The Impact of Human Immunodeficiency Virus Infection on Drug-resistant Tuberculosis

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Infection with human immunodeficiency virus (HIV) has been associated with increased rates of single- and multidrug-resistant (MDR) tuberculosis in the New York City area. In order to examine the relationship of HIV infection to drug-resistant tuberculosis in other selected regions of the United States, we established a registry of cases of culture-proven tuberculosis. Data were collected from sites participating in an NIH-funded, community-based HIV clinical trials group. All cases of tuberculosis, regardless of HIV status, which occurred between January 1992 and June 1994 were recorded. Overall, 1,373 cases of tuberculosis were evaluated, including 425 from the New York City area, and 948 from seven other metropolitan areas. The overall prevalence of resistance to one or more drugs was 20.4%, and 5.6% of isolates were resistant to both isoniazid and rifampin (MDR). In the New York City area, HIV-infected patients were significantly more likely than persons not known to be HIV-infected, to have resistance to at least one drug (37% versus 19%) and MDR (19% versus 6%). In other geographic areas, overall drug resistance was 16%, and only 2.2% of isolates were MDR. In multiple logistic regression analyses, HIV infection was shown to be a risk factor for drug-resistant tuberculosis, independent of geographic location, history of prior therapy, age, and race. We concluded that HIV infection is associated with increased rates of resistance to antituberculosis drugs in both the New York City area and other geographic areas. MDR tuberculosis is occurring predominantly in the New York City area and is highly correlated with HIV infection. Gordin FM, Nelson ET, Matts JP, Cohn DL, Ernst J, Benator D, Besch CL, Crane LR, Sampson JH, Bragg PS, El-Sadr W, and the Terry Beirn Community Programs for Clinical Research on AIDS. The impact of human immunodeficiency virus infection on drug-resistant tuberculosis.

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The association of human immunodeficiency virus (HIV) infection with the resurgence of tuberculosis in the United States has been well documented (1–3). HIV-infected persons are much more likely to experience reactivation tuberculosis than immunocompetent hosts, with rates of active tuberculosis occurring in 7 to 10% per year of dually infected patients (4–6). In addition, primary progression from tuberculosis infection to disease occurs more frequently and more rapidly in HIV-infected persons (7–9). Recent studies have documented that up to 40% of tuberculosis in this population may be due to recent acquisition of the organism (10, 11).

The increase in numbers of patients with both HIV infection and tuberculosis has been accompanied by a concern about increasing rates of resistance to antituberculosis drugs in this population. Outbreaks of multidrug-resistant (MDR) tuberculosis in HIV-infected patients have been reported from several hospitals in the New York City area (7, 12, 13). A survey of all isolates of *Mycobacterium tuberculosis* obtained in New York City during a 1-mo period in 1991 demonstrated HIV-infected persons to be twice as likely to have drug-resistant isolates, and over six times more likely to have MDR tuberculosis than persons with no documented HIV infection (14). While there have been reports of MDR tuberculosis outbreaks in HIV-infected patients in other cities (9, 15), there has been no survey of the overall impact of HIV infection on tuberculosis drug resistance in the United States.

We established a tuberculosis registry to collect information on patients with culture-proven tuberculosis from selected geographic regions throughout the United States. These data were evaluated to assess the characteristics of these cases, define resistance patterns, and determine the impact of HIV infection and other sociodemographic factors on the prevalence of drug-resistant tuberculosis.

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METHODS

A tuberculosis registry was developed using participating sites of the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA is a network of primary care providers located in private practice, hospitals, and clinics providing HIV-infected persons access to clinical trials, with a special emphasis on the recruitment of women, injecting drug users, African-Americans, and Latinos. These providers also care for a large number of HIV-negative patients; and for the purpose of this registry, participating sites collected data on all available tuberculosis cases seen at their site, regardless of HIV status.

Data were obtained by chart abstraction from culture-confirmed tuberculosis cases whose final culture and drug susceptibility results became available between January 1, 1992 and June 30, 1994. Only those patients 13 yr of age or older with available antimicrobial susceptibility results are included in this report. Information collected included demographic data, tuberculosis risk factors, HIV risk behaviors, HIV serostatus, and history of prior tuberculosis treatment. As the information was obtained by chart abstraction, data are missing for some variables for some patients.

Only initial culture specimens collected before or at the initiation of antituberculous therapy were used to determine drug susceptibility patterns. Participating units used local laboratories for the isolation and identification of organisms, as well as for determination of *in vitro* drug resistance. The site from which the isolates were obtained and the results of antimicrobial susceptibility tests were recorded. Patients were counted as having tuberculosis resistant to a particular drug if any of their initial isolates were resistant to that drug. Patients were defined as having an organism susceptible to a drug if all of their initial isolates were susceptible to that drug.

Patients were assigned unique case numbers and all data were transmitted to the national registry with no linkage between the case number and the patient's name. As a result, there was anonymity of all study participants, thus, no informed consent was required. This study was approved by the institutional review boards of all participating sites.

Fisher's exact tests and chi-square tests were used to assess the statistical significance of differences between proportions. Stepwise logistic regression was used in an iterative manner to asses the independent factors, and the odds ratios (OR), related to drug resistance. A forward/backward selection process was used. Because there was casewise deletion of each patient with any missing variable, a forward selection process was run and the least significant variable was deleted (backward) from the list of variables. The process was then repeated on the usually increased number of cases. Iterations of this process stopped when no further variable could be retained with $p < 0.10$. The following variables were initially included in the logistic regression: gender, age, race, sexual orientation, place of birth, homelessness, unemployment, alcohol use, street drug use, prior therapy for tuberculosis, intravenous (IV) drug use, HIV status, and geographic area. For HIV status, an indicator variable for unknown HIV status relative to negative HIV status was included to avoid casewise deletion of those with unknown status. As long as the HIV-positive variable had a $p < 0.10$, this variable was also included. There were four race categories (African-American, Latino, Asian, and White/Other) and three age groups (13 to 35, 36 to 50, and > 50 yr). Additional analyses were done using classification and regression trees (16) to explore the data for additional relationships including interactions not identified by the logistic regression. No important additional relationships were found. For multivariate analysis, only the logistic regression results are reported. All p values are two-sided. A p value less than 0.05 was considered statistically significant. No adjustments for multiple comparisons were made.

RESULTS

Thirteen units from eight metropolitan areas contributed 1,465 tuberculosis cases for the registry, of whom 92 cases were excluded because susceptibility testing was either not done or was nonretrievable. Of the remaining 1,373 cases, five units from northern New Jersey, Manhattan, Brooklyn, and the Bronx accounted for 425 cases from the "New York City area." Two units from Detroit, MI, and one each from Washington, DC, Denver, CO, Chicago, IL, New Orleans, LA, Richmond, VA, and Portland, OR, contributed a total of 948 cases from the "outside New York City" area. Pulmonary tuberculosis alone was the site of infection in 1,058 patients, extrapulmonary disease alone was present in 192, and both pulmonary and extrapulmonary disease were present in 123 individuals.

Demographic data, tuberculosis and HIV risk factors, and HIV serostatus are shown for the New York City area and outside New York City area groups in Table 1. Individuals with tuber-

TABLE 1

DEMOGRAPHIC, BEHAVIORAL, AND SELECTED CLINICAL CHARACTERISTICS OF PATIENTS WITH TUBERCULOSIS

	New York City Area (*n* = 425)		Outside New York City Area (*n* = 948)		
	% with Characteristic	N*	% with Characteristic	N*	p Value†
Male	66.6	425	71.2	947	0.098
Race		423		938	< 0.001
Black	59.3		50.3		
Latino	32.2		8.2		
Asian	0.2		12.7		
Other	8.3		28.8		
Age, yr		425		948	< 0.001
13–35	31.8		29.3		
36–50	51.5		36.0		
51+	16.7		34.7		
Homosexual/Bisexual	12.7	354	27.1	295	< 0.001
Born in United States	79.0	305	69.1	764	< 0.001
Homeless‡	13.0	394	3.7	755	< 0.001
Unemployed‡	63.9	330	19.3	679	< 0.001
Excessive use of alcohol‡	35.1	379	17.7	690	< 0.001
Used street drugs‡	44.1	404	9.9	576	< 0.001
Prior TB therapy	18.8	404	14.7	770	0.079
Used IV drugs	47.0	396	19.8	643	< 0.001
HIV-positive	78.7	324	29.0	617	< 0.001

* Number of patients with known data for each characteristic.
† p Value for difference between New York City area and outside New York City.
‡ For more than 1 yr.

TABLE 2

RELATIONSHIP OF HIV STATUS TO ANTITUBERCULOSIS DRUG RESISTANCE

HIV Status	Pan Susceptible*	Mono Resistant†	Resistant to ≥ 2 Drugs
New York City area			
Positive	161 (63.1%)‡	32 (12.6%)	62 (24.3%)
Negative	56 (81.2%)	9 (13.0%)	4 (5.8%)
Unknown	83 (82.2%)	11 (10.9%)	7 (6.9%)
Outside New York City area			
Positive	153 (85.5%)	20 (11.2%)	6 (3.4%)
Negative	364 (83.1%)	53 (12.1%)	21 (4.8%)
Unknown	276 (83.4%)	34 (10.3%)	21 (6.3%)

* Susceptible to all drugs for which susceptibility testing was performed.
† Resistant to only one of the drugs for which susceptibility testing was performed.
‡ $p = 0.001$ for comparison of resistance between HIV-positive and HIV-negative persons.

culosis from the New York City area were more likely to be less than 51 yr old and have a history of being homeless, being unemployed, using alcohol to excess, and using IV or street drugs, than persons from the non-New York City area. A history of prior antituberculosis therapy was similar in both areas. Of 324 patients with known HIV serostatus in the New York City area, 255 (79%) were positive, significantly higher than the rate of HIV infection reported in tuberculosis patients from other areas (178 of 617 [29%]).

As shown in Table 2, patients from the New York City area were more likely to have drug-resistant isolates (29%) than patients from other areas (16%) ($p < 0.001$). In the New York City area, individuals with HIV infection were more likely to have drug-resistant isolates than HIV-negative persons, whereas outside of the New York City area, HIV infection appeared to have no impact on overall tuberculosis drug resistance. Of all patients with drug-resistant strains, a higher percentage were resistant to two or more drugs in the New York City area (73 of 125 [58%]) than in the non-New York City area (48 of 155 [31%]) ($p < 0.001$). Of patients with isolates resistant to two or more drugs, 58 of 73 (79%) in the New York City area were resistant to both isoniazid and rifampin (MDR). Outside of the New York City area, resistance to both isoniazid and rifampin occurred in only 21 of 48 (44%) patients with isolates resistant to two or more drugs. Patients with MDR tuberculosis in the New York City area were predominantly HIV-infected (49 of 58), whereas in other areas, MDR tuberculosis occurred primarily in Asians born outside of the United States, in African-Americans (17 of 21), and in individuals who had received prior tuberculosis therapy (14 of 21), and was not univariately associated with HIV infection.

The impact of HIV infection on resistance to individual antituberculosis drugs is shown in Table 3. In the New York City area, HIV-infected persons had higher rates of resistance to isoniazid, rifampin, ethambutol, and streptomycin and were more likely to have MDR tuberculosis. In addition, the rate of resistance to pyrazinamide was almost twice as high in HIV-infected persons, although this was not statistically significant. Outside of the New York City area, the rate of resistance to antituberculous drugs did not differ by HIV status.

The univariate relation of a specific demographic, tuberculosis, and HIV risk factors to antituberculosis drug resistance rates is shown in Table 4. In the New York City area, only HIV infection and a history of prior tuberculosis therapy were significantly associated with a higher rate of drug resistance. Outside of the New York City area, being foreign-born or Asian, having a history of prior treatment, and being of younger age were significantly associated with increased drug resistance. Other socioeconomic factors such as being homeless, being unemployed, and using alcohol to excess were not found to be associated with drug resistance.

In the New York City area, HIV-infected patients were more likely to have drug resistance regardless of their history of prior tuberculosis, although there was only power to demonstrate statistical significance in individuals who had not been treated before for tuberculosis (32.3% of HIV-infected versus 17.2% of HIV-negative patients without prior treatment had tuberculosis drug resistance, $p = 0.03$). Outside of the New York City area, HIV infection also appeared to be a risk factor for drug resistance among U.S.-born individuals. Of U.S.-born persons living in the non-New York City area, 18.8% of HIV-positive persons had resistant isolates compared with only 11.1% of HIV-negative persons ($p = 0.06$).

Variables found to be independently associated with antituberculosis drug resistance were prior history of tuberculosis therapy, Asian race, younger age, living in the New York City area, and known infection with HIV (Table 5). Race categories were similar and thus were combined as were the two lower age categories.

DISCUSSION

This study is the first to examine the impact of HIV infection on rates of tuberculosis drug resistance in selected geographic regions throughout the United States. Our patient population

TABLE 3

PROPORTION OF PATIENTS WITH ISOLATES RESISTANT TO INDIVIDUAL ANTITUBERCULOSIS DRUGS BY GEOGRAPHIC AREA AND HIV STATUS

	INH		RIF		EMB		PZA		STM		INH and RIF	
HIV Status	n*	%	n	%	n	%	n	%	n	%	n	%
New York City area												
Positive	254	29.9†	252	22.6*	253	10.2†	190	12.1	231	15.6†	252	19.4†
Negative	69	13.0	69	5.8	69	1.5	49	6.1	68	5.9	69	5.8
Unknown	101	14.9	101	5.9	100	5.0	75	5.3	101	5.9	101	5.0
Non-New York City area												
Positive	179	8.4	179	3.9	179	1.7	90	3.3	174	3.5	179	2.8
Negative	438	9.8	437	2.1	438	1.8	202	3.0	432	4.9	473	1.4
Unknown	330	10.6	330	3.9	330	1.5	145	0.7	322	8.1	330	3.0

Definition of abbreviations: INH = isoniazid; RIF = rifampin; EMB = ethambutol; PZA = pyrazinamide; STM = streptomycin.
* n = number of patients' isolates tested for resistance; % = percent of those tested which were resistant.
† $p < 0.05$ for comparison between HIV+ and HIV−.

TABLE 4

PROPORTION OF PATIENTS WITH ISOLATES WITH ANTITUBERCULOSIS DRUG RESISTANCE BY GEOGRAPHIC AREAS AND OTHER FACTORS

	New York City Area		Outside New York City Area	
	n	% with Resistance	n	% with Resistance
Gender				
Male	283	30.7	674	16.2
Female	142	26.8	273	16.5
Race				
Black	251	27.5	472	14.7
Latino	136	30.9	77	14.3
Asian	1	100.0	119	38.7*
Other	35	37.1	270	10.7
Age, yr				
13-35	135	24.4	278	23.0*
36-50	219	34.3	341	15.5
51 +	71	23.9	329	11.6
Homosexual/Bisexual				
Yes	45	33.3	80	15.0
No	309	25.9	215	13.0
Born in United States				
Yes	241	32.4	528	13.6*
No	64	23.4	236	26.7
Homeless†				
Yes	51	35.3	28	14.3
No	343	28.6	727	17.3
Unemployed†				
Yes	211	32.2	131	17.6
No	119	27.7	548	16.2
Excessive use of alcohol†				
Yes	133	29.3	122	15.6
No	246	28.9	568	15.7
Used street drugs				
Yes	178	33.1	57	22.8
No	226	27.0	519	13.7
Used IV drugs				
Yes	186	33.9	127	17.3
No	210	25.2	516	14.9
Prior TB therapy				
Yes	76	44.7*	113	36.3*
No	328	25.6	657	15.3
HIV-positive				
Yes	254	36.9*	179	14.5
No	67	18.8	438	16.9

* $p < 0.05$.
† For more than 1 yr.

was not selected to reflect a sampling of all tuberculosis cases in those regions, and may reflect unknown biases that have occurred owing to characteristics of patients who use the facilities participating in this study. These biases may have included an overreporting of HIV-positive patients, or possible distortions due to different approaches to case finding used in different locations, and the data should be interpreted in this light. The demographics of our population do, however, mirror the demographics of tuberculosis in the United States as a whole, which is occurring predominantly in large urban areas, with overrepresentation of racial minorities, socioeconomically disadvantaged persons, HIV-infected persons, and the foreign-born (3).

In the New York City area, resistance to at least one of the primary tuberculosis drugs occurred in 37% of HIV-positive patients and 18% of persons with unknown or negative HIV status. Even more disturbing was that resistance to the two most effective drugs, isoniazid and rifampin occurred in 30% and 23%, respectively, of HIV-infected persons, and was also substantial in HIV-negative individuals. When isolates from HIV-infected persons in the New York City area were resistant, they were more likely to be resistant to multiple drugs (62 of 94 patients) than those from non-HIV-infected patients, with 49 HIV-infected patients resistant to both isoniazid and rifampin.

Our study showed that outside of the New York City area, 16% of patients were resistant to at least one drug. While the prevalence of resistance to isoniazid was 10%, the prevalence of resistance to rifampin and pyrazinamide was only 3% for each

TABLE 5

CHARACTERISTICS ASSOCIATED WITH DRUG RESISTANCE BY LOGISTIC REGRESSION

Characteristics	Odds Ratio	95% CI	p Value
HIV-negative	1.00	–	–
HIV-positive	1.76	(1.81, 2.62)	0.005
HIV unknown	1.15	(0.77, 1.71)	0.495
History of prior TB treatment	2.88	(2.03, 4.09)	< 0.001
Age ≤ 50 yr	1.54	(1.05, 2.27)	0.026
Asian	4.58	(2.88, 7.29)	< 0.001
New York City area	1.85	(1.31, 2.61)	< 0.001

drug. Resistance to two or more drugs was low (5%), and combined resistance to isoniazid and rifampin (MDR) was unusual (2.2%). Most patients with MDR tuberculosis had received prior tuberculosis treatment, were born outside the U.S., and were not known to be HIV-infected.

While HIV infection was associated with an almost twofold increased risk of drug resistance in the New York City area, our ability to evaluate the impact of HIV infection on drug resistance in the non-New York City area was hindered by a high proportion of foreign-born persons with tuberculosis and a relatively low proportion of persons with HIV infection reported from those areas. The overall prevalence of drug resistance found in foreign-born individuals living outside the New York City area was 27%. Most of these individuals were Asian and were reported from the Portland, OR site. When only U.S.-born individuals were evaluated, it became evident that HIV infection was, in fact, a risk factor for drug resistance outside of the New York City area: 19% of U.S.-born HIV-infected patients were resistant to at least one antituberculosis drug, versus 11% of U.S.-born patients not known to be HIV-infected ($p = 0.055$). Additionally, HIV infection was shown in logistic regression to be independently associated with drug resistance even after taking into account geographic area, Asian race, and history of prior treatment, providing additional evidence that HIV is an important risk factor for drug resistance in all areas of the country.

Caution should be used in interpreting Asian race as being associated with increased drug resistance. This was highly related to being born outside of the United States and thus may represent being foreign-born rather than Asian race. Use of street drugs or injected drugs was not selected in the regression even though in univariate analyses these variables appeared to have a borderline relationship to resistance. It may be that these variables are related to drug resistance, but that in this data set other factors were found to be more important.

Prior therapy with antituberculosis drugs is a known predictor of acquired drug resistance (17–18). In both the New York City area and elsewhere, patients with a history of prior therapy were almost twice as likely to have resistant isolates as persons without prior therapy. For persons from areas other than New York City, we found being foreign-born to be an additional risk factor for drug resistance. Socioeconomic factors (including a history of unemployment, homelessness, and excessive use of alcohol) that have been associated with high rates of tuberculosis and noncompliance with treatment (3, 18, 19) were not associated with an increased risk of drug resistance in any region.

Of the national surveys of tuberculosis drug resistance in the last decade, none have focused on the impact of HIV infection (17, 18, 20). The most recent Centers for Disease Control and Prevention (CDC) survey of *M. tuberculosis* isolates from the first quarter of 1991 demonstrated the prevalence of resistance to at least one drug to be 14.2%, and that 3.5% of all isolates were resistant to both isoniazid and rifampin (MDR) (18). Drug resistance was approximately four times more frequent in isolates from New York State than for the other participating sites combined; HIV serostatus was not reported. In our data, which examined isolates obtained from 1992 to 1994, the overall prevalence of drug resistance was 20.4%, and MDR strains accounted for 5.6% of all isolates. A direct comparison of our results with those of the CDC surveys should be interpreted with caution, however, as regions studied and sampling techniques were not identical (for example, 21% of the isolates for the 1991 CDC survey were from New York and New Jersey, whereas for our study 31% were from this area).

The association of HIV infection with increased occurrence of resistance to antituberculosis medications is logical based on our understanding of the natural history of tuberculosis. In immunocompetent hosts, the interval from infection to disease is usually one of many decades (21). Therefore, most HIV-negative individuals who have developed active tuberculosis in the past few years were infected with organisms during an era of low rates of resistance. Progression from infection to disease occurs much more rapidly in HIV-infected persons, with the time course telescoped into months or a few years. Clinical and molecular epidemiologic techniques have been used to demonstrate outbreaks of primary tuberculosis within clusters of HIV-infected persons (8–12), and that reinfection can occur in highly immunocompromised patients (22). Therefore patterns of resistance to antituberculosis drugs in HIV-infected patients are likely to be more reflective of recent trends in the community.

Resistance to antituberculosis medications has occurred since their introduction, and is known to occur as a result of inappropriate use of these medications on the part of either the provider or the patient (23). Decreases in public health funding, poor training of medical personnel in the treatment of tuberculosis, lapses in infection control techniques, worsening socioeconomic conditions, and the ongoing HIV epidemic have all combined to increase the occurrence of tuberculosis and resistance to antituberculosis agents in the United States. While we have found drug resistance to be high in the New York City area and of concern in other regions of the country, we have also demonstrated that the "battle" against tuberculosis has not been lost. In most areas of the United States, over 95% of tuberculosis could be well treated using currently available medications. Even in the New York City area, the majority of tuberculosis isolates in both HIV-positive and HIV-negative persons are susceptible to two or more primary drugs. We must take advantage of this opportunity to prevent further development of drug resistance and the increased public health threat it poses by implementing aggressive individual and public health measures including the use of directly observed therapy (24), and the initiation of appropriate four-drug therapy in all cases of proven or suspected disease (25).

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