

Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection

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Abstract

Rationale: Serious treatment-associated adverse events are thought to occur more frequently in individuals with tuberculosis who are co-infected with HIV.

Objectives and Methods: To assess the frequency of serious (Grade III/IV) adverse events and interruption of anti-tuberculosis treatment in the era of effective anti-retroviral therapy. We retrospectively compared the incidence of serious (Grade III/IV) adverse events in 312 individuals treated for tuberculosis, of whom 156 were co-infected with HIV.

Results: 111 (71%) of HIV-infected individuals received highly active antiretroviral therapy at the same time as anti-tuberculosis treatment. Serious (Grade III/IV) adverse events were recorded in 40% HIV infected and 26% HIV-uninfected individuals respectively ($p=0.008$). Peripheral neuropathy and persistent vomiting were more common in co-infected patients ($p<0.001$; $p=0.006$); although all cause interruption of anti-tuberculosis therapy occurred with similar frequency within each group (13% in the HIV-infected and 15% in the HIV-uninfected groups; $p=0.74$). In 85% of HIV-infected and 87% of HIV-uninfected individuals respectively this was due to hepatotoxicity, which typically presented within two months of starting treatment. The median delay in restarting therapy was 4 weeks; thus most individuals required full tuberculosis re-treatment.

Conclusion: Despite a greater rate of serious (Grade III/IV) adverse events among HIV infected individuals, we found that discontinuation of anti-tuberculosis treatment occurred with similar frequency in HIV-infected and HIV-uninfected individuals.

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Introduction

Although the response to anti-tuberculosis therapy among HIV co-infected patients is generally good, many require concurrent highly active anti-retroviral therapy (HAART) to achieve a successful long-term outcome (1,2). It has been reported that HIV/tuberculosis co-infected patients experience a higher rate of adverse drug reactions to treatment than those without HIV (3). Prior to use of HAART this may have reflected the additional toxicity of therapy for other opportunistic infections or that due to specific anti-tuberculosis agents such as thiacetazone (4,5). Few data exist in co-infected individuals since HAART became widely available, although a very high rate of adverse drug reactions has been described (6). We hypothesised that through careful selection of treatment regimens to minimise toxicity, the presence of HIV co-infection should have little impact on the frequency of serious (Grade III/IV) adverse events, especially those causing treatment interruption, even if HAART were co-administered.

Methods

Data were collected retrospectively at the North Middlesex, Royal Free and University College London Hospitals, London. We identified consecutive, unselected adult HIV-infected individuals who were treated for tuberculosis between February 1997 and November 2003. These were compared with a control group of HIV-uninfected individuals attending these treatment centres who were treated for tuberculosis during the study period. Over this time the policy on testing for HIV infection of patients with tuberculosis changed from it being offered at physician discretion, based on an assessment of risk, to one of all patients being offered a test regardless of risk. To minimise possible selection bias, therefore, we included consecutive HIV-uninfected individuals from the end of the study period working backwards in time until the two groups were of an identical size.

Tuberculosis was diagnosed if a patient had: (1) a positive culture for *Mycobacterium tuberculosis*; or (2) was culture negative but nucleic acid amplification assay positive (TB Strand Displacement Amplification assay, Becton-Dickinson, New Jersey, USA), with clinico-radiological features and response to treatment consistent with tuberculosis; or (3) had histological findings and response to treatment consistent with tuberculosis. Retrospective case-note review identified the occurrence of serious (Grade III/IV) adverse drug reactions and episodes of treatment interruption. Treatment interruption was defined as any period in which anti-tuberculosis therapy was discontinued due to an adverse drug reaction. Hepatotoxicity was defined as liver transaminases (AST/ALT) rising to >5 times the upper limit of normal, or a rising bilirubin level (7). Liver function was routinely checked at baseline (along with assessment of hepatitis B and C status) and repeated at two weeks. In individuals with normal test results, further blood tests were performed only in the event of new symptoms. In patients with chronic liver disease, liver function was checked every second week for two months and those with abnormal liver function pre-treatment or at week two were re-checked every second week until they had normalised or were clearly stable. HIV-infected individuals with tuberculosis generally had liver function tests monitored more frequently throughout their treatment course, although the

frequency of this was at the discretion of the treating physician. Following discontinuation, treatment was recommenced according to national guidelines (7). Other adverse events were as documented by the treating clinician in the patient notes and graded by the investigators based on a standard classification system (8). The definitions of the most notable serious adverse events were: *hepatotoxicity* as described above; *peripheral neuropathy* as a marked decrease in sensation to the level of the knees or wrists; *arthralgia* as joint pain causing marked impairment of activities of daily living or mobility; *persistent vomiting* as vomiting of all food/fluids for 24 hours; *rash* as vesiculation or moist desquamation or ulceration. If anti-tuberculosis therapy had been discontinued, re-introduction was attempted sequentially in the order: isoniazid, rifamycin, pyrazinamide, with the dose of each agent increased up to the therapeutic amount over two or three days, with a period of two or three days observation between restarting each agent (7). Data were recorded on a standard proforma and entered on a central database.

Prescription of HAART and anti-tuberculosis therapy was at the discretion of individual physicians using then-available treatment protocols. In all cases initial treatment of tuberculosis was rifamycin-based and was adjusted according to availability of mycobacterial susceptibility testing. A typical regimen would start with a rifamycin plus isoniazid and pyrazinamide (ethambutol was routinely commenced at North Middlesex and Royal Free, but not University College) for 2 months followed by a continuation phase of two drugs dependent on drug sensitivities. All patients receiving isoniazid were co-administered pyridoxine 10-25mg daily. Standard dose rifampicin (600 mg if >50kg, 450 mg if <50kg) was prescribed except with single or 'boosted' protease inhibitor-containing regimens, when rifabutin was given (150mg daily or 150mg three times per week, respectively). HAART was defined as use of ≥ 3 anti-retroviral drugs in combination. Standard practice was to prescribe all drugs as daily self-administered therapy. Comparisons between groups were performed using either the Chi-squared test or Fisher's exact test. The data was analysed using SAS version 8.2 (SAS Institute Inc, Cary, NC).

Results

One hundred and fifty six HIV-infected individuals were treated for tuberculosis during the study period (TB+HIV+). Characteristics of these individuals and of a control group of 156 HIV-uninfected individuals with tuberculosis (TB+HIV-) are compared in Table 1.

In the TB+HIV+ group the median CD4 count and HIV load at time of starting anti-tuberculosis therapy was 77 (range: 0 – 720) cells/ μ l and 5.1 log₁₀ (range: 1.7 – 5.9) viral copies/ml respectively. One hundred and eleven of 156 (71%) HIV-infected individuals received HAART while on anti-tuberculosis therapy. Twenty-nine of 111 (26%) were already using HAART when anti-tuberculosis therapy was started and the remaining 82 commenced HAART a median of 2 (range: 0 – 8) months later.

Treatment interruptions and common serious (Grade III/IV) adverse events are described in Table 2. Serious adverse events occurred in 63 of 156 (40%) TB+HIV+ and in 41 of 156 (26%) TB+HIV- individuals ($p=0.008$). The most frequent adverse event in TB+HIV+ individuals was peripheral neuropathy, which occurred in 22 (14%); compared with 3 (2%) of those without HIV co-infection ($p<0.0001$). Of these 22 TB+HIV+ individuals, 17 received concomitant HAART; and 11 used regimens containing the nucleoside reverse transcriptase inhibitors (NRTI) stavudine (d4T) and/or didanosine (ddI). However excluding those who received ddI and/or d4T in whom the only adverse event was peripheral neuropathy, the overall frequency of adverse events was little changed at 38%. In both tuberculosis populations hepatotoxicity developed in 20 (13%) of 156 individuals, all of whom were symptomatic. Only one case of hepatotoxicity occurred in an individual with hepatitis B co-infection and none were associated with hepatitis C co-infection.

Rash occurred frequently and at a similar incidence in both groups. Persistent vomiting was significantly more common among TB+HIV+ individuals ($p=0.006$); and a greater number of TB+HIV+ individuals had more than one serious adverse event compared with the TB+HIV- population ($p=0.02$) [Table 2].

Interruption of anti-tuberculosis therapy occurred in 13% TB+HIV+ individuals and 15% TB+HIV- individuals ($p=0.74$). In TB+HIV+ individuals 17 of 20 (85%) interruptions were secondary to hepatotoxicity. Other causes were rash in 2 and peripheral neuropathy in 1. Among TB+HIV- individuals 20 of 23 (87%) interruptions were secondary to hepatotoxicity: the other 3 were due to thrombocytopenia, vomiting and optic neuritis.

In both TB+HIV+ and TB+HIV- groups almost all anti-tuberculosis therapy interruptions occurred within the first 2 months of treatment. There was a median delay of 4 weeks before full anti-tuberculosis therapy could be restarted. All such interruptions lasted for at least one week. HAART was discontinued in eleven of 111 (10%) TB+HIV+ individuals while they were receiving anti-tuberculosis therapy. In four it resulted from HAART-related

adverse events (three had Immune Reconstitution Inflammatory Syndrome) and in seven it was due to virological failure. In a further 12 of 111 (11%), the HAART regimen was altered during the course of anti-tuberculosis therapy.

Comparison of the frequency of both adverse events and anti-tuberculosis treatment interruption in the black-African population showed that these were doubled in the HIV+TB+ group compared to those who were TB+HIV- (43% versus 21% for adverse events ($p=0.07$); 13% versus 6% for treatment interruption ($p=0.03$)). In the white population the frequency of adverse events and treatment interruption were similar in those with and without HIV co-infection (38% versus 32% for adverse events; 17% versus 19% for treatment interruption). It was not possible to perform a similar comparison in the Asian population as the number in the HIV infected group was very small. Asian TB+HIV- individuals showed high rates of both adverse events (33%) and anti-tuberculosis treatment-interruption (22%; all due to hepatotoxicity).

In the 82 HIV+TB+ individuals who started HAART after anti-tuberculosis therapy, 32 did so within 2 months (median [range] CD4 count 40 cells/ul (10-390) and 50 (median [range] CD4 count 52 cells/ul (10-400) after 2 months. The frequency of adverse events in those starting HAART within 2 months compared to later than 2 months was 53% versus 48% and for treatment interruption 16% versus 18% respectively. No differences were noted in the occurrence of adverse events or treatment interruption whether HAART was commenced before anti-tuberculosis treatment, within or after 2 months of starting anti-tuberculosis treatment or not at all ($p=0.73$ for adverse events; $p=0.55$ for interruption). In this group, 56 of 82 had a CD4 count at TB diagnosis of < 100 cells/ul and the frequency of adverse events and treatment interruption in these individuals were 52% and 16% respectively. Twenty-six of 82 had a CD4 count at TB diagnosis of >100 cells/ul with a frequency of adverse events and treatment interruption in these individuals of 48% and 22% respectively ($p=0.74$ for adverse events; $p=0.84$ for interruption).

Five HAART regimens were prescribed (involving 31 different combinations of drugs). The 5 regimens were: NRTI, 2 or 3 NRTI + non-nucleoside reverse transcriptase inhibitor (NNRTI), 2 or 3 NRTI + single protease inhibitor (PI), 2 or 3 NRTI + boosted PI and 2 or 3 NRTI + NNRTI + PI (Table 3). The frequency of adverse events, hepatotoxicity and anti-tuberculosis treatment-interruption were assessed in the 111 TB+HIV+ individuals according to the regimen of HAART prescribed. No differences were seen in frequency of events with different regimens although the numbers in some groups were small.

Discussion

Our data demonstrate that despite treatment of tuberculosis in HIV co-infected individuals being associated with a greater frequency of serious (Grade III/IV) adverse events than that seen in patients with tuberculosis alone (40% versus 26%), this did not translate into an increased frequency of treatment interruption (which occurred in approximately one in seven subjects). These findings did not appear to be altered by the level of immunosuppression, the type of HAART-regimen prescribed or its time of initiation.

The commonest reason for anti-tuberculosis therapy interruption was hepatitis. This occurred mainly within the first 2 months of treatment; with a median time off anti-tuberculosis therapy of 4 weeks. Thus most interruptions necessitated a full re-treatment. In contrast with other reports we found this to occur at a similar frequency in both HIV-infected and uninfected patients (9). The difference in study results may reflect the criteria used to perform liver function tests, as well as the point at which therapy would be discontinued given an abnormal result. We used national guidelines which combine both blood test results and symptoms in deciding whether to repeat liver function tests (7). These are formulated primarily for HIV-uninfected TB individuals; and it is likely that HIV-infected individuals with tuberculosis tend to undergo more frequent blood tests.

Previous studies have identified multiple risk factors for anti-tuberculosis therapy-induced hepatitis including disease extent, chronic hepatitis and alcohol use (9,10,11,12). Both groups had a low prevalence of chronic viral hepatitis, which made assessment of this as a risk factor unfeasible. We did not assess the extent of disease but sought to minimise the possibility that early in the study only the sickest patients were tested for HIV by identifying the HIV-uninfected cohort in reverse time order. In most cases the use of alcohol, recreational drugs and over-the-counter preparations was poorly recorded in the notes and we felt that findings based on incomplete data might be misleading.

Only in the black-African population did ethnicity appear to be important, with a significantly lower frequency of anti-tuberculosis treatment interruption observed in the HIV-uninfected group compared to the HIV-infected group. The effect of ethnicity in this area is not well-described but our data suggest that it may be important. Ethnicity may be one explanation for the marked difference in the observed frequency of hepatotoxicity necessitating treatment interruption in our series, compared to the figure of 3.2% noted in another study from the United Kingdom, in which 70% of the subjects were Asian (13).

An earlier study of the treatment of HIV/tuberculosis co-infection in the era of HAART observed an incidence of significant adverse events greater than 50% with one-third of subjects discontinuing anti-tuberculosis therapy (6). However it did not contain an HIV-uninfected comparator population, which makes it difficult to assess the relative contributions of HIV, HAART and anti-tuberculosis therapy.

A large proportion of the excess adverse event rate in HIV/tuberculosis co-infected individuals was due to peripheral neuropathy. We expected some of this to result from co-administration of d4T or ddl with isoniazid which is now not recommended due to a reported increase in neuropathy (14,15). However removing from the analysis those who received d4T/ddl and isoniazid did not substantially reduce the observed incidence suggesting the importance of other factors such as HIV itself (16).

The retrospective collection of data meant that some adverse events may not have been recorded. However rates of under-reporting should have been similar regardless of HIV status. Adherence was not formally assessed but we believe that it was generally very good – reflected in the high rates of treatment completion, a low rate of relapse of tuberculosis, and the good virological response to HAART [reported elsewhere (17)]. Other limitations of our study include potential bias due to ethnic mix, difficulties in assessing tuberculosis disease extent as well as alcohol and other drug use and the differing frequency of blood-test monitoring between groups.

In conclusion, our data suggest that despite a higher frequency of serious (Grade III/IV) adverse events during anti-tuberculosis therapy in individuals with HIV co-infection, treatment interruption occurs no more frequently than in HIV uninfected patients with tuberculosis.

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Table 1: Comparison of HIV-infected individuals with tuberculosis and a control group of HIV-uninfected patients with tuberculosis

	HIV-infected (n =156)	HIV-uninfected (n =156)
Median age [years] (range)	35 (20-73)	33 (16-82)
Male sex	81 (52%)	90 (58%)
Ethnicity: Black-African	122 (78%)	64 (41%)*
Asian	3 (2%)	45 (28%)
white	28 (18%)	47 (30%)
Other	3 (2%)	0 (0%)
Pulmonary TB	89 (57%)	80 (51%)
Duration of anti TB treatment Median (range) [months]	6 (1-24)	6 (1-36)
Discontinuation of anti- TB treatment	9 (6%)	6 (4%)
Incidence of TB recurrence	5 (3%)	2 (1%)
Incidence of hepatitis B or C co-infection	5 (3%)	5 (3%)

* p<0.0001

Table 2: Incidence of serious (Grade III or IV) adverse events (AE) during the treatment of tuberculosis according to HIV status

	HIV- infected (n = 156)	HIV- uninfected (n = 156)	P value
Individuals with at least one AE	63 (40%)	41 (26%)	0.008
Hepatotoxicity	20 (13%)	20 (13%)	1.00
Peripheral neuropathy	22 (14%)	3 (2%)	<0.0001
Rash	20 (13%)	13 (8%)	0.20
Persistent vomiting	15 (10%)	3 (2%)	0.006
Arthralgia	6 (4%)	1 (1%)	0.07
Individuals with more than one AE	11 (7%)	2 (1%)	0.02
Individuals requiring interruption of anti-TB treatment	20 (13%)	23 (15%)	0.74

Table 3: Comparison of the incidence of serious (Grade III or IV) adverse events, hepatotoxicity and anti-tuberculosis therapy-interruption according to regimen of HAART (n=111)

Type of HAART regimen	Patients receiving regimen [number]	Serious adverse events	Hepatotoxicity	Anti-TB therapy-interruption
Triple NRTI	9	5 (56%)	2 (22%)	2 (22%)
2NRTI + NNRTI	69	31 (45%)	9 (13%)	8 (12%)
2NRTI + PI	11	5 (45%)	2 (18%)	2 (18%)
2NRTI + 'boosted' PI	13	5 (38%)	0 (0%)	0 (0%)
2NRTI + PI + NNRTI	5	2 (40%)	1 (20%)	1 (20%)
Not recorded	4	0 (0%)	0 (0%)	0 (0%)

Key: NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor