Short Report: Drug-Resistant Tuberculosis Treatment Complicated by Antiretroviral Resistance in HIV Coinfected Patients: A Report of Six Cases in Lesotho

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Abstract. Treating drug-resistant tuberculosis (DR-TB) is particularly challenging in high human immunodeficiency virus (HIV) prevalence settings. Neither antiretroviral resistance testing nor viral load monitoring is widely available in sub-Saharan Africa, and antiretroviral resistance can complicate the clinical management for DR-TB/HIV coinfecting patients. We describe six cases of antiretroviral resistance in DR-TB patients with HIV coinfection in Lesotho. Two patients died before or immediately after antiretroviral resistance was detected by genotyping; the remaining four patients were switched to effective antiretroviral therapy (ART) regimens. Favorable DR-TB treatment outcomes in coinfecting patients require successful management of their HIV infection, including treatment with an effective ART regimen. Coinfecting patients undergoing DR-TB treatment may require closer monitoring of their response to ART, including routine viral load testing, to ensure that they receive an effective ART regimen concurrent with DR-TB treatment.

INTRODUCTION

An estimated 12 million people worldwide are coinfecting with human immunodeficiency virus (HIV) and tuberculosis (TB).¹ More than 80% live in sub-Saharan Africa, where undiagnosed resistance to first-line drugs threatens the progress of both TB and HIV treatment efforts. Drug resistance surveys in southern Africa suggest that the proportion of drug-resistant (DR) TB among TB cases has increased during the past 15 years, with multidrug-resistant (MDR) TB now accounting for 2.5–7.7% of new TB infections.² HIV-1 drug resistance has also been documented since the rollout of antiretroviral therapy (ART) in sub-Saharan Africa, with rates as high as 12.3% among ART-naïve individuals.³ Without sufficient laboratory capacity and resources for drug susceptibility testing (DST) and virologic monitoring, many of these patients with TB or HIV drug resistance continue to be treated with inadequate regimens, which can lead to poor treatment outcomes, ongoing transmission, and amplification of resistance.

Recently updated World Health Organization (WHO) guidelines recommend prompt initiation of ART for all coinfecting MDR-TB patients, irrespective of CD4 cell count.⁴ The guidelines were based on evidence that, without concurrent ART, coinfecting patients have significantly higher rates of treatment failure and mortality during DR-TB treatment compared with DR-TB patients without HIV coinfection.⁵ DR-TB/HIV coinfecting patients with undiagnosed resistance to first-line ART would be expected to have similarly poor outcomes. Here, we describe antiretroviral resistance in six patients with DR-TB/HIV coinfection in Lesotho, where an estimated 77% of all TB patients are coinfecting with HIV.

MATERIALS AND METHODS

A retrospective review of all HIV coinfecting patients who began treatment for DR-TB in Lesotho between July 27, 2007 and April 11, 2011 was performed. Patients with laboratory-confirmed DR-TB and at least one documented HIV-1 mutation conferring resistance to antiretrovirals were included. All patients were treated as part of the national DR-TB pro-

gram operated by the Lesotho Ministry of Health and Social Welfare, with support from the non-governmental organization Partners in Health.

The treatment protocol for DR-TB patients in Lesotho has been described elsewhere.⁶ DR-TB/HIV coinfecting patients were evaluated monthly by a clinician, and CD4 cell count testing was performed approximately every 6 months. Viral load testing was performed if ART failure was suspected. In general, clinicians followed WHO guidelines on immunological or clinical evidence of ART failure.⁷ Patients with a viral load > 2,000 copies/mL received subsequent HIV drug resistance testing.

Blood samples were sent to PathCare Laboratories in South Africa, where HIV drug resistance was analyzed using the ViroSeq HIV-1 Genotyping System (Celera, Alameda, CA), a sequencing-based assay that detects mutations in the HIV protease and HIV reverse transcriptase genes. Sputum samples were sent to the Lesotho National Reference TB Laboratory for culture and DST using a BACTEC MGIT 960 System (Becton-Dickson, Sparks, MD). The Partners HealthCare Human Research Committee approved this study and waived the requirement for informed consent, because it was a retrospective study of data collected during the course of routine clinical care.

RESULTS

Between July of 2007 and April of 2011, 372 HIV coinfecting patients with confirmed or suspected DR-TB were enrolled in treatment. Of these patients, 195 patients had confirmed DR-TB: 21 patients had rifampicin mono-resistance, 10 patients had isoniazid mono-resistance, and 164 patients had resistance to both rifampicin and isoniazid. HIV genotyping was performed in nine confirmed DR-TB patients in whom ART failure was suspected, and HIV-1 mutations conferring resistance to antiretrovirals were detected in six of these patients (Table 1). With the exception of one patient who had been diagnosed with HIV infection only 2 months before starting DR-TB treatment, all patients were already on ART at the time that they initiated DR-TB treatment and had previously received ART concurrently with earlier courses of rifampicin-containing TB treatment regimens. The median CD4 cell count at the time of DR-TB

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TABLE 1
Baseline clinical characteristics of patients with documented DR-TB and resistance to antiretroviral drugs

Case	At the time DR-TB treatment was initiated			ART regimens received before detection of HIV resistance	ART start relative to DR-TB treatment initiation	Drugs to which the TB isolate was resistant	HIV mutations detected	Antiretroviral drugs to which HIV mutations conferred resistance*
	Age (years)/sex	CD4 cell count (cells/mm ³)	BMI (kg/m ²)					
1	40/Male	8	22.5	(1) d4T, 3TC, EFV, (2) d4T, 3TC, NVP, (3) AZT, 3TC, NVP	2 weeks after	H, R, E, S, Eto	RT gene: M184V, D67N, T69N, K70R, K219Q, G190S, V75I RT gene: K103N, M184V	NNRTI (NVP, EFV, ETR), NRTI (ABC, 3TC, FTC, AZT, d4T)
2	59/Male	132†	21.2	(1) d4T, 3TC, NVP, (2) AZT, 3TC, EFV, (3) d4T, 3TC, EFV, (4) AZT, 3TC, EFV	11 weeks before	H, R, E, S		NNRTI (NVP, EFV), NRTI (3TC, FTC)
3	32/Female	323	16.9	(1) AZT, ddI, LPV/r‡	2.5 years before	H, R, E, S	RT gene: D67N; Protease gene: I54V, V82A, L33F, F53L	NRTI (AZT, d4T), PI (all except DRV)§
4	39/Male	181	18.2	(1) d4T, 3TC, NVP, (2) d4T, 3TC, EFV	2.5 years before	H, R, E, S	RT gene: K103N, M184V, V108I, M41L, T215F	NNRTI (NVP, EFV), NRTI (d4T, AZT, 3TC, FTC, ABC)
5	30/Male	14	24.9	(1) d4T, 3TC, EFV	2 years before	R	RT gene: M184V, Y188L, V179D; Protease gene: M36I	NNRTI (EFV, NVP, ETR), NRTI (3TC, FTC)
6	45/Male	45	–	(1) TDF, FTC, EFV, (2) TDF, 3TC, EFV	2 years before	H, R, E	RT gene: M184V, D67N, K103N, K101P, K70E	NNRTI (NVP, EFV, ETR, RPV), NRTI (d4T, AZT, TDF, 3TC, FTC, ABC)

ABC = abacavir; ATZ/r = ritonavir-boosted atazanavir; AZT = zidovudine; BMI = body mass index; ddI = didanosine; DRV = darunavir; d4T = stavudine; E = ethambutol; EFV = efavirenz; Eto = efavirenz; FTC = emtricitabine; H = isoniazid; IDV/r = ritonavir-boosted indinavir; LPV/r = ritonavir-boosted lopinavir; NVP = nevirapine; R = rifampicin; RPV = rilpivirine; RT = reverse transcriptase; S = streptomycin; TDF = tenofovir; TPV/r = ritonavir-boosted tipranavir; 3TC = lamivudine.

* Based on the Stanford University HIV drug resistance database¹⁷ and the International AIDS Society 2011 update of the drug resistance mutations in HIV-1.¹⁸

† This CD4 cell count was measured 2 years before DR-TB treatment; no CD4 cell count was recorded at the time of DR-TB treatment initiation.

‡ At the time that the patient transferred to the DR-TB treatment program, she was receiving a second-line ART regimen, and no previous first-line regimen was documented.

§ Given the combination of protease gene mutations detected, the patient's HIV resistance mutation score for LPV/r was 40.

|| The patient's HIV resistance mutation score for LPV/r was zero.

TABLE 2
Clinical management and outcomes of patients with documented DR-TB and resistance to antiretroviral drugs

Case	At the time antiretroviral resistance was detected				Reason for viral load testing	Modified ART regimen	DR-TB treatment outcome	CD4 cell count after ART regimen change (cells/mm ³)	Viral load after ART regimen change (copies/mL)
	Duration of DR-TB treatment (months)	ART regimen	CD4 cell count (cells/mm ³)	Viral load (copies/mL)					
1	15	AZT, 3TC, NVP	35	123,753	CD4 cell count dropped in month 13 (from 53 to 35 in 2 months)	TDF, 3TC, ABC, LPV/r	Cured in month 24*	140 (16 weeks later)	576 (8 weeks later)
2	29	AZT, 3TC, EFV	77	87,834	CD4 cell count dropped in month 27 (from 147 to 77 in < 3 months)	–	Died in month 29†	–	–
3	12	AZT, ddI, LPV/r	311	3,847	Losing weight and had not culture-converted after 11 months of DR-TB treatment	d4T, 3TC, EFV	Died in month 24	319 (3 months later), 379 (5 months later), 263 (9 months later)	–
4	22	d4T, 3TC, EFV	120	112,738	CD4 cell count dropped in month 17 (from 200 to 117 in 8 months)	TDF, 3TC, LPV/r	Cured in month 24	325 (18 months later)	–
5	1	d4T, 3TC, EFV	14	285,015	CD4 cell count was very low after 2 years on ART	ddI, AZT, LPV/r	Cured in month 24	79 (4 months later); 176 (8 months later); 438 (14 months later)	–
6	5	TDF, 3TC, EFV	30	830,130	CD4 cell count was low after 2 years on ART and dropped in month 2 (from 45 to 30 in < 2 months)	ABC, LPV/r, EFV (switched empirically)	Died in month 5‡	–	–

ABC = abacavir; AZT = zidovudine; ddI = didanosine; EFV = efavirenz; LPV/r = ritonavir-boosted lopinavir; NVP = nevirapine; TDF = tenofovir; 3TC = lamivudine.

* Cure was defined as at least five consecutive negative cultures at least 30 days apart in the final year of treatment.¹⁹

† The patient died immediately after receipt of HIV resistance test results.

‡ The patient died 5 days after switching ART regimens empirically (before the results of HIV resistance testing were available).

treatment initiation was 88.5 cells/mm³ (range = 8–323). Three patients had low CD4 counts (< 200 cells/mm³) at the time that DR-TB treatment was initiated, despite having received ART for more than 2 years (cases 4, 5, and 6).

Four patients underwent viral load testing and subsequent HIV drug resistance testing, because their CD4 cell counts were dropping while on DR-TB treatment and ART. One patient had no documented drop in CD4 cell count, but the patient's CD4 cell count was 14 cells/mm³ after 2 years of ART (case 5). Another patient had a CD4 cell count above 300 cells/mm³ with no CD4 cell drop observed; however, he underwent viral load testing, because he was losing weight, and he remained culture positive after 11 months of DR-TB treatment (case 3).

HIV genotyping revealed that the patients had mutations conferring resistance to nucleoside analog reverse-transcriptase inhibitors (NRTIs), and all but one patient also had mutations conferring resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs). One patient had documented resistance to protease inhibitors (PIs). The most common mutations were M184V (*N* = 5), D67N (*N* = 3), and K103N (*N* = 3).

Three of six patients died during DR-TB treatment. Two patients died before or immediately after the results of the HIV drug resistance testing became available (cases 2 and 6). Two of the patients who died had undergone DST for second-line anti-TB drugs, which showed susceptibility to all second-line drugs tested (cases 3 and 6). The remaining three patients culture-converted within 2 months of starting a DR-TB regimen and were cured after 24 months of treatment. They showed dramatic immunological and/or virological improvement after they were switched to an ART regimen containing ritonavir-boosted lopinavir (Table 2).

DISCUSSION

Although there is growing literature on the treatment of DR-TB in high-HIV prevalence settings, HIV drug resistance in DR-TB patients has not yet been described. In settings where routine viral load monitoring is unavailable, it can be difficult for clinicians to know when to test for antiretroviral resistance in DR-TB/HIV coinfecting patients. Patients receiving concurrent DR-TB treatment and ART can experience clinical deterioration for a number of reasons other than ART failure, including severe side effects of treatment, DR-TB treatment failure, new opportunistic infections, and TB-associated immune reconstitution inflammatory syndrome.⁸ However, the cases reported here document the occurrence of HIV drug resistance in DR-TB/HIV coinfecting patients and show the poor outcomes that can occur with late detection. Clinicians should, therefore, have a high suspicion for HIV drug resistance when managing DR-TB/HIV coinfecting patients with poor responses to therapy.

We suspect that the patients in this case series experienced late detection of HIV drug resistance in this setting where routine virologic monitoring is unavailable. Three patients had low CD4 counts at the time that DR-TB treatment was initiated, despite having received ART for more than 2 years. This finding suggests that they may have had undiagnosed antiretroviral resistance before DR-TB treatment. In that case, their continued treatment with antiretroviral drugs to which their HIV was resistant may have contributed to their infection with DR-TB and subsequent disease progression.

In practice, TB can cause a depression of CD4 cell count independent of virological failure,⁹ particularly in DR-TB patients, who often are clinically very ill by the time that TB drug resistance is detected. Therefore, immunological monitoring has even less specificity in this patient cohort. Viral load monitoring is more reliable than CD4 monitoring as an early way to detect HIV drug resistance in these patients.¹⁰ Given that this patient population suffers concurrently from two deadly diseases and generally experiences poor treatment outcomes,¹¹ routine virologic monitoring for DR-TB patients with HIV coinfection should be considered, even in the context of limited resources. We recommend that all DR-TB/HIV coinfecting patients receive viral load testing at the start of DR-TB treatment and every 6 months while on DR-TB treatment. Patients with elevated viral load should receive an adherence intervention and repeat viral load 2–3 months later.

There are a number of reasons why TB/HIV coinfecting patients might be at increased risk for both HIV and TB drug resistance, including non-adherence, pharmacokinetics in TB/HIV patients, and drug interactions. Patients receiving concurrent treatment of TB and HIV disease face a high pill burden and may be more likely to experience severe adverse effects, which in turn, are associated with higher rates of non-adherence and default.⁸ Studies have shown that non-adherence and treatment interruptions are associated with increased risk of mutations conferring resistance to antiretrovirals.¹² Acquired TB drug resistance is also thought to result primarily from patient non-adherence to first-line TB treatment.

Additionally, studies have reported that HIV infection is associated with reduced serum concentrations of first-line anti-TB drugs,¹³ commonly attributed to malabsorption associated with chronic diarrhea. However, whether the lower concentrations of anti-TB drugs generate acquired resistance among HIV patients on daily TB treatment has not been carefully studied.

Interactions between first-line anti-TB drugs and antiretroviral drugs may also lead to subtherapeutic levels of certain drugs in TB/HIV patients receiving concurrent treatment. Rifampicin induces expression of the cytochrome P450 liver enzyme system, which metabolizes nevirapine and efavirenz, and studies have documented decreased plasma concentrations of nevirapine and efavirenz when administered with rifampicin.^{8,14} The reduction of nevirapine concentrations with concomitant rifampicin use is greater than the reduction of efavirenz concentrations,^{8,14} and currently, coadministration of nevirapine and rifampicin is not recommended.¹⁵ However, clinical cohorts have shown excellent viral control with efavirenz regimens, despite coadministration of rifampicin,^{14,16} and current guidelines suggest that dose adjustment of efavirenz is unnecessary.¹⁵

To our knowledge, this study is the first published study describing HIV drug resistance in DR-TB patients with HIV coinfection. Without concurrent ART, coinfecting patients have as much as a fivefold increased risk of mortality during DR-TB treatment compared with HIV-negative patients.⁵ Thus, undiagnosed resistance to first-line ART has important implications for the outcomes of DR-TB treatment in coinfecting patients. In this case series, two patients died before or immediately after receipt of antiretroviral resistance testing results. The outcomes might have been more favorable if HIV drug resistance had been recognized earlier

and the patients switched to an effective ART regimen during DR-TB treatment.

A limitation of this case series is that we cannot comment on the frequency of antiretroviral resistance in this population. Not all coinfecting patients received HIV drug resistance testing. Only patients with suspected ART failure received viral load testing, and only those patients with viral load > 2,000 copies/mL received subsequent HIV genotyping. Given the limitations of relying on CD4 and clinical monitoring to detect ART failure, unknown numbers of patients with antiretroviral resistance likely were undetected.

This case series reminds clinicians to keep antiretroviral resistance in mind when managing DR-TB/HIV coinfecting patients with poor responses to therapy. Coinfecting patients undergoing DR-TB treatment may require closer monitoring of their response to ART, including routine viral load testing, to ensure that they receive an effective ART regimen concurrent with DR-TB treatment. Additional research is needed to determine the prevalence of and risk factors for HIV drug resistance in coinfecting DR-TB patients.

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