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JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES

Preceded by: Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology (ISSN: 1077-9450)

 Volume 39(4), 1 August 2005, pp 464-470

Outline

Graphics

Factors That Complicate the Treatment of Tuberculosis in HIV-Infected Patients

[Epidemiology and Social Science]

Dworkin, Mark S MD, MPH&TM, FACP*; Adams, Michael R*; Cohn, David L MD†; Davidson, Arthur J MD†; Buskin, Susan PhD, MPH‡; Horwitch, Carrie MD, MPH‡; Morse, Anne BS§; Sackoff, Judy PhD[//]; Thompson, Melanie MD¶; Wotring, Linda PhD#; McCombs, Scott B MPH*; Jones, Jeffrey L MD, MPH**

From the *National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA; †Denver Public Health, Denver, CO; ‡Public Health-Seattle and King County, Seattle, WA; §Louisiana Office of Public Health, New Orleans, LA; [//]The City of New York Department of Health, New York City, NY; ¶AIDS Research Consortium of Atlanta, Atlanta, GA; #Michigan Department of Community Health, Detroit, MA; and **National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

Received for publication June 7, 2004; accepted November 22, 2004.
Presented in part at the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January-February, 2000 [abstract 259].

Reprints: Mark S. Dworkin, Illinois Department of Public Health, Division of Infectious Diseases, 160 North LaSalle, #7 South, Chicago, IL 60601 (e-mail: mdworkin@idph.state.il.us).

Summary:

Treatment of tuberculosis (TB) in persons coinfected with HIV has become increasingly complex during the past decade. We describe the factors that complicate anti-TB therapy in a large observational cohort of HIV-infected persons in the United States. Among 367 HIV-infected patients with 372 episodes of culture-confirmed TB, 44.1% had injection drug use as a mode of HIV transmission. Hepatic disease was present at the time of TB diagnosis or during anti-TB therapy for 91 episodes (24.5%). Elevation at least twice the upper limits of normal of aminotransaminases was observed during the first month of anti-TB therapy in 116 (31.2%) of the episodes. The most commonly reported adverse effects occurring during therapy were rash (27.8%), nausea (26.2%), leukopenia or neutropenia (20.2%), diarrhea (19.3%), vomiting (18.5%), and elevated temperature (>101.5°F [38.6°C], 16.9%). Prescription of a rifamycin and a medication known to interact with rifamycins occurred during 270 (72.6%) episodes. Because HIV-infected patients with TB often have underlying complicating conditions, such as hepatic disease, and are treated with medications that may have toxicities and cause drug-drug interactions, we recommend that clinicians pay careful attention to these factors when treating coinfected patients.

Greater than one third of the estimated 36 million persons infected with HIV globally are coinfected with *Mycobacterium tuberculosis*.[1,2] In North America, 8% of HIV-infected persons are estimated to be coinfected with *M. tuberculosis*, and in the United States, approximately 9% to 15% of tuberculosis (TB) cases are reported in HIV-infected persons.[3-5] In the past decade, treatment of HIV and AIDS has become increasingly complex with the introduction of many new medications prescribed as long-term combination therapy. Several of these medications have the potential to interact with and complicate anti-TB therapy, especially by causing liver disease and cutaneous reactions.[6] Also, HIV-infected persons may have significant liver dysfunction associated with alcohol abuse, injection drug

use,[7] and coinfection with hepatitis viruses.[8]

The complexity of the treatment of HIV-infected persons coinfected with *M. tuberculosis* is a significant public health issue, because interference with optimal treatment of TB may lead to failure or interruption of therapy and further transmission of disease, promote the emergence of drug-resistant strains, and lead to additional morbidity and mortality. Underlying and newly recognized acute and chronic hepatitis, adverse drug reactions and side effects, drug interactions, and inability to adhere to long-term multiple-drug therapy are all complicating factors. Given these potential issues, quantitating the frequency of these factors provides important information to health care providers who treat patients with TB. Such information would be especially helpful when evaluating which of several medications may need to be discontinued when prescribed medications have overlapping adverse effects. We describe the prevalence of many of the factors that complicate anti-TB therapy in a large observational cohort of HIV-infected persons.

METHODS

The Adult and Adolescent Spectrum of HIV Disease project (ASD) is a national surveillance project of the Centers for Disease Control and Prevention (CDC), in collaboration with 11 state and local health departments, in which information is abstracted from the medical records of HIV-infected patients at selected public and private health care facilities.[9,10] All available medical records (inpatient, outpatient, and local health department) of HIV-infected patients with a confirmed diagnosis of TB who had been enrolled in the ASD were reviewed using a standardized supplemental abstraction form. Six of the 11 ASD sites elected to participate in this study. These sites were located in Atlanta (1989-1998), Denver (1989-2000), Detroit (1986-1999), New Orleans (1991-2000), New York City (1995-1998), and Seattle (1988-1999). Information collected included demographics and $CD4^+$ cell counts (from the ASD database), anatomic site of TB, information about treatment, adherence problems, conditions or illnesses present at the time of initial diagnosis or recognized after anti-TB therapy had begun, prescription of medications known to be contraindicated or reported to cause drug interactions with anti-TB medications, signs and symptoms of anti-TB medication adverse effects, and laboratory abnormalities that may be attributed to anti-TB medications.

All cases of TB were laboratory confirmed by isolation of *M. tuberculosis* from a clinical specimen.[11] For $CD4^+$ cell count calculations, we examined the time within 6 months before and after the diagnosis of TB (excluding the month of diagnosis). When a value was available before and after TB diagnosis, the earlier value was selected. If multiple earlier values were available, the most recent was used. When 2 values were available from the same month, the values were averaged. Hepatic disease was defined as a diagnosis of any active or chronic viral hepatitis, other (nonviral) hepatitis, alcoholic hepatitis, or any other form of chronic liver disease recorded in the medical record. For aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measurements, when a patient had more than 1 measurement during the period under review (eg, during the month before beginning therapy), the average of the measurements was included. The protocol for this study was approved by institutional review boards at the CDC and each of the participating ASD sites.

RESULTS

The study identified 367 HIV-infected patients with 372 episodes of culture-confirmed TB. Among the 5 patients with 2 episodes, the initial episode of treatment ranged from 8 months to 17 months and all these episodes were described as relapse or recurrence. The largest group by race/ethnicity was African Americans (238 patients [64.8%], 77.3% of these patients were male); male-male sex and injection drug use were the predominant modes of HIV exposure (Table 1). Among the 69 HIV-infected female patients, only 1 was pregnant at the time of TB diagnosis and none became pregnant during therapy. Among all episodes of TB, directly observed therapy (DOT) was commonly used for part or all of the anti-TB therapy (292 of 372 episodes [78.5%]); 171 (46.0%) episodes were treated with only DOT. The median $CD4^+$ cell count within 6 months of TB diagnosis was 120 cells/μL among the 239 patients (242 episodes) for whom this information was available (25th percentile: 30 cells/μL, 75th percentile: 234 cells/μL). The median $CD4^+$ cell count was 118 cells/μL for episodes with only pulmonary involvement and 126 cells/μL for extrapulmonary episodes. The anatomic sites of TB among all episodes (some patients may have had multiple sites involved) were pulmonary (293 [78.8%]); pleural (24 [6.5%]); lymphatic (84 [22.6%]); blood (23 [6.2%]); genitourinary (13 [3.5%]); bone and/or joint (10 [2.7%]); liver (7 [1.9%]); meningeal (6 [1.6%]); brain (5 [1.3%]); peritoneal (1 [0.3%]); and other disseminated, including miliary (57 [15.3%]). There were no cutaneous cases. Drug resistance was not common. Resistance to isoniazid (with or without resistance to other anti-TB medications) was reported

in 13 episodes (3.5%), rifampin monoresistance was reported in 3 episodes (0.8%), and multidrug-resistant TB (resistance to at least isoniazid and rifampin) was reported in 5 episodes (1.3%).

Characteristic	N (%)
Sex	
Male	298 (81.2)
Female	69 (18.8)
Race/ethnicity	
White	85 (23.2)
African-American	238 (64.8)
Hispanic	36 (9.8)
Asian/Pacific Islander	3 (0.8)
Native American	5 (1.4)
Mode of HIV exposure	
Male-male sex (MSM)	129 (35.1)
IDU (includes IDU-MSM)	162 (123 IDU, 39 MSM-IDU) (44.1)
Heterosexual	23 (6.3)
Hemophilia or blood transfusion	6 (1.6)
Other/unknown	47 (12.8)
City	
Atlanta	101 (27.5)
Denver	43 (11.7)
Detroit	63 (17.2)
New Orleans	82 (22.3)
New York City	31 (8.4)
Seattle	47 (12.8)
Year of TB diagnosis	
1986–1988	5 (1.3)
1989–1991	81 (21.8)
1992–1994	133 (35.7)
1995–1997	117 (31.4)
1998–2000	36 (9.7)
Administration of anti-TB therapy	
DOT only	171 (46.0)
DOT and self-administered therapy	121 (32.5)
Self-administered therapy only	40 (10.7)
Unknown	40 (10.7)

*Year of TB diagnosis and administration of therapy data are derived from number of episodes; all other data are derived from number of cases.
IDU indicates injection-drug user; MSM, men who have sex with men.

TABLE 1. Characteristics of 367 HIV-Infected Patients With 372 Episodes of Culture-Confirmed (1986-2000)*

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The most commonly used initial drug regimen was isoniazid, rifampin, pyrazinamide, and ethambutol, which was used for 223 episodes (59.9%). Sixty (16.1%) episodes were initially treated with isoniazid, rifampin, and pyrazinamide. Thirteen (3.5%) episodes were treated with isoniazid, rifampin, pyrazinamide, and streptomycin; another 12 (3.2%) episodes were treated with isoniazid, rifampin, pyrazinamide, and at least 1 other drug; 9 (2.4%) episodes were initially treated with isoniazid and rifampin only; and 47 (12.6%) episodes were treated with 1 of several other combinations. Eight (2.2%) did not have initial drug regimen data available. The median

number of regimens prescribed per patient during anti-TB therapy was 2 (range: 1-10 regimens). Among 332 episodes with information, the median number of months observed on treatment was 10.5 months (range: 1-51 months).

Among 505 changes in the anti-TB regimens, the reasons for changing were planned change in treatment (189 changes in 163 episodes [ie, from intensive to continuation phase]), unknown/missing (168 changes in 112 episodes), other (74 changes in 58 episodes), intolerance to anti-TB drugs (65 changes in 57 episodes), and *M. tuberculosis* isolate resistant to 1 or more drugs (27 changes in 22 episodes). Vitamin B_6 (pyridoxine) was prescribed for 327 (87.9%) episodes. Among first-line anti-TB drugs, intolerance led to regimen changes in 7.6% of regimens that included ethambutol (23 changes among 304 episodes), in 5.6% that included isoniazid (20 changes among 360 episodes), in 5.0% that included pyrazinamide (17 changes among 342 episodes), and in 4.8% that included rifampin (17 changes among 354 episodes). Streptomycin (3 changes among 44 episodes [6.8%]) and ethionamide (1 change among 11 episodes [9.1%]) were prescribed less often but caused changes more frequently. Twelve drug changes were attributed to intolerance to more than 1 drug.

Prescription of a rifamycin (rifampin, rifabutin, or rifapentine) and a medication known to interact with rifamycins occurred during 270 (72.6%) episodes. The most commonly prescribed combinations were a rifamycin with zidovudine (208 episodes [55.9%]), itraconazole or fluconazole (121 episodes [32.5%]), clarithromycin (28 episodes [7.5%]), a protease inhibitor (31 episodes [8.3%]), corticosteroids (23 episodes [6.2%]), methadone (16 episodes [4.3%]), and anticoagulants (7 episodes [1.9%]). Among 63 episodes of TB diagnosed during 1997 to 2000 (63 patients), a rifamycin was prescribed with a protease inhibitor in 28 episodes (44.4%).

Reasons for discontinuing anti-TB therapy included completing the course of therapy (229 episodes [61.6%]), moving away from the health care site (12 episodes [3.2%]), lost to follow-up (13 episodes [3.5%]), death (67 episodes [18.1%]), medication adverse effects (2 episodes [0.5%]), lack of cooperation or refusal to continue medications (10 episodes [2.7%]), and other and unknown reasons (30 episodes [8.0%]). Among those who died during anti-TB therapy, death occurred at a median of 7 months (range: 0.1-37 months). Poor adherence to anti-TB therapy was mentioned in the medical records of 142 (38.2%) of the episodes of treatment. Among 277

patients with information on whether any DOT was given and with at least 12 months of follow-up after the diagnosis of TB, 26 (18%) of 148 patients who received DOT died within 12 months versus 7 (24%) of 29 patients who did not receive DOT died within 12 months (P = 0.41).

Hepatic disease was present at the time of TB diagnosis or during anti-TB therapy for 91 episodes (24.5%; Table 2). For those patients who had AST (67 patients) or ALT (50 patients) measured at the time of TB diagnosis (within 1 month before onset of anti-TB therapy), the median AST level was 45 U/L (range: 15-574 U/L) and the median ALT level was 31 U/L (range: 4-589 U/L). A 2-fold, 5-fold, and 10-fold elevation greater than the upper limits of normal aminotransaminases was observed during the first month of anti-TB therapy in 116 (31.2%), 30 (8.1%), and 13 (3.5%) of the 372 episodes, respectively, and at least once during the entire course of anti-TB therapy in 173 (46.5%), 49 (13.2%), and 18 (4.8%) of the 372 episodes. Among all episodes, the median serum alkaline phosphatase and total bilirubin levels 4 to 8 weeks after diagnosis of TB were 113 U/L and 0.5 mg/L, respectively (210 serum alkaline phosphatase values and 215 total bilirubin values were available). The median first white blood cell count, hemoglobin, and platelet count at or after diagnosis of TB was 4950 cells/mm^3 (range: 1000-16,000 cells/mm^3), 11.0 g/dL (range: 4.2-18.1 g/dL), and 240,000 cells/mm^3 (range: 9000-713,000 cells/mm^3), respectively (301 white blood cell counts, 279 hemoglobin counts, and 286 platelet counts were available). Sixty-one (16.6%) patients died within 12 months of TB diagnosis. The median CD4$^+$ cell count for these patients was 39 cells/µL. Twenty-five (41%) of these patients had some form of liver disease at or after their TB diagnosis.

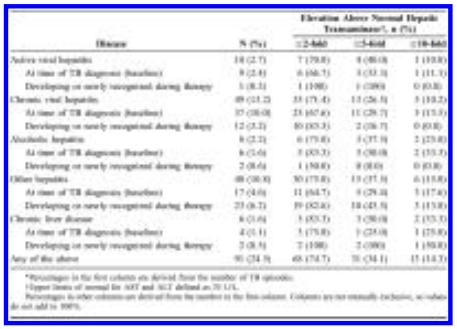

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TABLE 2. Hepatic Disease at the Time of TB Diagnosis or During Anti-TB Therapy Among 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients*

Among conditions reported to be adverse effects of anti-TB therapy,[12] the most commonly reported were rash, nausea, leukopenia or neutropenia, diarrhea, vomiting, and elevated temperature (>101.5°F [38.6°C]; Table 3). Medical record documentation indicating that these conditions were attributed to the anti-TB therapy was found for only a few cases, however. Among the few conditions attributed to anti-TB therapy by the health care provider, the most commonly reported were itching or flushing of skin (26.2%), nausea (24.0%), rash (other or unspecified, 29.4%), vomiting (22.1%), and peripheral neuropathy (14.3%). Medical record review discovered no persons with interstitial nephritis, retrobulbar neuritis, or other conditions associated with anti-TB medications [12] but not listed in Table 3.

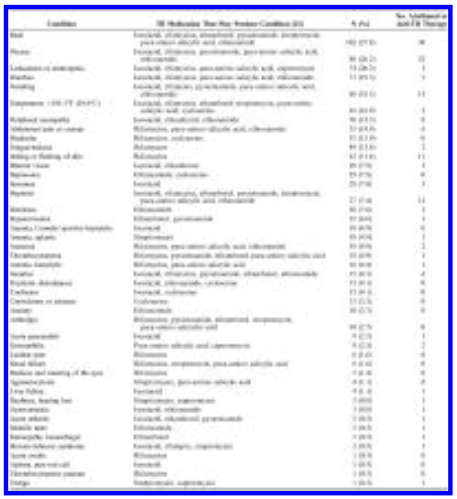

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TABLE 3. Selected Signs, Symptoms, and Conditions That May be Caused by Anti-TB Therapy, which were Diagnosed During Treatment of 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients

DISCUSSION

Among the many factors that may complicate the treatment of TB, HIV coinfection is one of the most important, because the many medications often prescribed put the patient at increased risk for drug-drug interactions, toxicity, and paradoxic reactions.[13] In addition, the presence of liver disease is relatively common among HIV-infected persons,[14] which may lead to an increased likelihood of

complications when prescribing potentially hepatotoxic medications, such as isoniazid, rifampin, and pyrazinamide. Our study quantifies how frequently these therapeutic issues arise among TB- and HIV-coinfected patients in the United States and, unlike most other studies, includes data from the era of highly active antiretroviral therapy (HAART) and detailed information on specific adverse effects encountered.

We found that prescription of medications known to interact with each other was relatively common; our study did not assess whether any complications resulted. Seventy-three percent of the anti-TB treatment episodes included a rifamycin and a medication known to interact with it. Forty-four percent of episodes during the era of HAART included such a combination of drugs. Drug interactions, such as rifampin with indinavir, ritonavir, or saquinavir, may cause decreased levels of these protease inhibitors.[6] Rifampin may cause indinavir and saquinavir levels to decline, thus compromising the potential efficacy of the prescribed antiretroviral regimen and increasing the likelihood of the emergence of antiretroviral resistance as a result of incomplete viral suppression.[13] For this reason, prescription of rifampin with indinavir or saquinavir (if the antiretroviral regimen does not also include ritonavir) is contraindicated.[6] Rifabutin prescribed with ritonavir can increase rifabutin levels 4-fold, thus increasing the likelihood of rifabutin dose-dependent side effects. Therefore, the dosage of rifabutin must be decreased when rifabutin is prescribed with ritonavir.[6] Also, although rifampin is known to decrease zidovudine levels,[15] this interaction is not considered clinically significant enough to warrant a change in therapy. Dosages of medications may have been adjusted in our study population; however, these were not measured in our study.

Our study demonstrates how commonly liver abnormalities may be present in these patients. Underlying liver disease is especially important, because commonly prescribed anti-TB medications like isoniazid, rifampin, and pyrazinamide are also potentially hepatotoxic, leading to the need for monitoring for liver disease during treatment. We found that nearly one fourth of all the episodes of anti-TB treatment occurred in patients with underlying liver disease or liver disease discovered during the treatment. Although a 2-fold elevation, which was documented in nearly half of all episodes, is usually not severe enough to warrant discontinuation of anti-TB hepatotoxic drugs,[16-18] it leads to concern regarding the use of these drugs during treatment, more frequent monitoring of serum aminotransaminases, and reconsideration of the anti-TB or other drug regimens the patient may need.

Our study demonstrates the frequency at which these conditions occur during treatment of TB and how often they are attributed to anti-TB medications. Adverse reactions may occur more frequently in HIV-infected patients compared with non-HIV-infected patients.[19,20] Ninety percent of these adverse reactions occur within the first 2 months of therapy, before successful eradication of TB is likely to have occurred.[20] Distinguishing which medication is the cause of the adverse effect leads to difficult decisions about treatment discontinuations. For example, peripheral neuropathy, which was observed in 15.3% of episodes of TB in our study, may be caused by isoniazid as well as by nucleoside reverse transcriptase inhibitors like didanosine, zalcitabine, and stavudine.[21] Our study shows that these complicating factors are relatively frequent regardless of whether or not it can be determined if the anti-TB therapy, other therapy, or the illness itself is the true cause.

Intolerance to anti-TB therapy accounted for a change in therapy in at least 15% of episodes of TB. Because the reasons for changes in therapy were not always well documented, we suspect the true number of changes for intolerance was higher. Change in therapy was required for 24% to 27% of patients in other studies.[22,23] In a study of multidrug-resistant TB in HIV-infected patients from Miami, 27% of patients required interruption, discontinuation, or change in medication because of serious treatment-related toxicities.[24] Patients with drug-resistant strains are more likely to be on second-line anti-TB drugs, which may be more likely to produce adverse effects.[25] It is possible that intolerance to therapy leading to a change in regimen occurs at least as frequently as reported in these older studies because of the increase in the number of antiretroviral drugs prescribed to HIV-infected patients since these studies were performed. A prospective study could clarify this issue.

We also demonstrated that problems with adherence to anti-TB medications in this population are common (nearly 40%). This was likely an underestimate, because we relied on medical record documentation of adherence problems without interviewing the patient or the patient's health care provider. The consequences of treatment complicated by incomplete adherence include increased risk for treatment failure and development of drug-resistant strains of *M. tuberculosis*, both of which are individual patient and public health concerns.[26] In addition, the difficulties of adherence to antiretroviral therapy underscore the recommendation by some experts to treat

In our study, the second most common reason for discontinuing anti-TB therapy was death (18.1%). We suspect that anti-TB therapy was infrequently the cause of death. Rather, it is more likely that these patients had other conditions, such as opportunistic infections or other noninfectious conditions, that led to their deaths, especially because death occurred at a median of 7 months into treatment. We did not collect information on specific causes of death. A careful examination of HIV-infected patients with TB who die during anti-TB therapy, although much less common in the era of HAART, would be useful as a future study because it could determine how often therapy is implicated.[13]

One limitation of our study was its observational methodology. Retrospective medical record abstraction may underestimate the prevalence of the conditions studied, because the patients may not have been screened for them in a uniform manner during routine care and because these conditions may have been present but not documented in the available records. Also, our study examined whether medications that can interact were prescribed together, but it neither evaluated whether such interactions actually occurred nor whether such prescriptions were inappropriate. We did not examine other factors that may also complicate anti-TB therapy, such as pill burden, mental health problems, active injection drug or alcohol use, diagnosis and treatment of other opportunistic infections and illnesses, and homelessness or unstable housing.[27] Because the ASD does not collect drug dosages, we did not ascertain if dosage adjustments were made when medications with the potential for interactions were prescribed. Also, because cause of death was not collected as part of this study, we cannot determine if deaths occurring within 12 months after diagnosis of TB were caused by TB. Finally, HIV RNA levels were available for a relatively small number of cases and thus were not included in the analysis.

Ideally, patients should be managed by physicians who are expert in the treatment of TB-HIV coinfection. If the HIV care provider is not the same person, communication between the TB and HIV care providers is essential and should occur frequently throughout the course of treatment.[6,25,28-32]

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Constance Gordon, William McCarthy, Julia Gable, Nicole Miller, Lexa Moongrace, John Frank, Peggy Messadi, Lourdes Yun, Maureen Gargan, Sharon Ritter, Dalia Kamarauskiene, and Vicki Peters for assistance with project abstractions and management. They also thank Kevin DeCock, Renee Ridzon, David Swerdlow, and Michael Iademarco for review of the manuscript.

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Key Words: tuberculosis; adverse events; hepatotoxicity

Accession Number: 00126334-200508010-00016

TABLE 3

Condition	TB Medication That May Produce Condition [12]	N (%)	No. Attributed to Anti-TB Therapy
Rash	Isoniazid, rifamycins, ethambutol, pyrazinamide, streptomycin, para-amino salicylic acid, ethionamide	102 (27.8)	30
Nausea	Isoniazid, rifamycins, pyrazinamide, para-amino salicylic acid, ethionamide	96 (26.2)	23
Leukopenia or neutropenia	Isoniazid, rifamycins, para-amino salicylic acid, capreomycin	74 (20.2)	3
Diarrhea	Isoniazid, rifamycins, para-amino salicylic acid, ethionamide	71 (19.3)	3
Vomiting	Isoniazid, rifamcins, pyrazinamide, para-amino salicylic acid, ethionamide	68 (18.5)	15
Temperature >101.5°F (38.6°C)	Isoniazid, rifamycins, ethambutol streptomycin, para-amino salicylic acid, cycloserine	62 (16.9)	3
Peripheral neuropathy	Isoniazid, ethambutol, ethionamide	56 (15.3)	8
Abdominal pain or cramps	Rifamycins, para-amino salicylic acid, ethionamide	53 (14.4)	6
Headache	Rifamycins, cycloserine	51 (13.9)	0
Fatigue/malaise	Rifamycins	49 (13.4)	2
Itching or flushing of skin	Rifamycins	42 (11.4)	11
Blurred vision	Isoniazid, ethambutol	29 (7.9)	3
Depression	Ethionamide, cycloserine	29 (7.9)	0
Insomnia	Isoniazid	28 (7.6)	3
Hepatitis	Isoniazid, rifamycins, ethambutol, pyrazinamide, streptomycin, para-amino salicylic acid, ethionamide	27 (7.4)	12
Dizziness	Ethionamide	28 (7.6)	1
Hyperuricemia	Ethambutol, pyrazinamide	25 (6.8)	1
Anemia, Coombs'-positive hemolytic	Isoniazid	18 (4.9)	0
Anemia, aplastic	Streptomycin	18 (4.9)	1
Anorexia	Rifamycins, para-amino salicylic acid, ethionamide	18 (4.9)	2
Thrombocytopenia	Rifamycins, pyrazinamide, ethambutol para-amino salicylic acid	18 (4.9)	1

Anemia, hemolytic	Rifamycins, para-amino salicylic acid	16 (4.4)	1
Jaundice	Isoniazid, rifamycins, pyrazinamide, ethambutol, ethionamide	15 (4.1)	6
Psychotic disturbances	Isoniazid, ethionamide, cycloserine	15 (4.1)	0
Confusion	Isoniazid, cycloserine	15 (4.1)	0
Convulsions or seizures	Cycloserine	13 (3.5)	0
Anxiety	Ethionamide	10 (2.7)	0
Arthralgia	Rifamycins, pyrazinamide, ethambutol, streptomycin, para-amino salicyclic acid	10 (2.7)	0
Acute pancreatitis	Isoniazid	9 (2.5)	1
Eosinophilia	Para-amino salicylic acid, capreomycin	9 (2.5)	2
Lumbar pain	Rifamycins	6 (1.6)	0
Renal failure	Rifamycins, streptomycin, para-amino salicylic acid	6 (1.6)	0
Redness and watering of the eyes	Rifamycins	5 (1.4)	0
Agranulocytosis	Streptomycin, para-amino salicylic acid	4 (1.1)	0
Liver failure	Isomiazid	4 (1.1)	1
Deafness, hearing loss	Streptomycin, capreomycin	3 (0.8)	1
Gynecomastia	Isoniazid, ethionamide	3 (0.8)	1
Acute arthritis	Isoniazid, ethambutol, pyrazinamide	2 (0.5)	1
Metallic taste	Ethionamide	2 (0.5)	1
Retinopathy, hemorrhagic	Ethambutol	2 (0.5)	1
Stevens-Johnson syndrome	Isoniazid, rifampin, streptomycin	2 (0.5)	1
Acute uveitis	Rifamycins	1 (0.3)	0
Aplasia, pure red cell	Isoniazid	1 (0.3)	0
Thrombocytopenic purpura	Rifamycins	1 (0.3)	0
Vertigo	Streptomycin, capreomycin	1 (0.3)	1

TABLE 3. Selected Signs, Symptoms, and Conditions That May be Caused by Anti-TB Therapy, which were Diagnosed During Treatment of 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients
From: Dworkin: J Acquir Immune Defic Syndr, Volume 39(4).August 1, 2005.464-470

TABLE 1

Characteristic	N (%)
Sex	
Male	298 (81.2)
Female	69 (18.8)
Race/ethnicity	
White	85 (23.2)
African-American	238 (64.8)
Hispanic	36 (9.8)
Asian/Pacific Islander	3 (0.8)
Native American	5 (1.4)
Mode of HIV exposure	
Male-male sex (MSM)	129 (35.1)
IDU (includes IDU-MSM)	162 (123 IDU, 39 MSM-IDU) (44.1)
Heterosexual	23 (6.3)
Hemophilia or blood transfusion	6 (1.6)
Other/unknown	47 (12.8)
City	
Atlanta	101 (27.5)
Denver	43 (11.7)

Denver	45 (11.7)
Detroit	63 (17.2)
New Orleans	82 (22.3)
New York City	31 (8.4)
Seattle	47 (12.8)
Year of TB diagnosis	
1986–1988	5 (1.3)
1989–1991	81 (21.8)
1992–1994	133 (35.7)
1995–1997	117 (31.4)
1998–2000	36 (9.7)
Administration of anti-TB therapy	
DOT only	171 (46.0)
DOT and self-administered therapy	121 (32.5)
Self-administered therapy only	40 (10.7)
Unknown	40 (10.7)

*Year of TB diagnosis and administration of therapy data are derived from number of episodes; all other data are derived from number of cases.

IDU indicates injection drug user; MSM, men who have sex with men.

TABLE 1. Characteristics of 367 HIV-Infected Patients With 372 Episodes of Culture-Confirmed (1986-2000)

From: Dworkin: J Acquir Immune Defic Syndr, Volume 39(4).August 1, 2005.464-470

TABLE 2

Disease	N (%)	Elevation Above Normal Hepatic Transaminase†, n (%)		
		≥2-fold	≥5-fold	≥10-fold
Active viral hepatitis	10 (2.7)	7 (70.0)	4 (40.0)	1 (10.0)
At time of TB diagnosis (baseline)	9 (2.4)	6 (66.7)	3 (33.3)	1 (11.1)
Developing or newly recognized during therapy	1 (0.3)	1 (100)	1 (100)	0 (0.0)
Chronic viral hepatitis	49 (13.2)	35 (71.4)	13 (26.5)	5 (10.2)
At time of TB diagnosis (baseline)	37 (10.0)	25 (67.6)	11 (29.7)	5 (13.5)
Developing or newly recognized during therapy	12 (3.2)	10 (83.3)	2 (16.7)	0 (0.0)
Alcoholic hepatitis	8 (2.2)	6 (75.0)	3 (37.5)	2 (25.0)
At time of TB diagnosis (baseline)	6 (1.6)	5 (83.3)	3 (50.0)	2 (33.3)
Developing or newly recognized during therapy	2 (0.6)	1 (50.0)	0 (0.0)	0 (0.0)
Other hepatitis	40 (10.8)	30 (75.0)	15 (37.5)	6 (15.0)
At time of TB diagnosis (baseline)	17 (4.6)	11 (64.7)	5 (29.4)	3 (17.6)
Developing or newly recognized during therapy	23 (6.2)	19 (82.6)	10 (43.5)	3 (13.0)
Chronic liver disease	6 (1.6)	5 (83.3)	3 (50.0)	2 (33.3)
At time of TB diagnosis (baseline)	4 (1.1)	3 (75.0)	1 (25.0)	1 (25.0)
Developing or newly recognized during therapy	2 (0.5)	2 (100)	2 (100)	1 (50.0)

Developing or newly recognized during therapy	2 (0.5)	2 (100)	2 (100)	1 (50.0)
Any of the above	91 (24.5)	68 (74.7)	31 (34.1)	13 (14.3)

*Percentages in the first column are derived from the number of TB episodes.

†Upper limits of normal for AST and ALT defined as 35 U/L.

Percentages in other columns are derived from the number in the first column. Columns are not mutually exclusive, so values do not add to 100%.

TABLE 2. Hepatic Disease at the Time of TB Diagnosis or During Anti-TB Therapy Among 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients

From: Dworkin: J Acquir Immune Defic Syndr, Volume 39(4).August 1, 2005.464-470

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Factors That Complicate the Treatment of Tuberculosis in HIV-Infected Patients

Mark S. Dworkin, MD, MPH&TM, FACP, Michael R. Adams,* David L. Cohn, MD,† Arthur J. Davidson, MD,† Susan Buskin, PhD, MPH,‡ Carrie Horwitch, MD, MPH,‡ Anne Morse, BS,§ Judy Sackoff, PhD,‖ Melanie Thompson, MD,¶ Linda Wotring, PhD,# Scott B. McCombs, MPH,* and Jeffrey L. Jones, MD, MPH***

Summary: Treatment of tuberculosis (TB) in persons coinfected with HIV has become increasingly complex during the past decade. We describe the factors that complicate anti-TB therapy in a large observational cohort of HIV-infected persons in the United States. Among 367 HIV-infected patients with 372 episodes of culture-confirmed TB, 44.1% had injection drug use as a mode of HIV transmission. Hepatic disease was present at the time of TB diagnosis or during anti-TB therapy for 91 episodes (24.5%). Elevation at least twice the upper limits of normal of aminotransaminases was observed during the first month of anti-TB therapy in 116 (31.2%) of the episodes. The most commonly reported adverse effects occurring during therapy were rash (27.8%), nausea (26.2%), leukopenia or neutropenia (20.2%), diarrhea (19.3%), vomiting (18.5%), and elevated temperature (>101.5°F [38.6°C], 16.9%). Prescription of a rifamycin and a medication known to interact with rifamycins occurred during 270 (72.6%) episodes. Because HIV-infected patients with TB often have underlying complicating conditions, such as hepatic disease, and are treated with medications that may have toxicities and cause drug-drug interactions, we recommend that clinicians pay careful attention to these factors when treating coinfected patients.

Key Words: tuberculosis, adverse events, hepatotoxicity

(*J Acquir Immune Defic Syndr* 2005;39:464–470)

Greater than one third of the estimated 36 million persons infected with HIV globally are coinfected with *Mycobacterium tuberculosis*.[1,2] In North America, 8% of HIV-infected persons are estimated to be coinfected with *M. tuberculosis*, and in the United States, approximately 9% to 15% of tuberculosis (TB) cases are reported in HIV-infected persons.[3–5] In the past decade, treatment of HIV and AIDS has become increasingly complex with the introduction of many new medications prescribed as long-term combination therapy. Several of these medications have the potential to interact with and complicate anti-TB therapy, especially by causing liver disease and cutaneous reactions.[6] Also, HIV-infected persons may have significant liver dysfunction associated with alcohol abuse, injection drug use,[7] and coinfection with hepatitis viruses.[8]

The complexity of the treatment of HIV-infected persons coinfected with *M. tuberculosis* is a significant public health issue, because interference with optimal treatment of TB may lead to failure or interruption of therapy and further transmission of disease, promote the emergence of drug-resistant strains, and lead to additional morbidity and mortality. Underlying and newly recognized acute and chronic hepatitis, adverse drug reactions and side effects, drug interactions, and inability to adhere to long-term multiple-drug therapy are all complicating factors. Given these potential issues, quantitating the frequency of these factors provides important information to health care providers who treat patients with TB. Such information would be especially helpful when evaluating which of several medications may need to be discontinued when prescribed medications have overlapping adverse effects. We describe the prevalence of many of the factors that complicate anti-TB therapy in a large observational cohort of HIV-infected persons.

METHODS

The Adult and Adolescent Spectrum of HIV Disease project (ASD) is a national surveillance project of the Centers for Disease Control and Prevention (CDC), in collaboration with 11 state and local health departments, in which information is abstracted from the medical records of HIV-infected patients at selected public and private health care facilities.[9,10] All available medical records (inpatient, outpatient, and local health department) of HIV-infected patients with a confirmed diagnosis of TB who had been enrolled in the ASD were reviewed using a standardized supplemental abstraction form. Six of the 11 ASD sites elected to participate in this study. These sites were located in Atlanta (1989–1998), Denver (1989–2000), Detroit (1986–1999), New Orleans (1991–2000), New York

Received for publication June 7, 2004; accepted November 22, 2004.
From the *National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA; †Denver Public Health, Denver, CO; ‡Public Health–Seattle and King County, Seattle, WA; §Louisiana Office of Public Health, New Orleans, LA; ‖The City of New York Department of Health, New York City, NY; ¶AIDS Research Consortium of Atlanta, Atlanta, GA; #Michigan Department of Community Health, Detroit, MA; and **National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.
Presented in part at the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January–February, 2000 [abstract 259].
Reprints: Mark S. Dworkin, Illinois Department of Public Health, Division of Infectious Diseases, 160 North LaSalle, #7 South, Chicago, IL 60601 (e-mail: mdworkin@idph.state.il.us).

City (1995–1998), and Seattle (1988–1999). Information collected included demographics and $CD4^+$ cell counts (from the ASD database), anatomic site of TB, information about treatment, adherence problems, conditions or illnesses present at the time of initial diagnosis or recognized after anti-TB therapy had begun, prescription of medications known to be contraindicated or reported to cause drug interactions with anti-TB medications, signs and symptoms of anti-TB medication adverse effects, and laboratory abnormalities that may be attributed to anti-TB medications.

All cases of TB were laboratory confirmed by isolation of *M. tuberculosis* from a clinical specimen.[11] For $CD4^+$ cell count calculations, we examined the time within 6 months before and after the diagnosis of TB (excluding the month of diagnosis). When a value was available before and after TB diagnosis, the earlier value was selected. If multiple earlier values were available, the most recent was used. When 2 values were available from the same month, the values were averaged. Hepatic disease was defined as a diagnosis of any active or chronic viral hepatitis, other (nonviral) hepatitis, alcoholic hepatitis, or any other form of chronic liver disease recorded in the medical record. For aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measurements, when a patient had more than 1 measurement during the period under review (eg, during the month before beginning therapy), the average of the measurements was included. The protocol for this study was approved by institutional review boards at the CDC and each of the participating ASD sites.

RESULTS

The study identified 367 HIV-infected patients with 372 episodes of culture-confirmed TB. Among the 5 patients with 2 episodes, the initial episode of treatment ranged from 8 months to 17 months and all these episodes were described as relapse or recurrence. The largest group by race/ethnicity was African Americans (238 patients [64.8%], 77.3% of these patients were male); male-male sex and injection drug use were the predominant modes of HIV exposure (Table 1). Among the 69 HIV-infected female patients, only 1 was pregnant at the time of TB diagnosis and none became pregnant during therapy. Among all episodes of TB, directly observed therapy (DOT) was commonly used for part or all of the anti-TB therapy (292 of 372 episodes [78.5%]); 171 (46.0%) episodes were treated with only DOT. The median $CD4^+$ cell count within 6 months of TB diagnosis was 120 cells/μL among the 239 patients (242 episodes) for whom this information was available (25th percentile: 30 cells/μL, 75th percentile: 234 cells/μL). The median $CD4^+$ cell count was 118 cells/μL for episodes with only pulmonary involvement and 126 cells/μL for extrapulmonary episodes. The anatomic sites of TB among all episodes (some patients may have had multiple sites involved) were pulmonary (293 [78.8%]); pleural (24 [6.5%]); lymphatic (84 [22.6%]); blood (23 [6.2%]); genitourinary (13 [3.5%]); bone and/or joint (10 [2.7%]); liver (7 [1.9%]); meningeal (6 [1.6%]); brain (5 [1.3%]); peritoneal (1 [0.3%]); and other disseminated, including miliary (57 [15.3%]). There were no cutaneous cases. Drug resistance was not common. Resistance to isoniazid (with or without resistance to other anti-TB medications) was reported in 13 episodes (3.5%), rifampin monoresistance was reported in 3 episodes (0.8%), and multidrug-resistant TB (resistance to at least isoniazid and rifampin) was reported in 5 episodes (1.3%).

TABLE 1. Characteristics of 367 HIV-Infected Patients With 372 Episodes of Culture-Confirmed TB (1986–2000)*

Characteristic	N (%)
Sex	
Male	298 (81.2)
Female	69 (18.8)
Race/ethnicity	
White	85 (23.2)
African-American	238 (64.8)
Hispanic	36 (9.8)
Asian/Pacific Islander	3 (0.8)
Native American	5 (1.4)
Mode of HIV exposure	
Male-male sex (MSM)	129 (35.1)
IDU (includes IDU-MSM)	162 (123 IDU, 39 MSM-IDU) (44.1)
Heterosexual	23 (6.3)
Hemophilia or blood transfusion	6 (1.6)
Other/unknown	47 (12.8)
City	
Atlanta	101 (27.5)
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New York City	31 (8.4)
Seattle	47 (12.8)
Year of TB diagnosis	
1986–1988	5 (1.3)
1989–1991	81 (21.8)
1992–1994	133 (35.7)
1995–1997	117 (31.4)
1998–2000	36 (9.7)
Administration of anti-TB therapy	
DOT only	171 (46.0)
DOT and self-administered therapy	121 (32.5)
Self-administered therapy only	40 (10.7)
Unknown	40 (10.7)

*Year of TB diagnosis and administration of therapy data are derived from number of episodes; all other data are derived from number of cases.

IDU indicates injection drug user; MSM, men who have sex with men.

The most commonly used initial drug regimen was isoniazid, rifampin, pyrazinamide, and ethambutol, which was used for 223 episodes (59.9%). Sixty (16.1%) episodes were initially treated with isoniazid, rifampin, and pyrazinamide. Thirteen (3.5%) episodes were treated with isoniazid, rifampin, pyrazinamide, and streptomycin; another 12 (3.2%) episodes were treated with isoniazid, rifampin, pyrazinamide, and at least 1 other drug; 9 (2.4%) episodes were initially treated with isoniazid and rifampin only; and 47 (12.6%) episodes were treated with 1 of several other combinations. Eight (2.2%) did not have initial drug regimen data available. The median number of regimens prescribed per patient during anti-TB

therapy was 2 (range: 1–10 regimens). Among 332 episodes with information, the median number of months observed on treatment was 10.5 months (range: 1–51 months).

Among 505 changes in the anti-TB regimens, the reasons for changing were planned change in treatment (189 changes in 163 episodes [ie, from intensive to continuation phase]), unknown/missing (168 changes in 112 episodes), other (74 changes in 58 episodes), intolerance to anti-TB drugs (65 changes in 57 episodes), and *M. tuberculosis* isolate resistant to 1 or more drugs (27 changes in 22 episodes). Vitamin B_6 (pyridoxine) was prescribed for 327 (87.9%) episodes. Among first-line anti-TB drugs, intolerance led to regimen changes in 7.6% of regimens that included ethambutol (23 changes among 304 episodes), in 5.6% that included isoniazid (20 changes among 360 episodes), in 5.0% that included pyrazinamide (17 changes among 342 episodes), and in 4.8% that included rifampin (17 changes among 354 episodes). Streptomycin (3 changes among 44 episodes [6.8%]) and ethionamide (1 change among 11 episodes [9.1%]) were prescribed less often but caused changes more frequently. Twelve drug changes were attributed to intolerance to more than 1 drug.

Prescription of a rifamycin (rifampin, rifabutin, or rifapentine) and a medication known to interact with rifamycins occurred during 270 (72.6%) episodes. The most commonly prescribed combinations were a rifamycin with zidovudine (208 episodes [55.9%]), itraconazole or fluconazole (121 episodes [32.5%]), clarithromycin (28 episodes [7.5%]), a protease inhibitor (31 episodes [8.3%]), corticosteroids (23 episodes [6.2%]), methadone (16 episodes [4.3%]), and anticoagulants (7 episodes [1.9%]). Among 63 episodes of TB diagnosed during 1997 to 2000 (63 patients), a rifamycin was prescribed with a protease inhibitor in 28 episodes (44.4%).

Reasons for discontinuing anti-TB therapy included completing the course of therapy (229 episodes [61.6%]), moving away from the health care site (12 episodes [3.2%]), lost to follow-up (13 episodes [3.5%]), death (67 episodes [18.1%]), medication adverse effects (2 episodes [0.5%]), lack of cooperation or refusal to continue medications (10 episodes [2.7%]), and other and unknown reasons (30 episodes [8.0%]). Among those who died during anti-TB therapy, death occurred at a median of 7 months (range: 0.1–37 months). Poor adherence to anti-TB therapy was mentioned in the medical records of 142 (38.2%) of the episodes of treatment. Among 277 patients with information on whether any DOT was given and with at least 12 months of follow-up after the diagnosis of TB, 26 (18%) of 148 patients who received DOT died within 12 months versus 7 (24%) of 29 patients who did not receive DOT died within 12 months ($P = 0.41$).

Hepatic disease was present at the time of TB diagnosis or during anti-TB therapy for 91 episodes (24.5%; Table 2). For those patients who had AST (67 patients) or ALT (50 patients) measured at the time of TB diagnosis (within 1 month before onset of anti-TB therapy), the median AST level was 45 U/L (range: 15–574 U/L) and the median ALT level was 31 U/L (range: 4–589 U/L). A 2-fold, 5-fold, and 10-fold elevation greater than the upper limits of normal aminotransaminases was observed during the first month of anti-TB therapy in 116 (31.2%), 30 (8.1%), and 13 (3.5%) of the 372 episodes, respectively, and at least once during the entire course of anti-TB therapy in 173 (46.5%), 49 (13.2%), and 18 (4.8%) of the 372 episodes. Among all episodes, the median serum alkaline phosphatase and total bilirubin levels 4 to 8 weeks after diagnosis of TB were 113 U/L and 0.5 mg/L, respectively (210 serum alkaline phosphatase values and 215 total bilirubin

TABLE 2. Hepatic Disease at the Time of TB Diagnosis or During Anti-TB Therapy Among 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients*

Disease	N (%)	Elevation Above Normal Hepatic Transaminase†, n (%)		
		≥2-fold	≥5-fold	≥10-fold
Active viral hepatitis	10 (2.7)	7 (70.0)	4 (40.0)	1 (10.0)
At time of TB diagnosis (baseline)	9 (2.4)	6 (66.7)	3 (33.3)	1 (11.1)
Developing or newly recognized during therapy	1 (0.3)	1 (100)	1 (100)	0 (0.0)
Chronic viral hepatitis	49 (13.2)	35 (71.4)	13 (26.5)	5 (10.2)
At time of TB diagnosis (baseline)	37 (10.0)	25 (67.6)	11 (29.7)	5 (13.5)
Developing or newly recognized during therapy	12 (3.2)	10 (83.3)	2 (16.7)	0 (0.0)
Alcoholic hepatitis	8 (2.2)	6 (75.0)	3 (37.5)	2 (25.0)
At time of TB diagnosis (baseline)	6 (1.6)	5 (83.3)	3 (50.0)	2 (33.3)
Developing or newly recognized during therapy	2 (0.6)	1 (50.0)	0 (0.0)	0 (0.0)
Other hepatitis	40 (10.8)	30 (75.0)	15 (37.5)	6 (15.0)
At time of TB diagnosis (baseline)	17 (4.6)	11 (64.7)	5 (29.4)	3 (17.6)
Developing or newly recognized during therapy	23 (6.2)	19 (82.6)	10 (43.5)	3 (13.0)
Chronic liver disease	6 (1.6)	5 (83.3)	3 (50.0)	2 (33.3)
At time of TB diagnosis (baseline)	4 (1.1)	3 (75.0)	1 (25.0)	1 (25.0)
Developing or newly recognized during therapy	2 (0.5)	2 (100)	2 (100)	1 (50.0)
Any of the above	91 (24.5)	68 (74.7)	31 (34.1)	13 (14.3)

*Percentages in the first column are derived from the number of TB episodes.
†Upper limits of normal for AST and ALT defined as 35 U/L.
Percentages in other columns are derived from the number in the first column. Columns are not mutually exclusive, so values do not add to 100%.

values were available). The median first white blood cell count, hemoglobin, and platelet count at or after diagnosis of TB was 4950 cells/mm^3 (range: 1000–16,000 cells/mm^3), 11.0 g/dL (range: 4.2–18.1 g/dL), and 240,000 cells/mm^3 (range: 9000–713,000 cells/mm^3), respectively (301 white blood cell counts, 279 hemoglobin counts, and 286 platelet counts were available). Sixty-one (16.6%) patients died within 12 months of TB diagnosis. The median CD4$^+$ cell count for these patients was 39 cells/μL. Twenty-five (41%) of these patients had some form of liver disease at or after their TB diagnosis.

Among conditions reported to be adverse effects of anti-TB therapy,[12] the most commonly reported were rash, nausea, leukopenia or neutropenia, diarrhea, vomiting, and elevated temperature (>101.5°F [38.6°C]; Table 3). Medical record documentation indicating that these conditions were attributed to the anti-TB therapy was found for only a few cases, however. Among the few conditions attributed to anti-TB therapy by the health care provider, the most commonly reported were itching or flushing of skin (26.2%), nausea (24.0%), rash (other or unspecified, 29.4%), vomiting (22.1%), and peripheral neuropathy (14.3%). Medical record review discovered no persons with interstitial nephritis, retrobulbar neuritis, or other conditions associated with anti-TB medications[12] but not listed in Table 3.

DISCUSSION

Among the many factors that may complicate the treatment of TB, HIV coinfection is one of the most important, because the many medications often prescribed put the patient at increased risk for drug-drug interactions, toxicity, and paradoxic reactions.[13] In addition, the presence of liver disease is relatively common among HIV-infected persons,[14] which may lead to an increased likelihood of complications when prescribing potentially hepatotoxic medications, such as isoniazid, rifampin, and pyrazinamide. Our study quantifies how frequently these therapeutic issues arise among TB- and HIV-coinfected patients in the United States and, unlike most other studies, includes data from the era of highly active antiretroviral therapy (HAART) and detailed information on specific adverse effects encountered.

We found that prescription of medications known to interact with each other was relatively common; our study did not assess whether any complications resulted. Seventy-three percent of the anti-TB treatment episodes included a rifamycin and a medication known to interact with it. Forty-four percent of episodes during the era of HAART included such a combination of drugs. Drug interactions, such as rifampin with indinavir, ritonavir, or saquinavir, may cause decreased levels of these protease inhibitors.[6] Rifampin may cause indinavir and saquinavir levels to decline, thus compromising the potential efficacy of the prescribed antiretroviral regimen and increasing the likelihood of the emergence of antiretroviral resistance as a result of incomplete viral suppression.[13] For this reason, prescription of rifampin with indinavir or saquinavir (if the antiretroviral regimen does not also include ritonavir) is contraindicated.[6] Rifabutin prescribed with ritonavir can increase rifabutin levels 4-fold, thus increasing the likelihood of rifabutin dose-dependent side effects. Therefore, the dosage of rifabutin must be decreased when rifabutin is prescribed with ritonavir.[6] Also, although rifampin is known to decrease zidovudine levels,[15] this interaction is not considered clinically significant enough to warrant a change in therapy. Dosages of medications may have been adjusted in our study population; however, these were not measured in our study.

Our study demonstrates how commonly liver abnormalities may be present in these patients. Underlying liver disease is especially important, because commonly prescribed anti-TB medications like isoniazid, rifampin, and pyrazinamide are also potentially hepatotoxic, leading to the need for monitoring for liver disease during treatment. We found that nearly one fourth of all the episodes of anti-TB treatment occurred in patients with underlying liver disease or liver disease discovered during the treatment. Although a 2-fold elevation, which was documented in nearly half of all episodes, is usually not severe enough to warrant discontinuation of anti-TB hepatotoxic drugs,[16–18] it leads to concern regarding the use of these drugs during treatment, more frequent monitoring of serum aminotransaminases, and reconsideration of the anti-TB or other drug regimens the patient may need.

Our study demonstrates the frequency at which these conditions occur during treatment of TB and how often they are attributed to anti-TB medications. Adverse reactions may occur more frequently in HIV-infected patients compared with non–HIV-infected patients.[19,20] Ninety percent of these adverse reactions occur within the first 2 months of therapy, before successful eradication of TB is likely to have occurred.[20] Distinguishing which medication is the cause of the adverse effect leads to difficult decisions about treatment discontinuations. For example, peripheral neuropathy, which was observed in 15.3% of episodes of TB in our study, may be caused by isoniazid as well as by nucleoside reverse transcriptase inhibitors like didanosine, zalcitabine, and stavudine.[21] Our study shows that these complicating factors are relatively frequent regardless of whether or not it can be determined if the anti-TB therapy, other therapy, or the illness itself is the true cause.

Intolerance to anti-TB therapy accounted for a change in therapy in at least 15% of episodes of TB. Because the reasons for changes in therapy were not always well documented, we suspect the true number of changes for intolerance was higher. Change in therapy was required for 24% to 27% of patients in other studies.[22,23] In a study of multidrug-resistant TB in HIV-infected patients from Miami, 27% of patients required interruption, discontinuation, or change in medication because of serious treatment-related toxicities.[24] Patients with drug-resistant strains are more likely to be on second-line anti-TB drugs, which may be more likely to produce adverse effects.[25] It is possible that intolerance to therapy leading to a change in regimen occurs at least as frequently as reported in these older studies because of the increase in the number of antiretroviral drugs prescribed to HIV-infected patients since these studies were performed. A prospective study could clarify this issue.

We also demonstrated that problems with adherence to anti-TB medications in this population are common (nearly 40%). This was likely an underestimate, because we relied on medical record documentation of adherence problems without interviewing the patient or the patient's health care provider.

TABLE 3. Selected Signs, Symptoms, and Conditions That May Be Caused by Anti-TB Therapy, Which Were Diagnosed During Treatment of 372 Episodes of Culture-Confirmed TB Among 367 HIV-Infected Patients

Condition	TB Medication That May Produce Condition [12]	N (%)	No. Attributed to Anti-TB Therapy
Rash	Isoniazid, rifamycins, ethambutol, pyrazinamide, streptomycin, para-amino salicylic acid, ethionamide	102 (27.8)	30
Nausea	Isoniazid, rifamycins, pyrazinamide, para-amino salicylic acid, ethionamide	96 (26.2)	23
Leukopenia or neutropenia	Isoniazid, rifamycins, para-amino salicylic acid, capreomycin	74 (20.2)	3
Diarrhea	Isoniazid, rifamycins, para-amino salicylic acid, ethionamide	71 (19.3)	3
Vomiting	Isoniazid, rifamcins, pyrazinamide, para-amino salicylic acid, ethionamide	68 (18.5)	15
Temperature >101.5°F (38.6°C)	Isoniazid, rifamycins, ethambutol streptomycin, para-amino salicylic acid, cycloserine	62 (16.9)	3
Peripheral neuropathy	Isoniazid, ethambutol, ethionamide	56 (15.3)	8
Abdominal pain or cramps	Rifamycins, para-amino salicylic acid, ethionamide	53 (14.4)	6
Headache	Rifamycins, cycloserine	51 (13.9)	0
Fatigue/malaise	Rifamycins	49 (13.4)	2
Itching or flushing of skin	Rifamycins	42 (11.4)	11
Blurred vision	Isoniazid, ethambutol	29 (7.9)	3
Depression	Ethionamide, cycloserine	29 (7.9)	0
Insomnia	Isoniazid	28 (7.6)	3
Hepatitis	Isoniazid, rifamycins, ethambutol, pyrazinamide, streptomycin, para-amino salicylic acid, ethionamide	27 (7.4)	12
Dizziness	Ethionamide	28 (7.6)	1
Hyperuricemia	Ethambutol, pyrazinamide	25 (6.8)	1
Anemia, Coombs'-positive hemolytic	Isoniazid	18 (4.9)	0
Anemia, aplastic	Streptomycin	18 (4.9)	1
Anorexia	Rifamycins, para-amino salicylic acid, ethionamide	18 (4.9)	2
Thrombocytopenia	Rifamycins, pyrazinamide, ethambutol para-amino salicylic acid	18 (4.9)	1
Anemia, hemolytic	Rifamycins, para-amino salicylic acid	16 (4.4)	1
Jaundice	Isoniazid, rifamycins, pyrazinamide, ethambutol, ethionamide	15 (4.1)	6
Psychotic disturbances	Isoniazid, ethionamide, cycloserine	15 (4.1)	0
Confusion	Isoniazid, cycloserine	15 (4.1)	0
Convulsions or seizures	Cycloserine	13 (3.5)	0
Anxiety	Ethionamide	10 (2.7)	0
Arthralgia	Rifamycins, pyrazinamide, ethambutol, streptomycin, para-amino salicyclic acid	10 (2.7)	0
Acute pancreatitis	Isoniazid	9 (2.5)	1
Eosinophilia	Para-amino salicylic acid, capreomycin	9 (2.5)	2
Lumbar pain	Rifamycins	6 (1.6)	0
Renal failure	Rifamycins, streptomycin, para-amino salicylic acid	6 (1.6)	0
Redness and watering of the eyes	Rifamycins	5 (1.4)	0
Agranulocytosis	Streptomycin, para-amino salicylic acid	4 (1.1)	0
Liver failure	Isomiazid	4 (1.1)	1
Deafness, hearing loss	Streptomycin, capreomycin	3 (0.8)	1
Gynecomastia	Isoniazid, ethionamide	3 (0.8)	1
Acute arthritis	Isoniazid, ethambutol, pyrazinamide	2 (0.5)	1
Metallic taste	Ethionamide	2 (0.5)	1
Retinopathy, hemorrhagic	Ethambutol	2 (0.5)	1
Stevens-Johnson syndrome	Isoniazid, rifampin, streptomycin	2 (0.5)	1
Acute uveitis	Rifamycins	1 (0.3)	0
Aplasia, pure red cell	Isoniazid	1 (0.3)	0
Thrombocytopenic purpura	Rifamycins	1 (0.3)	0
Vertigo	Streptomycin, capreomycin	1 (0.3)	1

The consequences of treatment complicated by incomplete adherence include increased risk for treatment failure and development of drug-resistant strains of *M. tuberculosis*, both of which are individual patient and public health concerns.[26] In addition, the difficulties of adherence to antiretroviral therapy underscore the recommendation by some experts to treat TB first when possible and to initiate antiretroviral therapy at least 4 to 8 weeks after anti-TB therapy.[13,25]

In our study, the second most common reason for discontinuing anti-TB therapy was death (18.1%). We suspect that anti-TB therapy was infrequently the cause of death. Rather, it is more likely that these patients had other conditions, such as opportunistic infections or other noninfectious conditions, that led to their deaths, especially because death occurred at a median of 7 months into treatment. We did not collect information on specific causes of death. A careful examination of HIV-infected patients with TB who die during anti-TB therapy, although much less common in the era of HAART, would be useful as a future study because it could determine how often therapy is implicated.[13]

One limitation of our study was its observational methodology. Retrospective medical record abstraction may underestimate the prevalence of the conditions studied, because the patients may not have been screened for them in a uniform manner during routine care and because these conditions may have been present but not documented in the available records. Also, our study examined whether medications that can interact were prescribed together, but it neither evaluated whether such interactions actually occurred nor whether such prescriptions were inappropriate. We did not examine other factors that may also complicate anti-TB therapy, such as pill burden, mental health problems, active injection drug or alcohol use, diagnosis and treatment of other opportunistic infections and illnesses, and homelessness or unstable housing.[27] Because the ASD does not collect drug dosages, we did not ascertain if dosage adjustments were made when medications with the potential for interactions were prescribed. Also, because cause of death was not collected as part of this study, we cannot determine if deaths occurring within 12 months after diagnosis of TB were caused by TB. Finally, HIV RNA levels were available for a relatively small number of cases and thus were not included in the analysis.

Ideally, patients should be managed by physicians who are expert in the treatment of TB-HIV coinfection. If the HIV care provider is not the same person, communication between the TB and HIV care providers is essential and should occur frequently throughout the course of treatment.[6,25,28–32]

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Constance Gordon, William McCarthy, Julia Gable, Nicole Miller, Lexa Moongrace, John Frank, Peggy Messadi, Lourdes Yun, Maureen Gargan, Sharon Ritter, Dalia Kamarauskiene, and Vicki Peters for assistance with project abstractions and management. They also thank Kevin DeCock, Renee Ridzon, David Swerdlow, and Michael Iademarco for review of the manuscript.

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