a_mtb2d= a_mtb2d+0;

      end;

*Number of people who missed tb pills three days ago;
a_mtb3d=0;

array mtb3d_{24} miss_tb_pills_3_days_ago2-miss_tb_pills_3_days_ago25;

      do i=1 to 24;
            if mtb3d_{i}=1 then a_mtb3d = a_mtb3d+1;
            else if mtb3d_{i}=0 then a_mtb3d= a_mtb3d+0;

      end;

*Create indicator variable for non-adherence indicated any time in the
study according to miss_tb_pills_yesterday;

      if a_mtby=. then a_nonadhy=.;
      else if a_mtby ge 1 then a_nonadhy=1;
      else if a_mtby=0 then a_nonadhy=0;

*Create indicator variable for non-adherence indicated any time in the
study according to miss_tb_pills_day_b4_yest;

      if a_mtb2d=. then a_nonadh2d=.;
      else if a_mtb2d ge 1 then a_nonadh2d=1;
      else if a_mtb2d=0 then a_nonadh2d=0;

*Create indicator variable for non-adherence indicated any time in the
study according to miss_tb_pills_day_b4_yest;

      if a_mtb3d=. then a_nonadh3d=.;
      else if a_mtb3d ge 1 then a_nonadh3d=1;
      else if a_mtb3d=0 then a_nonadh3d=0;

*Create indicator variable for non-adherence to TB medication indicated
AT ALL IN THE LAST THREE DAYS;

      if a_nonadhy=1 or a_nonadh2d=1 or a_nonadh3d=1
      then a_tb3dnonadh=1;
      else if a_nonadhy=0 and a_nonadh2d=0 and a_nonadh3d=0
      then a_tb3dnonadh=0;
      else if a_nonadhy=. and a_nonadh2d=. and a_nonadh3d=.
      then a_tb3dnonadh=.;

run;
```

DATA ANALYSIS:

Example code for select analyses

```
***WILCOXON MANN-WHITNEY/KRUSKAL WALLIS/ EXACT TEST FOR COMPARISON OF
MEDIANS***;
```

```
*Comparison of medians for baseline cd4 and viral load;
ods graphics on;

proc npar1way wilcoxon correct=no data=a.bladh;
      class tbtxcure;
      var v1cd4 v1vir logv1vir;
run;

ods graphics off;


***MCNEMAR'S EXACT TEST FOR COMPARISON OF TWO VARIABLES COLLECTED ON
THE SAME INDIVIDUALS***;

*Determine whether marginal PROPORTION of patients adherent to TB and
HIV meds are different;

proc freq data=a.bladhhiv;
      tables d3vas_tbnonadh*d3vas_hivnonadh/agree exact;
      tables nonadhvastb*nonadhvashiv/agree exact;
      tables tb30dnonadh*hiv30dnonadh/agree exact;
      tables a_tb3dnonadh*hiv3dnonadh/agree exact;
      tables tbnonadh*hivnonadh/agree exact;
      exact mcnem;
run;


***SE, SP, NPV, AND PPV***;


*Code repeated and adapted across all adherence exposure and outcome
variable combinations of interest*;

*COMPOSITE MEASURE WITH EITHER/BOTH 3-DAY RECALL AND VAS HIV;

*Crude relative risk;
proc freq data=a.adhrechiv;
      tables d3vas_hivnonadh*virfyn/fisher relrisk;
run;

*Se and Sp;
title 'Sensitivity';
proc freq data=a.adhrechiv;
      where virfyn=0;
      tables d3vas_hivnonadh / binomial(level="0");
      exact binomial;
run;

title 'Specificity';
proc freq data=a.adhrechiv;
      where virfyn=1;
      tables d3vas_hivnonadh / binomial(level="1");
      exact binomial;
run;

*ppv and npv;
```

```
title 'Positive predictive value';
proc freq data=a.adhrechiv;
      where d3vas_hivnonadh=0;
      tables virfyn / binomial(level="0");
      exact binomial;
run;

title 'Negative predictive value';
proc freq data=a.adhrechiv;
      where d3vas_hivnonadh=1;
      tables virfyn / binomial(level="1");
      exact binomial;
run;


***LOG BINOMIAL MODEL FOR ADJUSTED RISK RATIOS***;


*Using mdrtbadh: flipped adherence variable to model risk of TB tx cure
(1) if adherent to medication (1);

proc genmod data=a.bladh descending;
      model tbtxcure (event = "1") = mdrtbadh agecat
v1_patient_hiv_status patient_gender os_neur / link=log dist=binomial;
run;
```