

# Adherence Measured Using Electronic Dose Monitoring is Associated with Emergent Antiretroviral Resistance and Poor Outcomes in People with Human Immunodeficiency Virus/AIDS and Multidrug-Resistant Tuberculosis

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**Background.** Medication adherence is known to challenge treatment of human immunodeficiency virus (HIV)/AIDS and multidrug-resistant tuberculosis (MDR-TB). We hypothesized that adherence using electronic dose monitoring (EDM) would identify an antiretroviral therapy (ART) adherence threshold for emergent ART resistance and predict treatment outcomes in patients with MDR-TB and HIV on ART and bedaquiline-containing TB regimens.

**Methods.** A prospective cohort of adults with MDR-TB and HIV on ART and initiating MDR-TB treatment with bedaquiline were enrolled at a public hospital in KwaZulu-Natal, South Africa (PRAXIS Study). Participants received separate EDM devices that measure adherence to bedaquiline and ART (nevirapine or lopinavir/ritonavir). Adherence was calculated cumulatively over 6 months. Participants were followed through completion of MDR-TB treatment. HIV genome sequencing was performed at baseline and 2 and 6 months on samples with HIV RNA  $\geq 1000$  copies/mL.

**Results.** From November 2016 through February 2018, 198 persons with MDR-TB and HIV were enrolled and followed (median, 17.2 months; interquartile range, 12.2–19.6). Eleven percent had baseline ART resistance mutations, and 7.5% developed emergent ART resistance at 6 months. ART adherence was independently associated with ART resistance and mortality. Modeling identified a significant ( $P < .001$ ), linear association between ART adherence and emergent resistance, suggesting a strong association without a specific threshold.

**Conclusions.** Our findings highlight the need for ART resistance testing, especially in patients with MDR-TB and HIV, which is currently not the standard of care in resource-limited settings. Despite short follow-up duration, reduced ART adherence was significantly associated with emergent resistance and increased mortality.

**Clinical Trials Registration.** NCT03162107.

**Keywords.** antiretroviral adherence; electronic dose monitoring; South Africa; patients with HIV/AIDS and multidrug-resistant tuberculosis; emergent resistance.

Multidrug-resistant tuberculosis (MDR-TB) represents a growing global public health threat. In 2019, close to half a million people developed rifampicin-resistant TB, of whom 78% had MDR-TB [1]. The introduction of new antimycobacterial treatment regimens has revolutionized MDR-TB treatment

by reducing the number of required antimycobacterial drugs, eliminating the need for injectable agents, shortening treatment duration, improving mortality, and substantially improving treatment outcomes [2]. The diarylquinoline antibiotic bedaquiline, the first new antimycobacterial agent approved for TB treatment in 40 years, is a key component of all new World Health Organization (WHO)-recommended regimens for MDR-TB [3].

Living with MDR-TB and human immunodeficiency virus (HIV) is common in geographic areas where both are prevalent, including South Africa where an estimated 58% of incident cases of TB were coinfecting with HIV in 2019 [1]. Treatment integration of antiretroviral therapy (ART) and anti-TB

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medications may effectively reduce mortality in patients with HIV and TB, but this opportunity to improve outcomes is often missed or poorly implemented [4–8]. It has been shown that ART adherence is challenged by MDR-TB/HIV cotreatment with increased pill burden, drug interactions, need for medication switches, and increased incidence of adverse reactions [9].

Patient adherence to ART is a critical determinant of HIV treatment outcomes, and low ART adherence is an important risk factor for HIV virologic failure [10]. Multiple studies have shown the connection between ART medication interruption (measured by patient self-report, electronic dose monitoring, and other methods) and the development of ART resistance in patient populations around the world, including in sub-Saharan Africa [11–13].

However, there is an important knowledge gap regarding the impact of MDR-TB–HIV cotreatment on ART adherence and emergent ART resistance. We hypothesized that cellular-enabled electronic dose monitoring in an operational setting in South Africa would effectively predict treatment outcomes and identify an ART adherence threshold for emergent ART resistance in patients with MDR-TB and HIV being treated with ART and bedaquiline-containing TB regimens.

## METHODS

### Study Setting and Participants

This prospective, observational, cohort study enrolled patients in a public hospital and associated MDR-TB clinics in KwaZulu-Natal, South Africa, from November 2016 through February 2018. Participants were adults (aged  $\geq 18$  years) with MDR-TB and HIV confirmed by conventional or molecular testing initiating bedaquiline-containing regimens. All enrolled participants were either already taking ART or started ART within 2 weeks of enrollment. Participants were enrolled with written informed consent in either isiZulu or English within 2 weeks of initiating bedaquiline. Each participant received 2 electronic dose-monitoring (EDM) devices (Wisepill RT2000) to measure medication adherence to bedaquiline and ART. Only ART adherence to nevirapine or lopinavir/ritonavir was measured with the EDM device due to logistical reasons (ie, limited EDM pill capacity). ART and TB treatment regimens were constructed per national guidelines and at the discretion of treating clinicians. ART regimens included either nevirapine or lopinavir/ritonavir, each accompanied by lamivudine and tenofovir, based on WHO recommendations due to concern for drug–drug interactions with bedaquiline. Integrase strand transfer inhibitors (INSTIs) were not available in the South African public health system during the study period.

Hospital- and clinic-based physicians, nurses, and social workers, with additional support and training from study staff, provided adherence counseling to participants. Adherence support for MDR-TB medications at home and in the community

was provided by directly observed treatment supporters, per South African provincial health guidelines, and through study participation with monthly adherence-support counseling at clinic visits. Additional adherence support for ART was provided through monthly clinic-based counseling delivered routinely. Treatment support was assessed monthly using a questionnaire for the first 6 months and at the end of bedaquiline treatment.

Patients were followed monthly with study visits through 6 months during which clinical evaluations were performed. Sputum for TB culture was collected at baseline and monthly through 6 months, and blood samples to quantify HIV RNA (HIV viral load) were collected at baseline and 2 and 6 months after study enrollment. Subsequently, participants were followed with monthly clinic visits in the public health system and telephonically by study staff until the end of MDR-TB treatment (full protocol available in the [Supplementary Material](#)). Adherence data were captured daily using EDM, through monthly questionnaires about pill-taking practices, and pharmacy records. If patients did not have a 6-month blood sample (due to death, loss to follow-up, or other reason), HIV viral load was measured using the blood sample drawn at their month-2 study visit. If HIV viral loads were  $\geq 1000$  copies/mL, genotypic ART resistance testing was subsequently performed. ART resistance testing was not done in real time, so genotyping results were not available to guide clinical ART management.

### Laboratory Methods

Plasma samples with viral loads  $\geq 1000$  copies/mL were retrieved from the  $-80^{\circ}\text{C}$  biorepository and thawed to room temperature prior to viral RNA extraction. Each plasma sample was centrifuged to pellet the virus, as previously described [14]. Viral RNA was extracted from pelleted plasma using a Chemagic 360 (PerkinElmer, Waltham, MA) automated extraction system, and protease and reverse transcriptase genes were amplified using custom primers [15]. Successfully amplified polymerase chain reaction (PCR) products were purified using a QIAquick PCR purification kit (Qiagen, Hilden, Germany).

In preparation for capillary electrophoresis, sequencing reactions were performed using a BigDye Terminator v3.1 kit (Applied Biosystems, Foster City, CA), and sequencing reaction purifications was performed using a BigDye XTerminator v3.1 purification kit (Applied Biosystems). Capillary electrophoresis was performed on an ABI 3730 genetic analyzer, and the quality of sequences was assessed using Geneious software v8.1.9 (Biomatters Ltd, New Zealand) [16].

The Stanford University HIV Drug Resistance Database (version 8.6) algorithm was used to characterize phenotypic resistance profiles from genotypic results [17]. The algorithm scans each sequence for the presence of drug-resistant mutations characterized in the International Antiviral Society–United States of America (IAS–USA) listing [18] and assigns a final Stanford penalty score. The final degree of resistance was

defined as “high” if the computed score was  $\geq 60$ , “intermediate” if 30–59, or “low” if 15–29.

### Clinical Methods

Adherence to ART and bedaquiline was measured using the EDM device with Wisepill RT2000, with TB and ART medications each loaded in a separate device. Opening of the device activated a cellular signal that was monitored centrally with a cellular phone or laptop. Daily dose windows for bedaquiline and ART were constructed to allow for flexibility around dose timing. Using a prespecified algorithm and scripted call, study staff contacted the participants by telephone if excess missed doses, defined by prespecified criteria, were detected by EDM (see the protocol in the [Supplementary Material](#) for details). The study calls confirmed that the device had not failed, that it was not being stored in such a way that it could not transmit cellular signal, and that there was no limitation due to the battery charge. Cumulative adherence was calculated as observed doses within the dose windows divided by expected doses through 6 months, censored for death or loss to follow-up at the time of the event. At 6 months post-bedaquiline initiation, both EDM devices were retrieved from all participants since the standard duration of bedaquiline treatment was 6 months. Adherence was also assessed by monthly questionnaires based on patient recall; pharmacy records were obtained as available.

### Outcomes

The primary study outcome was emergent HIV antiretroviral resistance. This was defined as the presence of new antiretroviral resistance (Stanford penalty score  $\geq 15$ ) detected at 6 months following study initiation that was not present at baseline. Resistance-conferring mutations to any antiretroviral were included. However, patients with existing resistance at baseline were classified as having emergent resistance only when it occurred in a different antiretroviral class (nonnucleoside reverse transcriptase inhibitor [NNRTI] vs protease inhibitor [PI]). Secondary outcomes included all-cause mortality, ART adherence measures, and HIV virologic response [19].

### Statistical Methods

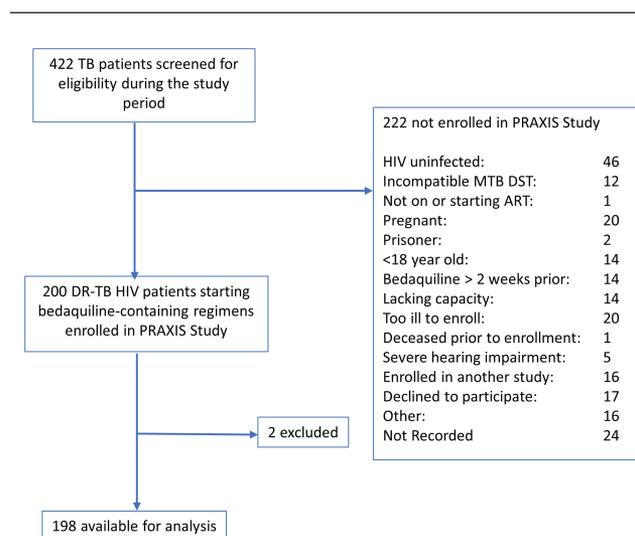
Univariate and multivariable analyses were performed using logistic regression and Cox proportional hazards modeling. Factors known to be associated with treatment failure were selected for univariate analysis. For inclusion in the multivariable model, we included univariate factors with a significant association with the outcome ( $P$  value  $< .05$ ) or an effect size modification  $> 10\%$  (ie, odds ratio  $> 1.1$  or hazards ratio  $< 0.9$ ). We also included conventionally important factors in the multivariable analysis that did not meet these criteria (eg, age and gender). Linearity of association of ART adherence to emergence of resistance was tested with a generalized additive model as well as cubic splines.

We considered ART adherence in multiple ways including as a continuous variable, with decile and quartile cutoffs, and using  $> 95\%$  adherence based on historical HIV adherence trials [20–22]. Statistical analyses were performed using IBM SPSS Statistics (version 27.1.00) and SAS (version 9.4). Heat maps to illustrate emergent ART resistance patterns were created using R (version 4.0.5).

### RESULTS

From November 2016 through February 2018, 422 patients were evaluated for inclusion (Figure 1). A total of 198 MDR-TB–HIV participants were enrolled and followed to the end of treatment, defined by standard MDR-TB treatment guidelines (median follow-up time, 17.2 months; interquartile range [IQR], 12.2–19.6). Consistent with other studies of drug-resistant TB and HIV in South Africa, participants were predominantly young and the majority were female (Table 1). Ninety-three percent ( $n = 183$ ) of enrolled participants were on ART at the time of enrollment, with 63% ( $n = 124$ ) on ART for more than 6 months at time of enrollment. Seven percent ( $n = 15$ ) of participants were started on ART at the time of enrollment.

At the time of enrollment (baseline), 197 of 198 (99.5%) had HIV viral load testing, and of these, 42 of 197 (21.3%) had HIV viral loads  $\geq 1000$  copies/mL, including the 15 participants not on ART at baseline. There were 175 of 198 initial participants who had HIV viral load testing at 6 months, and 23 of 198 did not (22 died prior to 6 months, 1 did not leave an available sample). Two-month samples were retrieved for 17 of 23 participants without a 6-month follow-up sample (5 died prior to



**Figure 1.** Enrollment flowchart showing number of patients screened, enrolled, and included in the analysis. \*One patient died 11 days after enrollment and had not initiated treatment; 1 patient was enrolled but subsequently was found to be ineligible. Abbreviations: ART, antiretroviral therapy; DR, drug resistant; DST, Drug sensitive; HIV, human immunodeficiency virus; MTB, Mycobacterium Tuberculosis; TB, tuberculosis.

month 2, 1 did not leave an available sample). A total of 192 participants had follow-up HIV viral load testing, and 34 of 192 (17.7%) had HIV viral loads  $\geq 1000$  copies/mL.

Overall, cumulative median ART adherence measured by EDM through 6 months was 89.0% (IQR, 66.3–96.2). There was a significant difference between the median ART adherence of participants on first-line NNRTI-based regimens (89.8%; IQR, 69.6–96.2) compared with second-line PI-based regimens

**Table 1. Baseline Characteristics of Patients With Drug-Resistant Tuberculosis and Human Immunodeficiency Virus on Bedaquiline and Antiretroviral Therapy (N = 198)**

Characteristic	N (%)
Gender	
Male	85 (42.9)
Female	113 (57.1)
Age, years	
Median (IQR)	35 (29–43)
Education	
No schooling	6 (3.0)
Attended primary	29 (14.7)
Attended secondary	148 (74.8)
Attended college or university	15 (7.6)
TB drug-susceptibility pattern	
MDR-TB	98 (49.5)
Pre-XDR TB	58 (29.3)
XDR-TB	42 (21.2)
Baseline HIV	
Undetectable HIV viral load (%) <sup>a</sup>	123 (62.1)
CD4 T-cell count, median (IQR) <sup>b</sup>	238 (105–451)
ART	
Nevirapine	147 (74.2)
Lopinavir/ritonavir	36 (18.8)
No baseline ART	15 (7.6)
ART for >6 months at enrollment	124 (62.6)
Baseline body mass index, kg/m <sup>2</sup>	
Median (IQR)	20.5 (18.3–23.8)
Previous TB history	
None reported	33 (16.6)
Drug-susceptible TB	125 (62.8)
MDR/XDR TB	41 (20.6)
Number of TB medicines in regimen	
Median medicines (IQR)	7 (7–8)
Directly observed treatment supporter <sup>c,d</sup>	137 (70.3)
History of imprisonment	
Yes	22 (11.1)
History of substance use	
Alcohol	90 (45.7)
Drugs	17 (8.6)
Cigarettes	53 (26.8)
None	83 (41.9)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MDR, multidrug resistant; pre-XDR, pre-extensively drug resistant; TB, tuberculosis; XDR, extensively drug resistant.

<sup>a</sup>Undetectable HIV viral load is defined as HIV RNA <40 copies/mL.

<sup>b</sup>N = 181.

<sup>c</sup>Cumulative number of participants reporting use of directly observed treatment supporter over first 6 months of treatment.

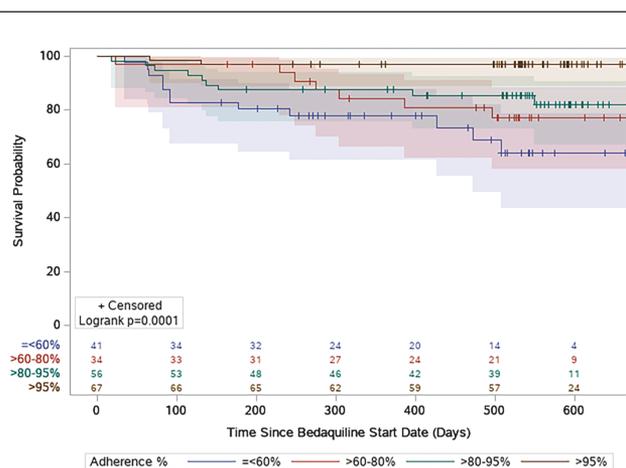
<sup>d</sup>N = 195.

(68.6%; IQR, 47.7–95.5;  $P = .023$ ). ART adherence was highly associated with undetectable HIV viral load at 6 months, even when adjusted for age, gender, TB type, and education ( $P < .001$ ; [Supplementary Table 1](#)). Participants' ART adherence was significantly lower than bedaquiline adherence (median 89.0% vs 97.0%,  $P < .001$ ) [23].

By Cox proportional hazards modeling, ART adherence was significantly protective for mortality with ART adherence considered a continuous variable (for each percent change in adherence, adjusted hazard ratio [aHR], 0.98; 95% confidence interval [CI], .970–.997;  $P = .017$ ). Baseline ART resistance was significantly associated with mortality after adjusting for potential confounders (aHR, 3.15; 95% CI: 1.32–7.57;  $P = .01$ ; [Supplementary Table 2](#)). Furthermore, there was statistically longer survival time in those with higher levels of ART adherence observed by Kaplan-Meier analysis ( $P = .0001$ ; [Figure 2](#)).

There were 22 of 198 (11%) participants who had at least 1 antiretroviral resistance mutation at baseline. Nineteen of the 22 (86%) participants with baseline resistance had been on ART, 3 of 19 (14%) were ART naive. All (22 of 22) had high-level resistance to nevirapine ([Supplementary Figure 1](#)). On multivariable logistic regression, older age and CD4 T-cell count >200 were independently associated with decreased odds of the presence of a baseline ART resistance conferring mutation ([Table 2](#)).

Fifteen of 198 (7.5%) participants developed emergent antiretroviral resistance at 2 or 6 months. Median cumulative adherence in participants with emergent antiretroviral resistance was 53.4% (IQR, 28.6–79.6), while the median adherence in those without emergent resistance was 90.0% (IQR, 68.6–96.2; [Supplementary Table 3](#)). On multivariable logistic regression, decreased ART adherence and CD4 T-cell count <200 were independently associated with emergent ART resistance conferring mutation. When considered as a continuous variable, ART adherence was an independent risk factor for ART resistance emergence, with a 5% reduced odds of emergent ART



**Figure 2.** Kaplan-Meier analysis comparing survival probabilities across 4 levels of antiretroviral adherence (≤60%, 60%–80%, 80%–95%, >95%) by log-rank test.

resistance per unit of increased adherence (OR, 0.95; 95% CI: .93–.98; Table 3). The most frequently occurring resistance-conferring mutations were M184V/I and K103N/S, which confer high-level resistance to lamivudine/emtricitabine and nevirapine/efavirenz, respectively (Supplementary Table 4). Two maps were created to illustrate phenotypic resistance that emerged to both NNRTIs and nucleoside reverse-transcriptase inhibitors (NRTIs) during the study period (Supplementary Figure 2A, 2B).

The proportion of participants with emergent resistance increased with each decreasing decile of adherence as follows: 1.1% of participants with greater than 90% adherence developed emergent ART resistance, 6.4% in those with between 80% and 90% adherence, 6.3% in those with between 70% and 80% adherence, 16.7% in those with between 60% and 70% adherence, 18.2% in those with between 50% and 60% adherence, and 20% in those with less than 50% adherence developed emergent ART resistance (Figure 3). Using a generalized additive model and a cubic spline model adjusted for multiple variables, we found a strong association between adherence and resistance emergence ( $P < .0001$ ), even after adjustment for potential confounding factors. However, the relationship was linear ( $P = .20$  for nonlinearity) and therefore there was no “natural” ART adherence threshold seen in our data (Figure 4).

## DISCUSSION

In this prospective, observational, cohort study, we found that reduced ART adherence measured using an EDM device was independently associated with emergent ART resistance, HIV treatment failure, and mortality. Eleven percent of study participants had baseline antiretroviral resistance (93% of participants were on ART at enrollment, 7% were not on ART), and an additional 7.5% developed emergent resistance

during early treatment. We did not identify an ART adherence threshold cut-point, which suggests that increased medication adherence is associated with reduced emergence of ART-resistant HIV through the range of measured ART adherence.

Compared with surveys of antiretroviral resistance in pre-treatment patients living with HIV in South Africa, our cohort had a higher prevalence of baseline ART resistance when adjusted to comparable denominators, reflecting our participants’ ART treatment experience [24, 25]. Similar to our findings, the most frequent mutations detected in these surveys conferred high-level resistance to the NNRTIs (eg, K103N). Similar to incidence data reported in high-burden settings [26], emergent ART resistance was seen in 7.5% of our participants during treatment. Of note, emergent resistance in our study was conservatively defined as new resistance to a new class of ART during treatment, so a patient with baseline NNRTI resistance would only be considered to have emergent ART resistance if they developed emergent mutations conferring resistance to NRTI or PI during treatment.

The increasing prevalence of NNRTI resistance in high-burden HIV settings [27], along with the advantageous safety, potency, and cost-effectiveness characteristics of INSTIs [28], has prompted the WHO to recommend INSTI-based ART as a preferred first-line regimen [29], including for patients with drug-resistant TB and HIV. However, a recent study suggested that NNRTI resistance prior to treatment may be associated with long-term failure of INSTI regimens, which could portend high rates of treatment failure in areas with high NNRTI resistance, creating an urgency to improve overall adherence to ART even with the availability of new regimens [30].

Strengths of our study include its prospective design, long follow-up interval, use of cellular-enabled EDM devices to enable minimally biased adherence measurement, and study of HIV-specific variables in a cohort with MDR-TB and HIV.

**Table 2. Logistic Regression Multivariable Model Identifying Risk Factors for Baseline Antiretroviral Therapy Resistance**

Variable	Univariate OR (95% CI)	PValue	Multivariable OR (95% CI)	PValue
Age <sup>a</sup>	0.92 (0.86–0.97)	.005	0.99 (0.93–1.07)	.97
Male gender	1.12 (0.46–2.74)	.80	2.15 (0.63–7.28)	.22
Tuberculosis type				
Multidrug resistant	Ref	-		
Pre-extensively drug resistant	1.02 (0.35–2.96)	.98	1.37 (0.39–4.84)	.62
Extensively drug resistant	1.47 (0.50–4.34)	.49	0.71 (0.13–3.81)	.69
CD4 T-cell count ≤200 cells/mL	3.99 (1.41–11.28)	.00	3.82 (0.98–14.87)	.053
On antiretroviral therapy <6 months	1.18 (0.48–2.92)	.72	2.63 (0.80–8.67)	.11
Substance use <sup>+</sup>	3.16 (1.02–9.76)	.046	0.81 (0.09–7.40)	.85
History of opportunistic infections	1.63 (0.59–4.47)	.35	0.48 (0.10–2.41)	.37
Body mass index	0.86 (0.75–0.98)	.024	0.94 (0.80–1.09)	.39

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Per year of increased age.

<sup>+</sup>Substance use is defined as self-reported current use of psychoactive drugs, including alcohol, at baseline.

**Table 3. Logistic Regression Multivariable Model Identifying Risk Factors for Emergent Antiretroviral Therapy Resistance at 6 Months**

Variable	Univariate OR (95% CI)	PValue	Multivariable OR (95% CI)	PValue
Age <sup>a</sup>	0.99 (0.93–1.05)	.66	0.97 (0.90–1.05)	.45
Male gender	2.11 (0.72–6.18)	.17	3.89 (0.84–18.07)	.083
CD4 T-cell count ≤200 cells/mL	4.51 (1.23–16.52)	.022	5.21 (1.13–24.01)	.034
On ART <6 months	2.72 (0.93–7.99)	.068	3.08 (0.85–11.21)	.088
ART adherence <sup>b</sup> (%)	0.96 (0.94–0.98)	.0002	0.95 (0.93–0.98)	.0002
Substance use <sup>c</sup>	0.62 (0.08–4.95)	.65	0.72 (0.07–7.37)	.78
History of opportunistic infections	0.61 (0.13–2.81)	.52	0.38 (0.07–2.22)	.28
Body mass index	0.90 (0.79–1.04)	.15	0.97 (0.82–1.15)	.76

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Per year of increased age.

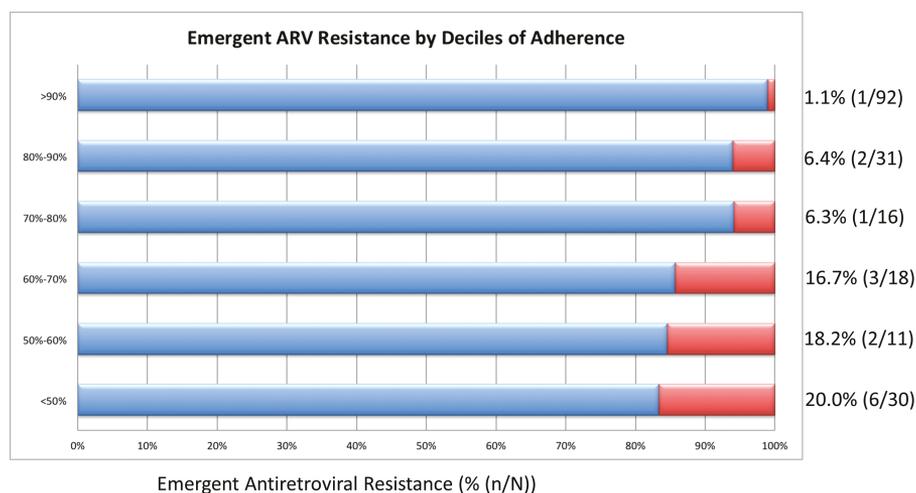
<sup>b</sup>Per percent of increased adherence, cumulative adherence measured by electronic dose measuring through 6 months.

<sup>c</sup>Substance use is defined as self-reported current use of psychoactive drugs, including alcohol, at baseline.

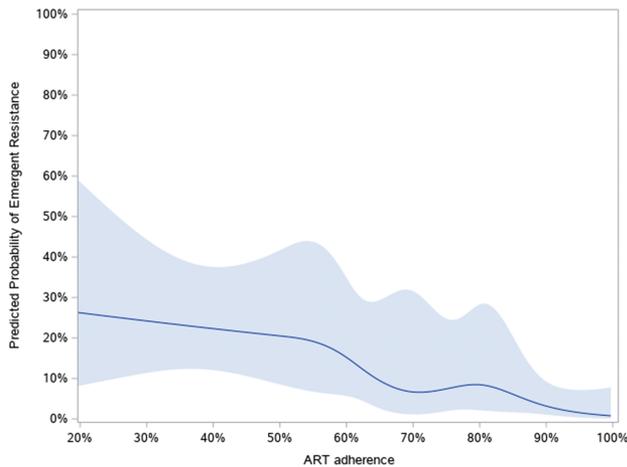
There are also limitations to our study. One potential limitation is that we did not perform genotyping in patients with HIV viral load <1000 copies/mL. In these patients, we assumed that there was no ART resistance. However, one South African study of 125 participants found that 79% of those with low-level viremia (defined as 5–999 copies/mL) had resistance mutations [31], indicating that ART resistance may have been underestimated in our study. Another limitation is that use of EDM pillbox openings as a surrogate for medication adherence could overcount adherence. However, this would presumably bias the effect of adherence on emergent resistance, HIV viral response, and mortality toward the null hypothesis. The intense burden of HIV disease on communities and health systems in KwaZulu-Natal, South Africa, may limit the generalizability of our findings. A second limit to generalizability is that INSTI-based regimens (which were not included in our study) are now recommended as first-line

ART, including in the setting of living with both MDR-TB and HIV. However, many features of the TB-HIV epidemic in KwaZulu-Natal are common to other southern African regions, and our findings may be broadly applicable in these settings. Further, although INSTI-based regimens are considered first-line ART, NNRTI-based ART regimens are still frequently prescribed in clinical settings in sub-Saharan Africa.

In conclusion, we found that poor adherence to ART is significantly associated with emergent ART resistance, HIV treatment failure, and mortality in patients with MDR-TB and HIV. Management of these patients with complex HIV and TB drug-resistance patterns in a setting with limited alternate therapeutic options is challenging. These data highlight the need for close monitoring and early intervention to support adherence for ART as well as TB medications [32], especially in patients receiving complex treatment and dosing. As



**Figure 3.** Bar graph showing the percentage of participants who developed resistance emergence at different deciles\* of adherence. \*Less than 50% adherence was used as a cutoff because of the small number of participants in deciles below 50%.



**Figure 4.** Likelihood of emergent resistance at 6 months by percent adherence.\* Effect plot of continuous association of percent treatment adherence with emergent resistance measured at 6 months using a logistic model with cubic splines indicating predicted probability (solid line) and the 95% confidence interval (shaded area). The  $P$  for linearity = .20\*\* and  $P$  for association <.0001. \*\*A  $P$  for linearity suggests the association is linear. Abbreviations: ART, antiretroviral therapy.

first-line ART moves to INSTI-based regimens throughout the world, these findings highlight the urgency of targeted interventions to improve adherence and prevent emergence of ART resistance.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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