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The association between HIV and antituberculosis drug resistance

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ABSTRACT: In the UK, HIV is considered to be a risk factor for antituberculosis drug resistance. Evidence of the association is, however, inconclusive and there are few population-level data. The present study investigated the association in England and Wales during the period 1999–2005.

National tuberculosis surveillance data for adults were matched to HIV/AIDS reports. Unmatched cases were assumed to be HIV-negative. Separate analyses were conducted on new tuberculosis cases and those with a previous diagnosis. Logistic regression was used for univariable and multivariable analyses.

There were 1,657 previously diagnosed cases (80 HIV-positive) and 18,130 new cases (1,156 HIV-positive). Isoniazid resistance was found in 8.1% of previously diagnosed cases and 6.6% of new cases, and multidrug resistance in 2.8% and 0.7%, respectively. There was no evidence of an association between HIV and antituberculosis drug resistance among previously diagnosed cases. Among new cases, there was no overall association between HIV and isoniazid or multidrug resistance after adjusting for confounding factors. White HIV-positive patients were more likely to have multidrug resistance, but numbers were small.

In contrast to some previous studies, this large, up-to-date study provides little evidence that HIV co-infected tuberculosis patients in England and Wales are at increased risk of firstline antituberculosis drug resistance.

KEYWORDS: Antituberculosis drug resistance, England and Wales, HIV, tuberculosis

The proportion of tuberculosis patients co-infected with HIV has been increasing alongside the increasing incidence of tuberculosis in England and Wales (UK) [1, 2]. Antituberculosis drug resistance makes tuberculosis more difficult to treat and may prolong the infectious period of the disease, resulting in increased transmission [3]. It also adversely affects clinical outcomes [4]. A recent survey of global antituberculosis drug resistance highlighted that the relationship between HIV and drug-resistant tuberculosis is not well understood and that there is a need for more population-level data on this association [5].

Antituberculosis drug resistance may be initial (*i.e.* in those with no previous tuberculosis treatment) or acquired (in those who have been previously treated) [5]. Infection with HIV could influence antituberculosis drug resistance through behavioural/environmental or biological mechanisms. For example, certain HIV-positive population groups, such as injecting drug users, may have behavioural risk factors that make them less likely to adhere to tuberculosis treatment, resulting in the development of resistant strains (acquired resistance), which are then transmitted within that community (resulting in initial resistance). Since immunocompromised patients are more likely to develop disease and to do so more rapidly than immunocompetent patients [6], extensive transmission of drug-resistant strains may occur. HIV-positive patients might also be more likely to frequent settings in which they could be exposed to drug-resistant strains of tuberculosis, such as hospitals [7], and may be more susceptible to drug-resistant tuberculosis strains that are possibly less virulent [8]. Furthermore, HIV infection may impair the absorption of some antituberculosis drugs, contributing to the development of resistance [9]. Drug interactions and adverse reactions may also be more likely among HIV co-infected patients [9] and could lead to treatment interruptions; this will again promote the development of resistance.

In the UK, HIV is considered to be a risk factor for antituberculosis drug resistance [10, 11]. The current evidence on the association between HIV and antituberculosis drug resistance is, however, inconclusive. During the late 1980s and early 1990s, a number of tuberculosis outbreaks occurred, involving the transmission of multidrug-resistant strains among HIV-positive persons in specific

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settings in the USA, including hospitals and correctional facilities [12, 13]. There is also evidence of an association in Europe and countries of the former Soviet Union [14–18]. In contrast, there is little evidence of an association in Africa [19–21], although the recent emergence of extensively drug-resistant tuberculosis, particularly in areas with high levels of HIV infection [22], is of concern. Two earlier studies in the UK have found that, during the early to mid-1990s, HIV-positive patients were more likely to have isoniazid and multidrug resistance, but these studies were based on univariable analysis only and did not separate new and previously diagnosed cases [23, 24]. CONATY *et al.* [25] found an increased risk of initial isoniazid resistance among HIV-positive patients during the period 1993–1994 but no association during 1999–2000, and an association with initial multidrug resistance in the combined periods. There was no evidence of any association between HIV and acquired drug resistance.

The present study investigates the association between HIV and firstline antituberculosis drug resistance in England and Wales during the period 1999–2005.

METHODS

In England and Wales, demographic and clinical information on tuberculosis cases (individuals with disease due to *Mycobacterium tuberculosis* complex: *M. tuberculosis*, *M. bovis* or *M. africanum*) is collected through the Enhanced Tuberculosis Surveillance (ETS) system. Drug susceptibility testing (DST) results are reported through MycobNet, the UK Mycobacterial Surveillance Network, and are matched to case reports annually. The ETS system does not collect information on HIV status, so this information was obtained by matching the ETS case reports (for 1999–2005) with the national HIV/AIDS reports database (for 1979–2006) using in-house matching software based on soundex surname code [26], forename initial, date of birth, sex, ethnic group and country of birth. Matching was not carried out on cases aged <15 yrs, as HIV in children is reported separately. Tuberculosis cases that were not matched to HIV/AIDS reports were considered to be HIV-negative (although it is recognised that they are more accurately described as ''not known to be HIV-positive''). Cases that were diagnosed with HIV >1 yr after the date of tuberculosis diagnosis were excluded, since it was unknown whether they were infected with HIV at the time of tuberculosis diagnosis.

Five mycobacterial reference laboratories in England and Wales carry out antituberculosis DST on initial isolates (the first isolate from a patient in a 12-month period). Isolates are tested for resistance to the four firstline drugs (isoniazid, rifampicin, ethambutol and pyrazinamide), and some second-line drugs. Reference laboratories use the resistance ratio or the proportion method, and are subject to quality assurance systems.

Proportions were calculated among cases with known information on that variable. Data were compared using the Chi-squared or Fisher's exact test, as appropriate. For linear variables, the Chi-squared test for trend was used. Separate analyses were conducted on new tuberculosis patients and those with a previous diagnosis, because of the inherent difference between initial and acquired drug resistance. The proportion of resistant cases at start of treatment was calculated as R/(R+S), where R is the number of resistant cases and S is the number of susceptible cases. Cases with *M. bovis* were excluded from calculations of pyrazinamide resistance since they are usually intrinsically resistant to it. For the calculation of multidrug resistance (resistance to at least isoniazid and rifampicin), R was the number of cases resistant to both isoniazid and rifampicin, and S was the number of cases susceptible to isoniazid or rifampicin or both. Logistic regression was used for univariable and multivariable analyses. Multivariable models were built using a forward-fitting approach, and interactions were assessed using the likelihood ratio test. The association of HIV with isoniazid and multidrug resistance was examined in detail owing to the clinical importance of these two types of resistance. Although rifampicin monoresistance is also of importance, levels are very low [27].

Ethics approval

The Health Protection Agency (UK) has Patient Information Advisory Group approval to hold and analyse national surveillance data for public health purposes under Section 60 of the Health and Social Care Act, 2001. The HIV surveillance system uses surname soundex codes in place of patient surnames. Strict confidentiality of all data is maintained.

RESULTS

Study population

During the period 1999–2005, 27,164 culture-confirmed tuberculosis cases aged ⩾15 yrs were reported in England and Wales, 117 of which were excluded because they were diagnosed with HIV >1 yr after their tuberculosis diagnosis. DST results (for at least isoniazid and rifampicin) were available for 92.1% (24,912 out of 27,047) of the remaining cases; these were eligible for inclusion in the study. Among the study population, 6.1% were known to be HIV-positive, the median (interquartile range) age was 36 (27–54) yrs, 56.9% were male, 42.5% were reported in London, and 70.8% were born abroad. The majority of cases belonged to the Indian/Pakistani/Bangladeshi (36.7%), white (26.3%), and black African (22.6%) ethnic groups.

Among those with missing DST results, the proportion of cases who were HIV-positive was similar (6.6%), the sex ratio was similar (56.2% were male), the median age was higher (44 (30–66) yrs), a slightly lower proportion was reported in London (39.1%) and was born abroad (61.7%), and a higher proportion was white (38.7%).

HIV co-infection among tuberculosis cases

Among cases with a previous tuberculosis diagnosis, 4.8% were known to be HIV-positive, and the proportion of co-infected cases increased over the study period ($p=0.003$). Levels of HIV co-infection were highest in the following groups: the 15–44 yrs age group (8.7%); cases reported in London (7.9%); black Africans (23.4%); and recent entrants to the UK, *i.e.* those who had entered the UK <2 yrs prior to being diagnosed with tuberculosis (15.4%; table 1).

There was a similar pattern among new tuberculosis cases: 6.4% were HIV-positive, and there was strong evidence of increasing levels of co-infection during the study period ($p<0.001$). Again, levels of HIV-co-infection were highest in the following groups: 15–44 yrs age group (8.2%); cases reported in London (7.3%); black Africans (21.1%); and recent

TABLE 1 Number and proportion of tuberculosis cases co-infected with HIV, according to case characteristics and previous tuberculosis diagnosis status[#] in England and Wales, UK, 1999–2005

Case characteristic	Previously diagnosed cases			New cases		
	Total	HIV-positive	p-value[¶]	Total	HIV-positive	p-value[¶]
Total	1657	80 (4.8)		18130	1156 (6.4)	
Year			0.003[+]			<0.001[+]
1999	219	5 (2.3)		2163	50 (2.3)	
2000	226	6 (2.7)		2231	81 (3.6)	
2001	210	8 (3.8)		2435	127 (5.2)	
2002	263	16 (6.1)		2656	188 (7.1)	
2003	240	12 (5.0)		2687	239 (8.9)	
2004	238	16 (6.7)		2805	238 (8.5)	
2005	261	17 (6.5)		3153	233 (7.4)	
Age group yrs			<0.001			<0.001
15–44	744	65 (8.7)		12082	987 (8.2)	
45–64	356	12 (3.4)		3424	158 (4.6)	
⩾65	557	3 (0.5)		2624	11 (0.4)	
Sex			0.697			<0.001
Male	945	44 (4.7)		10258	596 (5.8)	
Female	710	36 (5.1)		7845	558 (7.1)	
Place of reporting			<0.001			<0.001
Outside London	1072	34 (3.2)		10506	603 (5.7)	
London	585	46 (7.9)		7624	553 (7.3)	
Ethnic group			<0.001			<0.001
White	687	13 (1.9)		4644	166 (3.6)	
Black Caribbean	29	1 (3.5)		568	14 (2.5)	
Black African	261	61 (23.4)		4111	869 (21.1)	
Indian/Pakistani/Bangladeshi	525	2 (0.4)		6572	25 (0.4)	
Other	136	3 (2.2)		2009	63 (3.1)	
Place of birth (time since entry into the UK)			<0.001			<0.001
UK	670	10 (1.5)		4999	139 (2.8)	
Abroad (<2 yrs)	162	25 (15.4)		2469	304 (12.3)	
Abroad (⩾2 yrs)	557	32 (5.7)		7974	547 (6.9)	
Abroad (unknown)	157	11 (7.0)		1781	128 (7.2)	
Site of disease			0.619			<0.001
Extrapulmonary	398	16 (4.0)		6170	328 (5.3)	
Pulmonary sputum smear positive	713	38 (5.3)		6287	401 (6.4)	
Other pulmonary	545	26 (4.8)		5628	427 (7.6)	

Data are presented as n or n (%), unless otherwise stated. [#]: cases with missing information on previous tuberculosis diagnosis status are not shown; [¶]: for overall differences between groups; [+]: test for trend.

entrants to the UK (12.3%). In addition, females had higher levels of co-infection (7.1%; table 1).

Antituberculosis drug resistance among tuberculosis cases

Levels of resistance to the firstline antituberculosis drugs are given in table 2. Isoniazid resistance was found in 8.1% of those with a previous diagnosis and 6.6% of new cases, and multidrug resistance in 2.8% and 0.7%, respectively.

Association between HIV and antituberculosis drug resistance among cases with a previous tuberculosis diagnosis

There was no evidence of an association between HIV and any type of drug resistance among cases with a previous tuberculosis diagnosis (table 2). Owing to the small numbers of HIV-positive drug-resistant cases, no further analyses were conducted on this group.

Association between HIV and antituberculosis drug resistance among new tuberculosis cases

Among new tuberculosis cases, HIV-positive individuals were more likely to be resistant to rifampicin (odds ratio (OR) 2.03, 95% confidence interval (CI) 1.29–3.18; p=0.002) and to have multidrug-resistant tuberculosis (OR 1.86, 95% CI 1.06–3.26; p=0.029). There was only weak evidence of an increased risk of pyrazinamide resistance (OR 2.04, 95% CI 1.01–4.10; p=0.047) and any firstline drug resistance (OR 1.24, 95% CI 1.00–1.54; p=0.047). There was no evidence that the level of

TABLE 2 Antituberculosis drug resistance among previously diagnosed and new tuberculosis cases by HIV status, England and Wales, UK, 1999–2005

Type of resistance	All cases	HIV-negative	HIV-positive	OR (95% CI)#	p-value
Previously diagnosed cases					
Isoniazid	135/1657 (8.1)	131/1577 (8.3)	4/80 (5.0)	0.58 (0.21–1.61)	0.297
Rifampicin	62/1657 (3.7)	57/1577 (3.6)	5/80 (6.3)	1.78 (0.69–4.57)	0.232
Ethambutol	20/1656 (1.2)	19/1576 (1.2)	1/80 (1.3)	1.04 (0.14–7.85)	0.972
Pyrazinamide¶	17/1650 (1.0)	16/1570 (1.0)	1/80 (1.3)	1.23 (0.16–9.39)	0.842
Any first-line drug	153/1655 (9.2)	146/1575 (9.3)	7/80 (8.8)	0.94 (0.42–2.08)	0.876
MDR	47/1657 (2.8)	45/1577 (2.9)	2/80 (2.5)	0.87 (0.21–3.66)	0.853
New cases					
Isoniazid	1195/18130 (6.6)	1108/16974 (6.5)	87/1156 (7.5)	1.17 (0.93–1.46)	0.186
Rifampicin	183/18130 (1.0)	161/16974 (0.9)	22/1156 (1.9)	2.03 (1.29–3.18)	0.002
Ethambutol	63/18123 (0.3)	57/16968 (0.3)	6/1155 (0.5)	1.55 (0.67–3.60)	0.309
Pyrazinamide¶	74/18016 (0.4)	65/16864 (0.4)	9/1152 (0.8)	2.04 (1.01–4.10)	0.047
Any first-line drug	1288/18077 (7.1)	1189/16924 (7.0)	99/1153 (8.6)	1.24 (1.00–1.54)	0.047
MDR	125/18130 (0.7)	111/16974 (0.7)	14/1156 (1.2)	1.86 (1.06–3.26)	0.029

Data are presented as number of resistant cases/total cases (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; MDR: multidrug resistance. #: HIV-positive cases compared with HIV-negative cases; ¶: cases with *Mycobacterium bovis* were excluded from calculations of pyrazinamide resistance, since they are usually intrinsically resistant.

resistance to isoniazid or ethambutol was different among HIV-positive cases compared with HIV-negative cases (table 2).

Table 3 shows that isoniazid resistance increased linearly with year of reporting ($p=0.031$), and was more common in younger age groups ($p<0.001$), the cases reported in London ($p<0.001$), non-white ethnic groups ($p<0.001$) and those born abroad ($p=0.002$). There was no evidence that sex ($p=0.098$) or site of disease ($p=0.307$) were associated with isoniazid resistance. After adjusting for age, ethnic group and place of residence (there was little evidence to keep any other factors in the model), there remained no evidence of an association between HIV and isoniazid resistance (adjusted OR 1.02, 95% CI 0.80–1.30; $p=0.895$).

On univariable analysis, multidrug resistance was more common in younger age groups ($p<0.001$), cases reported in London ($p=0.009$), non-white ethnic groups (except black Caribbeans; $p<0.001$) and those born abroad ($p<0.001$). There was no evidence that year of reporting ($p=0.165$), sex ($p=0.382$) or site of disease ($p=0.322$) were associated with multidrug resistance (table 4).

After adjusting for age group, ethnic group and time since entry into the UK (there was little evidence to keep any other factors in the model), there was no overall evidence that HIV-positive patients had an increased risk of multidrug resistance (adjusted OR 0.91, 95% CI 0.47–1.76; $p=0.775$; table 4). There was, however, evidence of an interaction between HIV and ethnic group in the model (likelihood ratio test for interaction $p=0.006$): there was an increased risk of multidrug resistance among white HIV-positive patients (adjusted OR 6.30, 95% CI 1.70–23.40), although the numbers of cases were small (3 out of 166 *versus* 10 out of 4,478). Meanwhile, among black Africans there was no increased risk (adjusted OR 0.71, 95% CI 0.33–1.53; 11 out of 869 *versus* 40 out of 3,242). There were no HIV-positive multidrug-resistant cases in the other ethnic groups. The three white HIV-positive multidrug-resistant cases were all male and were reported in broadly the same area of England. However, they were reported during different years and there was no evidence to suggest that they were associated.

DISCUSSION

The present study provides national data on the association between HIV and firstline antituberculosis drug resistance in England and Wales during the period 1999–2005. In contrast to previous studies from the UK and some other Western countries [12–18, 23–25], this large, up-to-date study provides little evidence that HIV co-infected patients are at increased risk of drug-resistant tuberculosis. Among cases with a previous tuberculosis diagnosis, there was no evidence of an association, although numbers were small. Among new tuberculosis cases, there was no overall association between HIV and isoniazid or multidrug resistance after adjusting for confounding factors. White HIV-positive patients were more likely to have multidrug resistance, but numbers were very small.

The present analysis used national surveillance data from seven consecutive years, which provided a large and representative dataset. One of the main limitations of the study is that, in order to obtain information on HIV status, it was necessary to match tuberculosis cases to HIV/AIDS reports. It is likely that the number of co-infected cases has been underestimated. Although HIV is known to be an important risk factor for the development of tuberculosis disease [6], there is currently no policy in the UK to test all tuberculosis cases for HIV. Therefore, it is probable that there are a number of tuberculosis cases with undiagnosed HIV. Furthermore, since no information is available on individuals with negative HIV test results, it is not known what proportion of patients

TABLE 3 Univariable and multivariable analyses for isoniazid resistance among new tuberculosis cases in England and Wales, UK, 1999–2005

Case characteristic	Resistance	Univariable analysis			Multivariable analysis		
		OR	95% CI	p-value	AOR	95% CI	p-value
HIV status				0.186			
Negative	1108/16974 (6.5)	1			1		0.895
Positive	87/1156 (7.5)	1.17	0.93–1.46		1.02	0.80–1.30	
Year (linear variable)		1.03	1.00–1.06	0.031#			
Age group yrs				<0.001			<0.001
15–44	957/12082 (7.9)	1			1		
45–64	177/3424 (5.2)	0.63	0.54–0.75		0.70	0.59–0.83	
⩾65	61/2624 (2.3)	0.28	0.21–0.36		0.34	0.26–0.44	
Sex				0.098			
Male	704/10258 (6.9)	1					
Female	490/7845 (6.2)	0.90	0.80–1.02				
Place of reporting				<0.001			<0.001
Outside London	534/10506 (5.1)	1			1		
London	661/7624 (8.7)	1.77	1.58–1.99		1.52	1.34–1.72	
Ethnic group				<0.001			<0.001
White	193/4644 (4.2)	1			1		
Black Caribbean	91/568 (16.0)	4.40	3.37–5.74		3.11	2.36–4.08	
Black African	324/4111 (7.9)	1.97	1.64–2.37		1.22	1.00–1.50	
Indian/Pakistani/Bangladeshi	400/6572 (6.1)	1.49	1.25–1.78		1.18	0.99–1.42	
Other	168/2009 (8.4)	2.10	1.70–2.61		1.40	1.12–1.76	
Place of birth (time since entry into the UK)				0.002			
UK	275/4999 (5.5)	1					
Abroad (<2 yrs)	182/2469 (7.4)	1.37	1.13–1.66				
Abroad (⩾2 yrs)	562/7974 (7.0)	1.30	1.12–1.51				
Abroad (unknown)	116/1781 (6.5)	1.20	0.96–1.50				
Site of disease				0.307			
Extrapulmonary	427/6170 (6.9)	1					
Pulmonary sputum smear positive	415/6287 (6.6)	0.95	0.83–1.09				
Other pulmonary	350/5628 (6.2)	0.89	0.77–1.03				

Resistance data are presented as number of resistant cases/total number of cases (%). OR: odds ratio; CI: confidence interval; AOR: adjusted OR. #: test for trend.

was tested. Misclassification of HIV status may underestimate any association, but it is possible that patients with drug-resistant tuberculosis are more likely to be tested for HIV; this may result in an overestimation of the association between HIV and antituberculosis drug resistance.

The lack of DST results for 10% of cases is likely to be due to limitations of the process for matching ETS cases reports with MycobNet isolates, rather than differential testing. In addition, the characteristics of these excluded cases were reasonably similar to those of the study population; thus, the exclusion of these cases is unlikely to have resulted in any substantial bias. Meanwhile, any misclassification of drug resistance will most likely be due to random laboratory or data input errors, or limitations of the matching procedure. Such misclassification is likely to be minimal and would not be influenced by HIV status. Therefore, any resulting bias would be nondifferential. Information on previous tuberculosis diagnosis is generally self-reported and is thus subject to recall bias. This is unlikely to be a serious concern, owing to the nature of tuberculosis treatment, *i.e.* patients are generally unlikely to forget having been previously treated. However, as the analyses were stratified by previous history of tuberculosis, cases with missing data on this variable could not be included in the analysis; this may have introduced some bias, and will have reduced the power of the study.

There was no evidence of an association between HIV and isoniazid resistance in this study. Earlier studies in the UK have found an increased risk of isoniazid resistance among HIV-positive cases during the 1990s [23, 24] but, because these studies did not analyse new and previously diagnosed cases separately, it is difficult to compare the results with those of the present study. CONATY *et al.* [25] found an increased risk of initial isoniazid resistance among HIV-positive patients in England and Wales during 1993–1994 but no association in 1999–2000. An outbreak of isoniazid-resistant tuberculosis began in 1999–2000 [28] and has not been associated with HIV infection.

TABLE 4 Univariable and multivariable analyses for multidrug resistance (MDR) among new tuberculosis cases in England and Wales, UK, 1999–2005

Case characteristic	MDR	Univariable analysis			Multivariable analysis		
		OR	95% CI	p-value	AOR	95% CI	p-value
HIV status				0.029			0.775
Negative	111/16974 (0.7)	1			1		
Positive	14/1156 (1.2)	1.86	1.06–3.26		0.91	0.47–1.76	
Year (linear variable)		1.07	0.97–1.17	0.165#			
Age group yrs				<0.001			0.010
15–44	108/12082 (0.9)	1			1		
45–64	12/3424 (0.4)	0.39	0.21–0.71		0.52	0.27–0.99	
⩾65	5/2624 (0.2)	0.21	0.09–0.52		0.35	0.14–0.90	
Sex				0.382			
Male	66/10258 (0.6)	1					
Female	59/7845 (0.8)	1.17	0.82–1.66				
Place of reporting				0.009			
Outside London	58/10506 (0.6)	1					
London	67/7624 (0.9)	1.60	1.12–2.27				
Ethnic group				<0.001			0.323
White	13/4644 (0.3)	1			1		
Black Caribbean	3/568 (0.5)	1.89	0.54–6.66		1.40	0.39–5.01	
Black African	51/4111 (1.2)	4.47	2.43–8.24		2.02	0.88–4.64	
Indian/Pakistani/Bangladeshi	39/6572 (0.6)	2.13	1.13–3.99		1.33	0.61–2.90	
Other	16/2009 (0.8)	2.86	1.37–5.96		1.39	0.56–3.45	
Place of birth (time since entry into the UK)				<0.001			0.028
UK	19/4999 (0.4)	1			1		
Abroad (<2 yrs)	37/2469 (1.5)	3.99	2.29–6.95		2.23	1.08–4.63	
Abroad (⩾2 yrs)	53/7974 (0.7)	1.75	1.04–2.97		1.19	0.59–2.38	
Abroad (unknown)	11/1781 (0.6)	1.63	0.77–3.43		1.24	0.53–2.91	
Site of disease				0.322			
Extrapulmonary	35/6170 (0.6)	1					
Pulmonary sputum smear positive	46/6287 (0.7)	1.29	0.83–2.01				
Other pulmonary	44/5628 (0.8)	1.38	0.88–2.16				

MDR data are presented as number of MDR cases/total number of cases (%). OR: odds ratio; CI: confidence interval; AOR: adjusted OR. #: test for trend.

In the present study, there was no overall association between HIV and initial multidrug resistance after adjusting for confounding factors. An earlier UK study [25], as well as several studies in Western Europe [15–17], found an association between HIV and initial multidrug-resistant tuberculosis. The reason for the differing finding in the present study could be related to the different time periods studied, lack of adjustment for confounders in previous studies [17], or possibly the differing demographics of tuberculosis cases. Meanwhile, although there is well-documented evidence of the transmission of multidrug-resistant tuberculosis among HIV-positive patients in the USA, this occurred during outbreaks in specific settings [12, 13].

The finding of an association between HIV and multidrug-resistant tuberculosis only in the white ethnic group suggests a behavioural, rather than biological, explanation. The ETS system does not collect information on behavioural factors, such as problem drug use, imprisonment and homelessness, so these could not be adjusted for in the current analysis. Such factors are known to play an important role in the epidemiology of tuberculosis [29] and may be confounders of the observed association. The collection of information on these factors is an important consideration for future surveillance. Meanwhile, further investigation, including the use of strain-typing data, may help determine the cause of the association in the white ethnic group and inform appropriate public health interventions. That the association between HIV and antituberculosis drug resistance seems to vary in different parts of the world may support the suggestion of a behavioural explanation in the present study. Associations have been most commonly observed in countries with a low incidence of both tuberculosis and HIV, *e.g.* Western Europe and the USA, and in these areas both diseases tend to be concentrated in population subgroups, *e.g.* in those with unique risk factors, such as problem drug use [29, 30]. Conversely, both diseases are much more widespread in the general population in Africa, where there is little evidence of an association [19–21]. This is also consistent with the finding of no increased risk among HIV-positive black Africans in the present study.

Conclusion

Overall, the present study provides little evidence that HIV co-infected tuberculosis patients are at increased risk of initial or acquired drug-resistant tuberculosis. Although there is some evidence of an increased risk of initial multidrug-resistant tuberculosis among white HIV-positive patients, the risk is still very low (<2%), and may be due to behavioural factors. Routine HIV testing of tuberculosis patients would help inform clinical care and allow a better understanding of the impact of HIV co-infection on the epidemiology of tuberculosis.

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