MAJOR ARTICLE

Outcome of HIV-Associated Tuberculosis in the Era of Highly Active Antiretroviral Therapy

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Background. The benefit of highly active antiretroviral therapy (HAART) in the treatment of patients coinfected with tuberculosis (TB) and human immunodeficiency virus (HIV) is unclear because of concerns about treatment-related complications.

Methods. We compared outcomes in patients starting TB treatment during the pre-HAART era (before 1996; $n = 36$) with those in patients starting treatment during the HAART era (during or after 1996; $n = 60$).

Results. During a median of 3.6 years of follow-up, 49 patients died or had an AIDS event. Compared with patients in the pre-HAART group, those in the HAART group had a lower risk of death (cumulative at 4 years, 43% vs. 22%; $P = .012$) and of death or having an AIDS event (69% vs. 43%; $P = .023$). Event risk within the first 2 months of TB treatment was exceptionally high in patients with $CD4^+$ cell counts <100 cells/mm^3 and declined thereafter. HAART use during follow-up was associated with a marked reduction in event risk (adjusted hazard ratio, 0.38 [95% confidence interval, 0.16–0.91]).

Conclusions. HAART substantially reduces new AIDS events and death in coinfected patients. Those with a $CD4^+$ cell count <100 cells/mm^3 have a high event risk during the intensive phase of anti-TB treatment. These data should be taken into account when deciding to delay HAART in coinfected patients with $CD4^+$ cell counts <100 cells/mm^3.

Despite adequate antituberculous therapy, many individuals coinfected with tuberculosis (TB) and HIV have an accelerated course of HIV disease and shortened survival [1]. In developed countries, such as the United Kingdom and the United States, coinfected patients often have advanced levels of immunosuppression, with low $CD4^+$ cell counts and high HIV RNA loads at the time of diagnosis of TB [2, 3].

Since the advent of highly active antiretroviral therapy (HAART), death from many HIV-related opportunistic infections has markedly decreased [4]. It would be expected that the same should apply to TB. However, the introduction of HAART in this particular group of patients is problematic because there are potential complex drug interactions, overlapping adverse reactions, noncompliance due to the pill burden of multidrug therapy, and drug malabsorbtion [5]. There is also increasing concern about paradoxical reactions, which may be severe [5–7]. Therefore, it is unclear how HAART will affect the outcome in such coinfected patients. Published data that have directly assessed the effect of HAART on survival and new AIDS-defining illnesses are few [8, 9], there are no data on long-term outcome, and current antiretroviral treatment guidelines for coinfected patients are largely based on expert opinion [10, 11]. Moreover, in severely immunocompromised patients (those with a $CD4^+$ cell count <100 cells/mm^3), clinicians are faced with the dilemma of delaying HAART to avoid treatment-related complications and paradoxical reactions or risking death or morbidity from new AIDS-defining illnesses. This risk assessment, which is influenced by the level of immunosuppression and the likelihood of opportunistic infection, is difficult because there are no data on the rates of death and new AIDS-defining illnesses during the intensive and continuation phases of TB treatment

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in patients receiving HAART. We therefore compared the characteristics and outcome of patients coinfected with TB and HIV who were treated for TB before or during the HAART era (before or after 1 January 1996) and investigated the effect of HAART and other factors on the occurrence of death and new AIDS-defining illnesses.

PATIENTS AND METHODS

Study population. Patients who were coinfected with TB and HIV who had been treated and followed up at a London HIV clinic from 1 October 1988 to November 2001 were identified from the HIV clinic database. Their medical records were reviewed to provide information on TB treatment and adverse events. Additional information on demographic characteristics, antiretroviral therapy (ART), $CD4^+$ cell counts, AIDS diagnoses, and death was obtained from the HIV clinic database. This database is compiled by regular medical record reviews performed by a trained researcher.

Definitions. To be included in the study, patients had to fulfil the criteria for diagnosis of TB given below, have started TB treatment, and have the potential for at least 12 months of follow-up from the date of starting TB treatment (unless death occurred during that period).

For the diagnosis of TB, patients had to fulfil $\geqslant$1 of the following criteria: (1) culture positive test for *Mycobacterium tuberculosis* on sputum, bronchial washings, pleural fluid, or lymph node and bone-marrow aspirates; (2) organ biopsy evidence of TB (acid-fast bacilli with granuloma formation) from a lymph node, liver, bone, or brain; (3) a positive nucleic acid amplification test (strand displacement amplification; Becton Dickinson) for *M. tuberculosis* [12]; and, in the remaining patients, (4) a clinical diagnosis based on appropriate radiological evidence of TB after the exclusion of other causes by bronchoscopy or organ biopsy, with improvement seen during TB treatment and/or a positive smear result for acid-fast bacilli and/or a positive tuberculin skin test (Heaf grade 2–4). HAART use was defined as the use of a combination of $\geqslant$3 antiretroviral drugs.

Follow-up was for death and the occurrence of new (non-TB) AIDS-defining illnesses, and data are complete until March 2003. To ensure comparable follow-up for patients in different calendar periods, a maximum of 6 years of follow-up was used for each patient.

Statistical methods. Patients were categorized into 2 groups according to whether TB treatment was started before 1996 (group 1) or during or after 1996 (group 2). The 2 calendar periods broadly represent the pre-HAART and HAART eras. The groups were compared with respect to demographic factors, disease, and treatment characteristics by use of χ^2 and Mann-Whitney *U* tests and, with respect to the subsequent risk of total death and the occurrence of death or a new (non-TB) AIDS-defining illness, by use of the Kaplan-Meier method and the log-rank statistic. The time of the AIDS-defining illness was measured from the time of starting TB treatment; if the end point in question did not occur, the time of the AIDS-defining illness was censored at the date the patient was last seen or at 6 years. Cox proportional-hazards models were used to assess the effect of calendar period when TB treatment was started and other factors on the risk of each end point. The effect of HAART use during follow-up was examined by use of a time-updated variable that took the value 0 if the patient was either untreated or was receiving <3 antiretroviral drugs and the value 1 if the patient was receiving $\geqslant$3 antiretroviral drugs. In these models, all other factors were fixed at the baseline value. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was assessed by use of the likelihood-ratio statistic. Analyses were done by use of SAS software (version 8.02; SAS Institute).

RESULTS

Demographic and other baseline characteristics. A total of 101 patients fulfilled the criteria for TB/HIV coinfection, of whom 5 were excluded because of inadequate follow-up (within 6 months of starting TB treatment, 4 patients transferred their care to another center or country, and 1 patient was untraceable). Among the remaining 96 patients, a positive diagnosis of TB was based on culture or biopsy results for 66 patients and on amplification test results for 18 patients, and a "clinical" diagnosis was made for 12 patients. All patients had a compatible clinical and radiographic profile. Thirty-six patients started TB treatment before 1996 (group 1), and 60 started TB treatment during or after 1996 (group 2). Characteristics of the 2 groups are shown in table 1. Patients in group 2 were older, on average, and were more likely to be women, black African, and in the heterosexual risk group. At the time of starting TB treatment, patients in group 2 were more likely to be receiving ART and were much more likely to be receiving HAART than those in group 1.

Risk of death and new AIDS-defining illnesses. During a median of 3.6 years of follow-up (maximum, 6 years), there were 30 deaths (18 in group 1 and 12 in group 2) occurring at a median (range) of 1.8 (0.03–6.0) years from the start of TB treatment. In group 1, causes of death were 6 HIV-related opportunistic infections (OIs), 5 HIV-related malignancies, and 7 unknown causes; in group 2, causes of death were 4 HIV-related OIs, 3 HIV-related malignancies, 1 cardiovascular event, 2 hypothermias secondary to alcohol or drug use, and 2 unknown causes. Figure 1*A* shows the Kaplan-Meier estimates of cumulative survival according to calendar period of starting TB treatment. The risk of death was increased for patients who started TB treatment during the earlier, compared with the later,

Table 1. Characteristics at baseline in 96 patients with HIV-associated tuberculosis (TB), according to the date of starting TB treatment.

Characteristic	Group, start of TB treatment		P^a
	1, before 1996 (n = 36)	2, during or after 1996 (n = 60)	
Median date of starting TB treatment (range)	April 1994 (Oct 1988–Oct 1995)	September 1998 (Jan 1996–Nov 2000)	
Age, median (range), years	30.8 (23–59)	35.7 (24–62)	.004
Male sex	30 (83.3)	33 (55.0)	.005
Ethnicity			
White	17 (47.2)	16 (26.7)	.040
Black African	16 (44.4)	38 (63.3)	(white vs. other)
Other/unknown	3 (8.3)	6 (10.0)	
Risk group			
Homosexual	14 (38.9)	13 (21.7)	.069
Heterosexual	17 (47.2)	41 (68.3)	(Homosexual vs. other)
IDU	3 (8.3)	3 (5.0)	
Other/unknown	2 (5.6)	3 (5.0)	
$CD4^+$ cell count at time of starting TB treatment median (range), cells/mm^3	157 (0–670)	124 (6–1039)	.30
$CD4^+$ cell count, cells/mm^3			
<100	11 (30.6)	24 (40.0)	.35
100–199	4 (11.1)	17 (28.3)	(<100 vs. other)
⩾200	14 (38.9)	15 (25.0)	
Missing data	7 (19.4)	4 (6.7)	
Extrapulmonary TB	18 (50.0)	26 (43.3)	.53
Previous AIDS (non-TB)	10 (27.8)	16 (26.7)	.91
Rifabutin use	2 (5.9)	21 (35.0)	.001
New HIV diagnosis[b]	14 (38.9)	31 (51.7)	.22
No. of ART drugs at start of TB treatment			
0	29 (80.6)	42 (70.0)	.032
1 or 2	7 (19.4)	8 (13.3)	
⩾3	0	10 (16.7)	
Ever received ART	11 (30.6)	20 (33.3)	.78

NOTE. Data are no. (%) of patients, unless stated otherwise. ART, antiretroviral therapy; IDU, injection drug user.

[a] χ^2 or Mann-Whitney U test.

[b] Less than 2 months before starting TB treatment.

calendar period (P = .012, log rank test, group 1 vs. group 2). Cumulative death for groups 1 and 2, respectively, was 20% and 10% at year 1 and 43% and 22% at year 4.

During the follow-up period, a new AIDS-defining illness occurred among 23 and 20 patients in groups 1 and 2, respectively, at a median time (range) of 0.4 (range, 0.02–4.2) years from the start of TB treatment. In group 1, there were 8 cases of oesophageal candidiasis, 5 cases of *Pneumocystis jiroveci* pneumonia (PcP), 2 cases of Kaposi sarcoma (KS), and 8 other AIDS-defining illnesses (each with 1 occurrence). In group 2, there were 3 cases of oesophageal candidiasis, 3 cases of PcP, 2 cases of KS, 2 cases of infection with *Mycobacterium avium* complex, 3 cases of toxoplasmosis, 2 cases of cytomegalovirus infection, and 5 other AIDS-defining illnesses (each with 1 occurrence). By use of a combined end point of death or a new AIDS-defining illness, the numbers of AIDS-defining illnesses in groups 1 and 2, respectively, were 25 and 24. Figure 1*B* shows that the risk of a new AIDS-defining illness or death during the follow-up period was lower for those starting TB treatment during the later calendar period (P = .023, log rank test, group 1 vs. group 2). The cumulative risk of an AIDS-defining illness for groups 1 and 2, respectively, was 40% and 34% at year 1 and 69% and 43% at year 4.

Predictors of death and AIDS-defining illnesses. The risk of death during the follow-up period was reduced by 60% for group 2, compared with group 1 (HR, 0.40 [95% CI, 0.19–0.84]; P = .014). A low or missing baseline $CD4^+$ cell count tended to increase the risk of death (vs. $CD4^+$ cell counts ⩾200/mm^3: HR, 1.83 [95% CI, 0.56–6.02] for $CD4^+$ cell counts 100–199 cells/mm^3; HR, 2.87 [95% CI, 1.02–8.09] for $CD4^+$ cell counts <100 cells/mm^3; and HR, 3.42 [95% CI, 1.04–11.21] for missing $CD4^+$ cell counts; P = .10). A previous diagnosis of AIDS was also associated with a greatly increased risk of death (HR, 2.58 [95% CI, 1.24–5.32]; P = .014). There was no significant effect of age, sex, ethnicity, risk group, extrapulmonary TB, new HIV diagnosis, or previous ART on the risk of death.

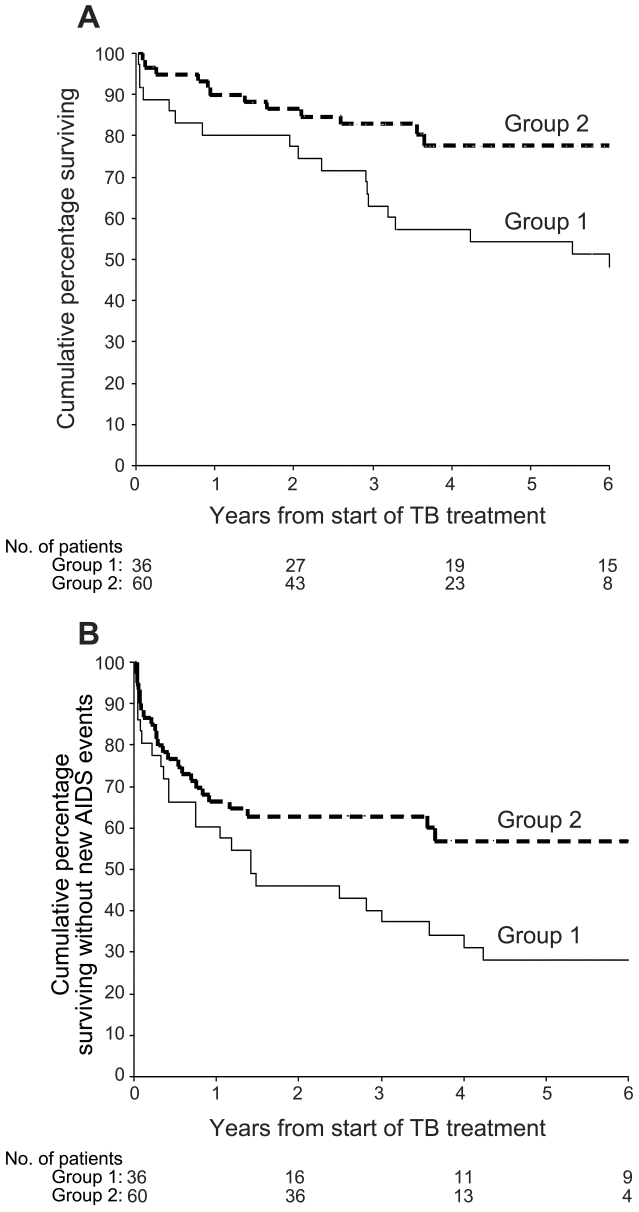

Figure 1. *A,* Kaplan-Meier curves comparing outcomes (total death) of patients coinfected with tuberculosis (TB) and HIV who started TB treatment before 1996 (group 1, *solid line,* $n = 36$, 18 deaths) and during or after January 1996 (group 2, *dashed line,* $n = 60$, 12 deaths). Nos. below the graph indicate the no. of patients at risk at the start of each year of follow-up. Log-rank test for comparison of survival curves, $P = .012$ (analysis was done by use of SAS version 8.02). *B,* Kaplan-Meier curves comparing outcomes (total death or new AIDS-defining illnesses) for patients coinfected with TB and HIV who started TB treatment before 1996 (group 1, *solid line,* $n = 36$, 25 events) and during or after January 1996 (group 2, *dashed line,* $n = 60$, 24 events). Nos. below the graph indicate the no. of patients at risk at the start of each year of follow-up. Log-rank test for comparison of survival curves, $P = .023$ (analysis was done by use of SAS version 8.02).

The associations of these factors with the occurrence of death or a new AIDS-defining illness were similar. Table 2 shows multivariable models for each end point. The association between calendar period and death was even stronger after adjustment for baseline $CD4^+$ cell count (adjusted HR, 0.28 [95% CI, 0.13, 0.63], group 2 vs. group 1). Previous diagnosis of AIDS and a low baseline $CD4^+$ cell count were also significant independent predictors of death. Calendar period (adjusted HR, 0.34 [95% CI, 0.18–0.63]) and low $CD4^+$ cell count were significant independent predictors of death or a new AIDS-defining illness.

Risk of AIDS-defining illness by follow-up period after starting TB treatment. Table 3 gives the rates of death or new AIDS-defining illnesses (per 100 person-years) by period of follow-up, according to calendar period of starting TB treatment and baseline $CD4^+$ cell count. The risk of an AIDS-defining illness was particularly high during the first 2 months after the start of TB treatment, after which time it decreased considerably ($P < .001$, for trend, Poisson regression). This trend was apparent within each subgroup. Throughout follow-up, the risk of an AIDS-defining illness tended to be higher for group 1 than for group 2 ($P = .027$) and for patients with a $CD4^+$ cell count <100 cells/mm^3 at baseline, compared with those with other or missing data on $CD4^+$ cell count ($P = .001$). Of the 15 patients who died or had an AIDS-defining illness during the first 2 months after starting TB treatment, 73% ($n = 11$) had a baseline $CD4^+$ cell count <100 cells/mm^3 (median, 50 cells/mm^3).

HAART and outcome. The number of patients who were receiving HAART at the time of starting TB treatment was 0 in group 1 and 10 in group 2 (table 1). Of the remaining 86 patients, 63 started HAART during follow-up: in groups 1 and 2, respectively, 0 and 14 during the first 2 months, 3 and 23 after 2 months but within 1 year, and 17 and 6 at least 1 year after starting TB treatment. HAART regimens were combinations of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 protease inhibitor ($n = 29$), combinations of 2 NRTIs and 1 nonnucleotide reverse-transcriptase inhibitor ($n = 16$), other 3-drug combinations ($n = 8$), or 4-drug combinations ($n = 12$). The most common NRTIs were zidovudine/lamivudine ($n = 26$) and stavudine/lamivudine ($n = 19$). Thirteen of 14 patients who started HAART during the first 2 months after the start of TB therapy had a baseline $CD4^+$ cell count <200 cells/mm^3.

The effect of HAART use (vs. mono- or dual therapy or no therapy) during follow-up was assessed directly by use of a time-updated variable in a model adjusting for baseline $CD4^+$ cell count group, previous diagnosis of AIDS, and calendar period of starting TB treatment (table 4). HAART use was associated with a marked decrease in the risk of death (adjusted HR, 0.18 [95% CI, 0.06–0.52]) and the risk of death or a new AIDS-defining illness (adjusted HR, 0.38 [95% CI, 0.16–0.91]).

Table 2. Independent associations of calendar period, CD4+ cell count, and AIDS-defining illness, with risk of death and previous diagnosis of AIDS in 96 HIV-infected patients with tuberculosis.

	Total death (n = 30 events)		Total death/new AIDS-defining illness (n = 49 events)	
Characteristic	AHR (95% CI)	P	AHR (95% CI)	P
Calendar period				
Before 1996	1		1	
During or after 1996	0.28 (0.13–0.63)	.002	0.34 (0.18–0.63)	.001
CD4+ cell count, cells/mm^3				
⩾200	1	.045	1	.002
100–199	2.79 (0.81–9.60)		1.96 (0.78–4.93)	
<100	4.28 (1.44–12.74)		4.38 (1.98–9.69)	
Missing	2.68 (0.81–8.89)		1.57 (0.61–4.07)	
Previous diagnosis of AIDS				
No	1		1	
Yes	2.27 (1.09–4.74)	.029	1.47 (0.80–2.70)	.22

NOTE. Statistical analysis was done by use of a Cox proportional-hazards model. AHR, adjusted hazard ratio; CI, confidence interval.

When HAART use was included in the models, the effect of calendar period was attenuated, although calendar period remained a significant independent predictor of death or a new AIDS-defining illness. The effect of HAART was virtually unchanged after the exclusion of the 12 patients who had a clinical diagnosis of TB only.

TB treatment, adverse events, and paradoxical reactions. The median duration of TB treatment was 35.4 weeks; 30 patients (18 in group 1 and 12 in group 2) were treated for >1 year. Rifabutin use was much more common in group 2 than in group 1 (35% vs. 6%). Adverse events that required the interruption of TB treatment occurred in 4 patients (11%) in group 1 and in 7 patients (12%) in group 2. Poor compliance was noted for 5 patients in group 1 and for 2 patients in group 2, whereas resistance to TB drugs was noted for 2 patients in group 1 and for 4 patients in group 2. There were 1 and 2 cases of relapse of TB in groups 1 and 2, respectively. Among the 40 patients who were receiving HAART during the first year after starting TB treatment, 6 patients stopped HAART during that time because of virologic failure ($n = 2$), adverse events ($n = 3$), and patient choice ($n = 1$).

Six patients (10%) in group 2 (25% of patients with a CD4+ cell count <100 cells/mm^3 in this group) and 0 in group 1 had paradoxical reactions (defined as the worsening of existing disease or the development of new lesions while receiving treatment) that were deemed severe enough to warrant steroid therapy. Patients had ⩾1 of the following clinical features: 4 patients had new or expanding lymph nodes, 2 had enlarging intracranial tuberculomas, 2 had persistent pyrexia, 1 had worsening pulmonary infiltrates, and 1 had serositis. In all cases, the reactions occurred within 15–30 days of starting HAART. The median baseline CD4+ cell count was 40 cells/mm^3 (range, 24–75 cells/mm^3).

DISCUSSION

In the present study, we have reported outcomes in patients coinfected with TB and HIV who were treated before and during the HAART era. When the effect of HAART was examined directly, it was found to be associated with marked reductions in the risks of death and new AIDS-defining illnesses during a median follow-up period of 3.6 years. Although complications of treatment—such as drug interactions, drug toxicity, and paradoxical reactions—did arise, they did not translate into compromised survival for coinfected patients receiving HAART. A history of AIDS and a low CD4+ cell count were also independently associated with the risk of death and new AIDS-defining illnesses. Two previous reports studied the effect of HAART on outcome in coinfected patients [8, 9]. One of these evaluated fatal outcome only. In the other study, the risk of an AIDS-defining illness was compared between patients who had received HAART and those who had not. However, that analysis may be subject to bias because survivors had a greater chance of receiving HAART than did those who died early during follow-up. To account for this, we assessed the effect of HAART on the risk of an AIDS-defining illness by use of a time-updated variable in a Cox regression model.

The most noteworthy finding of the present study was the high rate of death and new AIDS-defining illnesses within the first 2 months of TB treatment and a decline thereafter, particularly in patients with a CD4+ cell count <100 cells/mm^3. Rates of AIDS-defining illnesses in this group were exception-

Table 3. Rates of new AIDS-defining illness or death, by follow-up period according to calendar period of starting tuberculosis (TB) treatment and baseline CD4+ cell count.

Time since starting TB treatment	Group, calendar period of starting TB treatment		$CD4^+$ cell count at baseline, cells/mm^3	
	1, before 1996 (n = 36)	2, during or after 1996 (n = 60)	⩾100 or missing (n = 61)	<100 (n = 35)
0–1.99 months	138.8 (7)	88.3 (8)	41.3 (4)	248.6 (11)
2 months–0.99 years	35.6 (7)	32.6 (12)	26.3 (11)	54.9 (8)
1–6 years	17.5 (11)	3.6 (4)	8.3 (12)	10.3 (3)
Total, 0–6 years	28.5 (25)	15.4 (24)	13.8 (27)	45.6 (22)

NOTE. Data are rate/100 person-years (no. of events). The risk of an AIDS-defining illness was greater in patients with a baseline $CD4^+$ cell count <100 cells/mm^3 than in those with a baseline $CD4^+$ cell count >100 cells/mm^3 or with missing data (P = .001) and in group 1 vs. group 2 (P = .027), and the risk decreased over time since the start of TB treatment (P < .001 for trend, Poisson regression). Comparative rates of AIDS-defining illnesses per 100 person-years for all HIV-positive patients at our center were ~35 before 1996 and 5 during or after 1996.

ally high, at least 10-fold higher than the overall rate for all HIV-infected patients at our center (F.C.L., M.A.J., C. Loveday, et al., unpublished data). In most patients who died, death was due to HIV-related causes rather than to TB itself. Rates of death and new AIDS-defining illnesses during the intensive and continuous phases of TB treatment have not previously been reported for patients receiving HAART. Although, in the present study, rates of AIDS-defining illnesses were lower among patients who started TB treatment during the HAART era than among those who started treatment earlier, the initial risk was very high, even in the HAART group. This may be because a minority of patients who started HAART did so within the first 2 months, and the initial $CD4^+$ cell immunological response to HAART may take place over the course of 4–8 weeks [13]. Nevertheless, HAART use appeared to reduce the risk of an AIDS-defining illness throughout the follow-up period.

Despite the improved survival associated with HAART, paradoxical reactions that were deemed severe enough to warrant steroid treatment occurred in 25% of the patients in the HAART group who had a $CD4^+$ cell count <100 cells/mm^3. Consistent with other published data [6], these were patients with advanced immunosuppression who had reactions shortly after starting HAART. Some clinicians have suggested that, even at low $CD4^+$ cell counts, HAART should be withheld until the

Table 4. Association of highly active antiretroviral therapy (HAART) use during follow-up and other factors with risk of death and new diagnosis of AIDS in 96 HIV-infected patients with tuberculosis.

Characteristic	Total death (n = 30)		Total death/new AIDS-defining illnesses (n = 49)	
	AHR (95% CI)	P	AHR (95% CI)	P
$CD4^+$ cell count, cells/mm^3				
⩾200	1	.044	1	.003
100–199	3.29 (0.93–11.57)		2.37 (0.87–6.48)	
<100	4.98 (1.64–15.13)		5.30 (2.09–13.45)	
Missing data	2.38 (0.72–7.89)		1.49 (0.54–4.16)	
Previous diagnosis of AIDS				
No	1		1	
Yes	2.56 (1.21–5.44)	.014	1.78 (0.93–3.40)	.083
Calendar period				
Before 1996	1		1	
During or after 1996	0.51 (0.22–1.19)	.12	0.42 (0.21–0.84)	.015
No. of ART drugs (time updated)[a]				
<3	1		1	
⩾3	0.18 (0.06–0.52)	.002	0.38 (0.16–0.91)	.029

NOTE. Statistical analysis was done by use of a Cox proportional-hazards model with HAART use as the time-updated variable. AHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval.

[a] Baseline value updated with the latest value during follow-up.

completion of the intensive phase of TB treatment, to reduce both the severity of paradoxical reactions and the pill burden [5]. However, our data suggest that the deferment of HAART in this subgroup is at the expense of a significant risk of death and new AIDS-defining illnesses during this early period.

Although the start of HAART may precipitate paradoxical reactions [6], it is also possible that TB itself may exert an immunosuppressive effect that is reduced with progressive antimycobacterial treatment. Hence, TB treatment could contribute to immune reconstitution and a delayed inflammatory response to TB or other occult infections [14]. However, the lower rates of AIDS-defining illnesses in group 2 at all stages of TB treatment suggest that the net effect of HAART is a reduction of the risk of OI and death in coinfected patients.

The obvious limitations of a retrospective study like ours are bias generated by the exclusion of patients who were transferred to other centers, missing data, variability in the prescribing habits of clinic doctors, and the possibility that we may not have identified all coinfected patients, despite our best efforts. It is also possible that some patients may have died before HIV testing. However, death in patients in group 1 (15% at 6 months and 20% at 12 months) was consistent with the results of prospective studies that have reported survival data in coinfected patients [15, 16]. The lack of prospective designed studies in coinfected patients receiving HAART may reflect the difficulty in obtaining sufficient numbers of case subjects to have adequate power to identify the optimal time and $CD4^+$ cell count at which HAART should be introduced.

To ensure that our cohort was representative of day-to-day practice, we used a broader diagnostic definition of TB by including patients with a clinical diagnosis of TB. Because approximately one-third of patients coinfected with TB and HIV who complete a course of TB therapy turn out to be culture negative [17], limiting analyses to culture-positive TB [8, 9] may bias the study findings. It might be argued that our broader inclusion criteria may overdiagnose TB. However, our survival outcomes were similar when patients with a clinical diagnosis of TB were excluded from our analysis. The difference in demographic characteristics between the 2 groups of coinfected patients in our study reflects the increased entry of immigrants and refugees to the United Kingdom in recent years from countries where TB is endemic.

In conclusion, our data suggest that the use of HAART in patients coinfected with TB and HIV results in a substantial reduction in the immediate and long-term risk of death and the development of new AIDS-defining illnesses. Coinfected patients with a $CD4^+$ cell count <100 cells/mm^3 are at particularly high risk of death or new AIDS-defining illnesses during the early phase of TB treatment. However, it is this very group, which is at significant risk for immune reconstitution, that should be closely monitored for paradoxical reactions if HAART is begun concurrently with TB treatment. Our findings based on retrospective observational data require confirmation in prospective studies.

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