

Acquired Rifampicin Resistance in Thrice-Weekly Antituberculosis Therapy: Impact of HIV and Antiretroviral Therapy

Gopalan Narendran,¹ Pradeep Aravindan Menon,¹ Perumal Venkatesan,¹ Krishnamoorthy Vijay,¹ Chandrasekaran Padmapriyadarsini,¹ Santhanakrishnan Ramesh Kumar,¹ Kannabiran Perumal Bhavani,¹ Lakshmanan Sekar,¹ Sivaramakrishnan Narayan Gomathi,¹ Chockalingam Chandrasekhar,² Satagopan Kumar,² Rathinam Sridhar,³ and Soumya Swaminathan¹

¹National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Chetpet, ²Government Hospital of Thoracic Medicine, Tambaram Sanatorium, and ³Government Stanley Hospital, Tondiarpet, Chennai, India

Background. Risk factors for acquired rifampicin resistance (ARR) in human immunodeficiency virus (HIV)/tuberculosis coinfection, in the highly active antiretroviral therapy (HAART) era, needs evaluation. We studied the impact of HIV and HAART on ARR among patients taking thrice-weekly antituberculosis therapy.

Methods. This cross-protocol analysis included patients with newly diagnosed, rifampicin-susceptible pulmonary tuberculosis, with and without HIV, enrolled in clinical trials (who took >80% of medication) at the National Institute for Research in Tuberculosis between 1999 and 2013. All patients received rifampicin and isoniazid for 6 months reinforced with pyrazinamide and ethambutol in the first 2 months, given thrice-weekly throughout the study along with HAART in one of the groups. Outcomes were categorized and multivariate logistic regression analysis performed to identify risk factors for ARR.

Results. The per-protocol results included patients with tuberculosis: 246 HIV-uninfected patients (HIV⁻TB⁺), 212 HIV patients not on HAART (non-HAART), and 116 HIV-infected patients on HAART. Median CD4 counts of the latter 2 groups were 150 and 93 cells/ μ L, respectively, and the median viral loads were 147 000 and 266 000 copies/mL, respectively. Compared with HIV⁻TB⁺, the relative risks (RRs) for an unfavorable response in the coinfecting, non-HAART and HAART groups were 2.1 (95% confidence interval [CI], 1.7–14.8; $P < .0001$) and 2.1 (95% CI, .9–5.2; $P = .3$), whereas for ARR, the RRs were 21.1 (95% CI, 2.6–184; $P < .001$) and 8.2 (95% CI, .6–104; $P = .07$), respectively.

Conclusions. HIV-infected patients with tuberculosis treated with a thrice-weekly antituberculosis regimen are at a higher risk of ARR, compared with HIV-uninfected patients, in the presence of baseline isoniazid resistance. HAART reduces but does not eliminate the risk of ARR.

Keywords. HIV; tuberculosis; drug-resistant tuberculosis; intermittent therapy; acquired rifampicin resistance.

Human immunodeficiency virus (HIV) and tuberculosis coinfection continues to be a global health problem, complicated further by emergence of drug resistance [1]. Despite drug–drug interactions, the ability of

rifampicin to destroy intracellular and intermittently growing *Mycobacterium tuberculosis* makes it indispensable in the treatment of HIV-associated tuberculosis [2]. Non-rifampicin-containing regimens have shown inferior cure rates [3].

A unique phenomenon complicating management of HIV-associated tuberculosis despite supervised therapy is the emergence of acquired rifampicin resistance (ARR). ARR has been reported with the use of once-, twice-, and thrice-weekly administered rifamycins in the pre–highly active antiretroviral therapy (HAART) era [4–6]. ARR in HIV-negative tuberculosis is infrequent [4, 7].

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Correspondence: Soumya Swaminathan, MD, DNB, National Institute for Research in Tuberculosis, No. 1, Mayor Sathiyamoorthy Road, Chetput, Chennai, India 600031 (doctorsoumya@yahoo.com).

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In India, the Revised National Tuberculosis Control Program (RNTCP) recommends a fully intermittent thrice-weekly anti-tuberculosis treatment (ATT) regardless of HIV status [8]. The efficacy of this thrice-weekly ATT regimen in HIV-uninfected patients with tuberculosis treated under trial conditions was found to be 96% among new smear-positive cases [9]. The effectiveness of the same intermittent regimen was 74% under field conditions [10]. Vashishtha et al found no differences between HIV-infected and -uninfected patients with respect to tuberculosis failures or relapses, using the RNTCP regimen [10]. However, a recent meta-analysis favored a daily instead of an intermittent ATT regimen, in the context of HIV [11]. Current World Health Organization (WHO) guidelines recommend daily treatment, at least in the intensive phase, for HIV-coinfected tuberculosis patients. However, supporting evidence from randomized controlled clinical trials (RCTs) for the shift to a daily regimen is lacking [12].

We performed a cross-protocol analysis, comparing 3 distinctive cohorts of patients with newly diagnosed pulmonary tuberculosis: (1) those who were HIV uninfected; (2) those who were HIV infected and not on HAART; and (3) those who were HIV infected and on HAART. All patients were being treated with an identical thrice-weekly ATT regimen given for 6 months. This enabled us to evaluate the influence of HIV and the role of HAART in preventing ARR.

SUBJECTS AND METHODS

Study Cohorts

The present analysis used data collected from patients with newly diagnosed pulmonary tuberculosis patients enrolled in 4 RCTs. These trials were conducted at the National Institute for Research in Tuberculosis, Chennai, India. All patients had culture-positive pulmonary tuberculosis, with rifampicin-susceptible isolates at baseline. Patients with >80% treatment adherence (per-protocol results) were included in this analysis.

A double-blind RCT that evaluated the role of inhaled steroids in reducing lung function impairment in pulmonary tuberculosis, between 1999 and 2001, enrolled HIV-uninfected patients with tuberculosis (“HIV⁻TB⁺” group). The RCT comparing a fully intermittent 6- and 9-month antituberculosis regimen (NCT 0376012) formed the “HIV⁺TB⁺, non-HAART” group. This study was conducted in the pre-HAART era between 2000 and 2005. The 9-month regimen in this trial was essentially identical to the 6-month regimen but with an additional 3 months of continuation phase. Hence, analysis was done by combining the 2 regimens, but restricting the observations to the first 6 months in the longer regimen [6]. The third group consisted of patients enrolled in 2 trials (NCT 00332306 and NCT0933790), receiving the same regimen of intermittent ATT along with efavirenz-based HAART (“HIV⁺TB⁺HAART”

group). The first trial comparing efficacy and safety of once-daily nevirapine and efavirenz-based antiretroviral therapy (ART) in HIV-associated tuberculosis (NCT 00332306) [13] enrolled HIV-infected patients with tuberculosis between 2006 and 2008. The second trial (NCT 0933790) [14], comparing daily vs intermittent ATT, included only patients on thrice-weekly regimen (ongoing from 2009).

Baseline Investigations

Baseline laboratory investigations included HIV testing, hepatitis B and C serology, complete blood count (automated hematology analyzer, ABX), liver and renal function tests, and random plasma glucose (automated analyzer, Olympus Corporation). Estimation of CD4⁺ T-cell count (FACSCount flow cytometer, Becton Dickinson), and plasma HIV RNA load (Roche Amplicor automated viral load monitor) were done only for HIV-infected patients.

Three sputum specimens were examined for acid-fast bacilli by fluorescent microscopy and cultured on solid media (Lowenstein-Jensen) every month during the entire treatment period. Two positive cultures at baseline and all subsequent positive cultures were subjected to species identification and drug susceptibility testing using standard techniques [15, 16]. Chest radiographs were taken at baseline and the second and sixth months of ATT. Tuberculosis patients in the age group >15 years in the HIV-uninfected cohort and >18 years in the 2 HIV-infected cohorts were enrolled. All study subjects had to satisfy the clinical, sociological, and laboratory eligibility criteria for enrollment. DNA fingerprinting was performed on paired isolates from stored cultures (at baseline and at the time of failure with bacteriological confirmation). Three molecular methods—namely, IS6110 analysis, mycobacterial interspersed repetitive unit-variable number tandem repeat typing, and spacer oligonucleotide typing (spoligo-typing)—were used for identification of the mycobacterial strain on these paired isolates. The trials were individually approved by the Institutional Ethics Committee. Written informed consent was obtained from all study participants prior to enrollment.

Treatment Details

All tuberculosis patients were treated with a thrice-weekly intermittent regimen consisting of isoniazid (INH) 600 mg and rifampicin 450 mg or 600 mg (based on weight <60 or >60 kg) for 6 months, reinforced with ethambutol 1200 mg and pyrazinamide 1500 mg in the first 2 months of therapy. All tuberculosis drugs were assayed for content as part of quality assurance. Treatment was fully supervised in all except the NCT0376012 trial, where the continuation phase had only 1 of 3 doses supervised. Patients selected from the NCT0033206 study were initiated on HAART at 2 months of ATT. The HAART regimen consisted of didanosine (250/400 mg for body weight <60 or >60 kg), lamivudine (300 mg), and efavirenz (600 mg) given once daily [13].

Table 1. Pretreatment (Baseline) Characteristics of Patients in the 3 Cohorts

Characteristic ^a	HIV-TB ⁺ (n = 246)	HIV ⁺ TB ⁺ , Non-HAART (n = 212)	HIV ⁺ TB ⁺ HAART ⁺ (n = 116)	P Value
Age, y, mean (SD)	30 (12)	35 (8)	36 (8)	<.01
Male sex, %	66	80	87	<.001
Weight, kg, mean (SD)	42.7 (6.9)	43.4 (8.3)	41.6 (7.2)	.41
HIV-related parameters				
Viral load, copies/mL, median (IQR)	Not done	147 000 (31 800–504 000)	266 000 (71 700–750 000)	<.001
CD4 count, cells/ μ L, median (IQR)	Not done	150 (82–283)	93 (44–158)	<.001
Tuberculosis-related evaluation				
Chest radiographic findings				
Cavitation, %	63	16	12	<.001
Radiographic lesions \geq 3 zones, %	75	19	59	<.001
Mycobacteriology (sputum)				
Smear positive for AFB, %	99	76	85	<.001
Culture grading 2+ or higher, %	91	57	65	<.001
Susceptible to all first-line drugs, No. (%)	224 (90)	182 (88)	106 (91)	
Isoniazid resistance, No. (%)	12 (5)	10 (5)	5 (5)	
Streptomycin resistance, No.	6	3	3	
S/H resistance, No.	3	9	0	
S/H/E resistance, No.	0	2	0	
Sensitivity unavailable, No. ^b	0	6	2	
Overall isoniazid resistance, No. (%)	15 (6)	21 (10)	5 (5)	.12

Abbreviations: AFB, acid-fast bacilli; E, ethambutol; H, isoniazid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; S, streptomycin; SD, standard deviation; TB, tuberculosis.

^a Among patients with culture-confirmed, rifampicin-sensitive pulmonary tuberculosis at enrollment.

^b Sensitivity could not be set as they had a colony growth of <10 or culture was contaminated.

Those patients, included from the NCT0933790 trial [14], had either tenofovir (300 mg once daily) or zidovudine (300 mg twice daily), along with lamivudine (150 mg twice daily) and efavirenz (600 mg once daily), initiated within the first 2–8 weeks (based on prevailing ART guidelines) [17, 18]. All HIV-infected patients were given cotrimoxazole double strength, 1 tablet daily, if their CD4 count was <350 cells/ μ L, in addition to pyridoxine 10 mg daily.

Outcome Definition

A cure or favorable response to treatment was defined as all available cultures (6 in number) in the last 2 months of treatment being negative. Unfavorable responses included failure and death due to tuberculosis. Failure was further classified as bacteriological when patients had at least 2 positive cultures in the last 2 months of treatment or persistent culture positivity after 4 months of treatment, and clinical when clinical and /or radiographic deterioration mandated change or extension of ATT, without accompanying positivity in sputum culture.

Statistical Analysis

Per-protocol results from the 3 groups were analyzed using SPSS software, version 20. The χ^2 and Fisher exact tests were used for testing differences between proportions. The relative

risk for ARR and unfavorable responses was calculated taking HIV-uninfected patients with tuberculosis as the standard, and comparing it with the 2 HIV-infected groups with and without HAART. A multiple logistic regression model was used to identify factors contributing to ARR, after adjusting for covariates. Baseline variables that were considered important (age, sex, weight, CD4 count, HAART use, culture grade, and INH resistance) were used to fit the regression model, and odds ratios with 95% confidence intervals (CIs) were computed. Furthermore, the backward elimination method was used to identify the significant covariates associated with ARR. Regression analysis was done for the whole group as well as within the HIV-infected group separately.

RESULTS

This retrospective cross-protocol analysis included data from 246 HIV-uninfected patients with tuberculosis (HIV-TB⁺), 212 HIV-infected patients with tuberculosis not on HAART (HIV⁺TB⁺, non-HAART), and 116 HIV-infected patients with tuberculosis and on HAART (HIV⁺TB⁺HAART). Baseline/pretreatment characteristics of the 3 groups, including their drug susceptibility patterns, are shown in Table 1. The bacteriologic failures among the HIV-TB⁺ group, HIV⁺TB⁺,

Table 2. Tuberculosis Treatment Outcome in the 3 Groups

Outcome	HIV ⁻ TB ⁺ (n = 246)	HIV ⁺ TB ⁺ , Non-HAART (n = 212)	HIV ⁺ TB ⁺ HAART ⁺ (n = 116)
Cured, No. (%)	237 (96)	174 (82)	107 (92)
Unfavorable, No. (%)	9	38	9
Bacteriologic failure	9 (4)	19 (9)	6 (5)
Clinical failure	0	4	1
Deaths	0	15	2
ARR among failures, No. (%)	1/9 (11)	19/19 (100)	4/6 (67)
RR for unfavorable responses (95% CI)	1	5.1 (1.7–14.8); <i>P</i> < .0001	2.1 (.9–5.2); <i>P</i> = .3
RR for ARR (95% CI)	1	21.1 (2.6–184); <i>P</i> < .001	8.2 (.6–104); <i>P</i> = .07

Abbreviations: ARR, acquired rifampicin resistance; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; RR, relative risk; TB, tuberculosis.

non-HAART group, and HIV⁺TB⁺HAART group were 4% (9/246), 9% (19/212), and 5% (6/116), respectively. Details of tuberculosis treatment outcomes are provided in Table 2.

In addition, 4 patients (3 with lesions in the brain and 1 with clinical and radiological deterioration in the chest radiograph) in the HIV⁺TB⁺, non-HAART group as well as 1 patient (who developed an open pneumothorax) in the HIV⁺TB⁺HAART group, were classified as clinical failures, as their clinical condition necessitated extension of treatment beyond 6 months. None of the patients in the HIV-uninfected group required ATT extension beyond 6 months.

Compared with the HIV-uninfected group, the relative risk of an unfavorable response was 5.1 (95% CI, 1.7–14.8; *P* = .00009) in the HIV⁺TB⁺, non-HAART group and 2.12 (95% CI, .9–5.2; *P* = .3) in the HIV⁺TB⁺HAART group (Table 2). Among HIV-infected patients, the relative risk for unfavorable response was 2.4 times more (95% CI, 1.2–4.7; *P* = .0045) in the absence of HAART. The sputum culture negativity by month in the 3 groups is depicted in Figure 1.

Comparison of the drug susceptibility pattern among bacteriologically confirmed cases, at pretreatment and at failure, in each of the groups is provided in Table 3. All 19 patients who

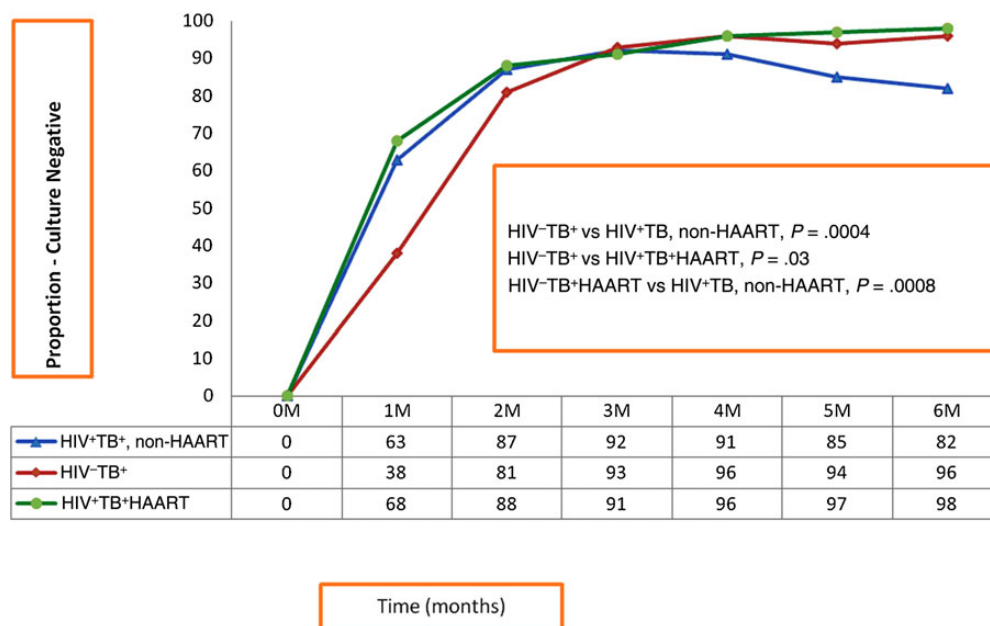


Figure 1. Proportion (%) of patients with tuberculosis (rifampicin-susceptible strain at baseline) becoming culture negative during the course of antituberculosis treatment (ATT), by month, in the 3 groups. Abbreviations: HIV⁻TB⁺, human immunodeficiency virus uninfected, tuberculosis infected; HIV⁺TB⁺, non-HAART, human immunodeficiency virus infected, tuberculosis infected, not on highly active antiretroviral therapy; HIV⁺TB⁺HAART, human immunodeficiency virus infected, tuberculosis infected, on highly active antiretroviral therapy; HIV⁻TB⁺HAART, human immunodeficiency virus uninfected, tuberculosis infected, on highly active antiretroviral therapy.

Table 3. Drug Susceptibility Pattern at Baseline and at the Time of Failure Among Patients With Bacteriologically Confirmed Failure

Susceptibility Pattern	HIV ⁻ TB ⁺ (n = 9)		HIV ⁺ TB ⁺ , Non-HAART (n = 19)		HIV ⁺ TB ⁺ HAART (n = 6)	
	Baseline	Failure	Baseline	Failure	Baseline	Failure
Susceptible to all first-line drugs	6	3	9	0	4	2
Isoniazid monoresistance	3	5	5	0	2	0
Resistant to S/H	0	0	4	0	0	0
Resistant to S/H/E	0	0	1	0	0	0
Rifampicin monoresistance	0	0	0	4	0	1
Multidrug resistance (H/R)	0	1	0	15	0	3
% of ARR among failures		11		100		67

Abbreviations: ARR, acquired rifampicin resistance; E, ethambutol; H, isoniazid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; R, rifampicin; S, streptomycin; TB, tuberculosis.

failed therapy in the HIV⁺TB⁺, non-HAART group had emergence of ARR. Fifteen of the 19 patients developed multidrug-resistant tuberculosis (resistance to both isoniazid and rifampicin), with 4 developing rifampicin monoresistance. Three of the 6 bacteriological failures in the HIV⁺TB⁺HAART group and 1 of the 9 failures in the HIV⁻TB⁺ group had emergence of ARR. The relative risk of ARR was 21.1 (95% CI, 2.6–184; $P < .001$) and 8.2 (95% CI, .6–104; $P = .07$) when the HIV⁺TB⁺, non-HAART group and the HIV⁺TB⁺HAART group were compared with the HIV⁻TB⁺ group. Analysis within the HIV group showed that the risk of ARR was 2.6 (95% CI, .90–7.4; $P = .06$) in the absence of HAART.

Multiple logistic regression analysis showed that INH resistance and HIV infection were significant risk factors for ARR. When logistic regression was restricted to HIV-infected patients, INH resistance was found to be a highly significant risk factor, along with lower CD4 count and higher sputum culture grade at baseline (Table 4). DNA fingerprinting was available for 18 of 25 paired isolates (comprising 15 of 19 failures in the HIV⁺TB⁺, non-HAART group and 3 of 6 in the HIV⁺TB⁺HAART group), and confirmed that 78% (14/18) of bacteriological failures were due to the same strain. Four failures (4/18) in the HIV⁺TB⁺, non-HAART group were caused by a different strain of *M. tuberculosis*.

DISCUSSION

This unique comparison of tuberculosis treatment outcomes from 3 different groups of patients, treated with an identical thrice-weekly ATT in the same setting, enabled us to evaluate the impact of HIV and HAART on ARR. Failures during treatment truly reflected the strength of the regimen rather than recurrences, which could be influenced by tuberculosis endemicity in that region and the level of immunodeficiency in the patient [19, 20]. We found that failing tuberculosis

treatment and speed of culture conversion were relatively similar in HIV⁻TB⁺ and HIV⁺TB⁺HAART patients, despite advanced immunodeficiency in the latter group (Figure 1). The advanced stage of HIV in the HIV⁺TB⁺HAART group (higher viral load and lower CD4 count), with possibly prolonged period of immunodeficiency, could explain why HAART initiation did not completely offset the tendency for emergence of ARR, even though it significantly improved overall tuberculosis outcomes. Hence, the WHO recommendation for early and concomitant initiation of HAART for all HIV-infected patients with tuberculosis irrespective of CD4 counts, while reducing treatment failures, may not fully protect against emergence of ARR [18].

Table 4. Multiple Logistic Regression Analysis to Identify Baseline Risk Factors for Acquired Rifampicin Resistance Among Patients With Tuberculosis on Thrice-Weekly Antituberculosis Therapy

Baseline Risk Factors	P Value	OR	95% CI
Among the 3 cohorts			
Sex	.21	0.53	.19–1.44
Age	.20	1.03	.95–1.06
Resistance to INH	. . .	9.97	3.43–28.37
Weight	.17	0.95	.91–1.03
Sputum culture grade	.34	1.31	.88–2.55
HIV infected	.01	2.02	1.58–16.77
Among HIV-coinfected patients			
Sex	.12	0.42	.14–1.26
Age	.69	0.99	.92–1.06
Resistance to INH	. . .	13.28	4.25–41.37
Weight	.52	0.98	.92–1.05
Sputum culture grade	.03	2.00	1.01–3.70
On HAART	.08	2.68	.88–8.1
CD4 count at nadir	.03	0.98	.97–.99

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; INH, isoniazid; OR, odds ratio.

Pretreatment INH resistance is a known risk factor for amplification of drug resistance among tuberculosis patients on ATT [21]. In fact, the incidence of ARR, even among HIV-uninfected patients with tuberculosis, was 5 times higher in the presence of initial INH resistance compared with patients harboring fully drug-susceptible organisms [7].

Varying plasma levels of INH and rifampicin, due to differential half-lives, cause functional monotherapy. Malabsorption of ATT drugs in HIV may further potentiate occurrence of ARR [22–24]. Our study similarly revealed that pretreatment INH resistance was a significant risk factor for development of ARR among tuberculosis patients, irrespective of HIV status. Among HIV-infected patients with tuberculosis, a low CD4 count and a higher mycobacterial burden at baseline were additional risk factors. It would be interesting to study the occurrence of ARR among HIV patients on HAART, with a relatively higher CD4 count at the time of tuberculosis diagnosis, as well as among those receiving daily ATT.

Incidence of ARR was observed to be high among failures and relapses when intermittent tuberculosis therapy was used in the presence of HIV infection. In our previous study, all patients who failed therapy had ARR [6]. Further, subgroup analysis revealed that patients who developed ARR had a significantly lower CD4 cell count, lymphocyte percentage, and higher sputum culture grade at baseline, compared with those who did not [6, 25]. In the study by Vernon et al, 4 of 5 patients who relapsed in the once-weekly rifampentine arm compared with none in the twice-weekly rifampicin arm (given in the continuation phase along with INH), developed ARR [4]. Risk factors identified included younger age, lower CD4 count, extrapulmonary tuberculosis, and concomitant antifungal treatment. Of note, none of the HIV-uninfected patients enrolled in that trial developed ARR [4].

Additionally, in a study of 169 patients with advanced HIV, Burman et al [24] found that 8 of 9 patients (with CD4 count <100 cells/ μ L) with failure or relapse had ARR. A recent retrospective survey from a California tuberculosis registry reported a 5 times higher risk of ARR in dual infection. Cavitation at baseline and absence of directly observed therapy were other risk factors in that study [26].

Nosocomial transmission facilitated by prolonged or frequent hospitalization, which is inevitable without HAART, could partly explain the higher rates of ARR in our HIV⁺TB⁺, non-HAART group [6, 20, 24, 27].

Li et al [28] found that patients relapsed with ARR when intermittent dosing of tuberculosis drugs was used throughout the treatment period. However, ARR was infrequent when a daily intensive phase was followed by an intermittent continuation phase. In a meta-analysis of published studies, Lew et al [29] identified initial drug resistance as the main predisposing factor for ARR. The incidence of ARR was 0.8%, 6%, and 14% when

patients harbored pan-susceptible, single-drug resistant, and polydrug-resistant organisms, respectively [29].

Another meta-analysis among dually infected patients by Khan et al [30] concluded that thrice-weekly antituberculosis regimens were associated with more failures, relapses, and acquisition of drug resistance (to tuberculosis). This trend was reduced considerably with HAART administration. They also found that a daily administration of ATT during the intensive phase, with rifampicin given throughout for at least 6 months, improved tuberculosis treatment outcomes in HIV-infected patients [30].

Preliminary results from an ongoing RCT comparing daily with intermittent antituberculosis regimens in patients with culture-positive pulmonary tuberculosis (NCT0933790) revealed a significantly higher rate of culture conversion at 2 months, as well as a trend toward lower incidence of ARR in the daily arm [14, 31].

The strengths of our study were that all patients had identical tuberculosis regimens. Quality-assured drugs were used and patients were treated under similar trial conditions. High compliance rate and intense clinical monitoring was ensured. Mycobacterial culture and drug susceptibility testing were performed every month at a supranational reference laboratory.

The limitations were that these were not head-to-head comparisons, but rather nonconcurrent trials. The numbers eligible for this analysis from the HIV⁺TB⁺HAART group were relatively small. Other limitations were the differences in drug supervision patterns and the varying time of ART initiation within the HIV cohorts.

In conclusion, HIV-infected patients with tuberculosis are at a higher risk of ARR than are HIV-uninfected patients, when treated with a thrice-weekly antituberculosis regimen, especially in the presence of baseline INH resistance. HAART reduces but does not eliminate the risk of ARR completely. Daily tuberculosis treatment, prompt diagnosis of HIV, and earlier HAART initiation preserving immune function in HIV-infected tuberculosis patients could potentially prevent amplification of drug resistance.

Notes

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