Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study

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Summary

Background Studies of the effect of highly active antiretroviral therapy (HAART) on the risk of HIV-1-associated tuberculosis have had variable results. We set out to determine the effect of HAART on the risk of tuberculosis in South Africa.

Methods We compared the risk of tuberculosis in 264 patients who received HAART in phase III clinical trials and a prospective cohort of 770 non-HAART patients who were attending Somerset Hospital adult HIV clinic, University of Cape Town, between 1992 and 2001. Poisson regression models were fitted to determine risk of tuberculosis; patients were stratified by CD4 count, WHO clinical stage, and socioeconomic status.

Findings HAART was associated with a lower incidence of tuberculosis (2·4 *vs* 9·7 cases per 100 patient-years, adjusted rate ratio 0·19 [95% CI 0·09–0·38]; p<0·0001). This finding was apparent across all strata of socioeconomic status, baseline WHO stage, and CD4 count, except in patients with CD4 counts of more than 350 cells/μL. The number of tuberculosis cases averted by HAART was greatest in patients with WHO stage 3 or 4 (18·8 averted cases per 100 patient-years, adjusted rate ratio 0·22 [0·09–0·41]; p=0·03) and in those with CD4 counts of less than 200 cells/μL (14·2 averted cases per 100 patient-years, adjusted rate ratio 0·18 [0·07–0·47]; p<0·0001).

Interpretation HAART reduced the incidence of HIV-1-associated tuberculosis by more than 80% (95% CI 62–91) in an area endemic with tuberculosis and HIV-1. The protective effect of HAART was greatest in symptomatic patients and those with advanced immune suppression.

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Introduction

More than 70% of the 36·1 million HIV-1-infected individuals worldwide live in sub-Saharan Africa, and a high proportion of these are co-infected with tuberculosis.[1,2] An accelerated course of HIV-1 infection after the onset of tuberculosis has been reported in many studies.[3–6]

Tuberculosis is the leading cause of morbidity and mortality among HIV-1-infected patients in sub-Saharan Africa.[7–9] Unlike other HIV-1-related opportunistic infections, tuberculosis occurs at all levels of CD4 count,[9–11] is infectious, and its prevention is a major public-health priority.

Tuberculosis control programmes based on passive case finding and treatment of sputum-smear-positive disease by short-courses of directly observed chemotherapy (DOTS) have been successful in developed countries. However, these strategies have failed to achieve similar success in countries with high burdens of HIV-1 infection.[12,13] Consequently, WHO has formulated a strategic framework aimed at functional integration of control programmes for tuberculosis and HIV/AIDS.[14]

The survival benefits associated with highly active antiretroviral therapy (HAART) are well documented; however, studies assessing the effect of HAART on tuberculosis have shown variable results. Although some studies have shown that HAART can reduce the risk of tuberculosis by more than 80%,[15–17] others have reported no significant reduction.[18,19] No similar studies have been done in sub-Saharan Africa because only a tiny minority of the population presently has access to HAART. The UN has mobilised the Great Global Alliance to facilitate increased access to antiretroviral therapy in resource-limited settings.[20]

We did an observational study to compare the risk of tuberculosis in indigent cohorts of HIV-1-infected patients without access to HAART and in those receiving this treatment through participation in phase III randomised trials at a public health-care facility in Cape Town, South Africa.

Methods

Patients

New Somerset Hospital HIV Clinic, University of Cape Town, South Africa, is a major public health-care facility dedicated to HIV-1-infected patients in Cape Town. It was established in 1986, and serves largely indigent patients who are referred to the clinic from a wide range of primary health-care facilities in Cape Town. Antiretroviral therapy is not available in the public sector in South Africa, and patients access HAART through participation in clinical trials. Patients who expressed interest in joining the ongoing HAART clinical trials at the hospital were invited to participate on a first-come first-served basis. The desired sample

	HAART (n=264)	Non-HAART (n=770)	p
Mean (SD) age (years)	34·5 (9)	32·9 (9)	0·51
Number of women	115 (44%)	497 (65%)	<0·0001
Number with WHO stage 3 or 4	122 (46%)	227 (29%)	<0·0001
CD4 T-lymphocyte count (cells/μL)			
Median (IQR)	254 (140–364)	303 (159–468)	0·01*
<200	102 (38%)	233 (32%)	0·08
200–350	90 (35%)	189 (26%)	0·01
>350	72 (27%)	310 (42%)	<0·0001
NA	..	38 (5%)	..
Mean viral load (log_{10} [copies/μL])		5·4	NA
Number with low socio-economic status	120 (46%)	454 (59%)	0·0003

HAART=highly active antiretroviral therapy. NA=not available. *Median test.

Table 1: **Baseline demographic and clinical characteristics**

sizes were achieved in all the clinical trials. All studies were fully recruited. Participants gave informed consent, and protocols were approved by the University of Cape Town Clinical Research Ethics Committee.

Inclusion criteria common to all 12 HAART clinical trials carried out between 1995 and 2001, from which the treated cohort of this study was accrued, were: age at least 16 years; a minimum baseline plasma HIV-1 RNA concentration of 1000–5000 copies/mL (5000–30 000 copies/mL range in one study); and a CD4 count of more than 50 cells/μL (one trial), more than 100 cells/μL (three trials), more than 200 cells/μL (two trials), less than 200 cells/μL (one trial), and less than 350 cells/μL (one trial). The remaining four had no CD4 restrictions. Exclusion criteria were: acute opportunistic infection, significant laboratory abnormalities, current evidence of active substance abuse, pregnancy or lactation, and treatment with immune-modulating or systemic chemotherapeutic agents. All patients received at least three antiretroviral drugs: a non-nucleoside reverse transcriptase inhibitor with two nucleoside analogues, three nucleoside analogues, or a protease inhibitor with two nucleoside analogues. Follow-up was every 2–3 months, or more frequently if clinically indicated. At each visit, the attending health-care personnel recorded clinical, immunological, and virological information.

Patients who presented to the clinic between 1992 and 2000, and who were not participating in the clinical trials, were included in the study as a comparison group. In this cohort, patients were followed up every 3–6 months, or more frequently if clinically indicated. CD4 count was measured about every 6 months by flow cytometry. Owing to resource constraints, viral-load measurements were not available in public health-care facilities, and therefore were not analysed in this group. HIV-1 infection was confirmed by ELISA or western blot on two blood specimens. At each visit, the patient's disease was staged by use of WHO clinical criteria,[21] and laboratory data were recorded. Patients who were taking antiretroviral monotherapy or dual therapy were excluded from this study.

To account for variability in socioeconomic circumstances in the two cohorts, the Cape Metropolitan Council suburbs composite index was used.[22] This index is based on household income (proportion of households earning less than US$1500 per year), education level (proportion of adults with less than 8 years of schooling), unemployment status (unemployed adults who are actively seeking work as a proportion of all adults), welfare status (proportion of household heads who are single women with three or more children), and overcrowding status (households with more than 1·5 people per habitable room). In this composite index, a score of more than 28·5 correlated well (r=0·7) with poor living conditions,[22] and therefore patients were categorised into low or high socioeconomic status by means of this cut-off.

Further uniform exclusion criteria were applied to both cohorts. Patients were excluded if they presented with tuberculosis at their initial clinic visit, if the diagnosis of tuberculosis did not fulfil the case definition, or if they had used prophylactic isoniazid 6 months before presentation or at any time during follow-up. The tuberculosis case definition in this study was either "definite" (culture of *Mycobacterium tuberculosis* or an autopsy diagnosis of active tuberculosis) or "probable" (presence of acid-fast bacilli or a histological finding of caseating granulomata).

Statistical analysis

Differences in proportions were compared by χ^2 test, and differences in means by Student's t test. Time to tuberculosis was calculated as the time from the initial clinic visit to the date of confirmed diagnosis. Tuberculosis incidence was defined as the number of new episodes occurring in each group per 100 patient-years of follow-up. The analysis was further stratified by the baseline CD4 count, WHO clinical stage, and socioeconomic status. Number of tuberculosis cases averted by HAART was calculated with the adjusted rate ratio estimates of the Poisson multivariate regression analyses described later, and was reported with 95% CI (calculated by Poisson distribution). The choice of Poisson regression was based on the small frequency of tuberculosis events in the HAART cohort. All tests were two-sided and a p value of 0·05 was regarded as significant.

	HAART			Non-HAART			Adjusted risk ratio (95%CI)	p	Adjusted number of cases averted (95% CI)
	Number of cases of tuberculosis	Patient-years	Incidence*	Number of cases of tuberculosis	Patient-years	Incidence*			
Overall	9	375·1	2·4	82	848·2	9·7	0·19 (0·09–0·38)	<0·0001	7·3 (4·7–9·8)
CD4 count (cells/μL)									
<200	5	148	3·4	41	235	17·5	0·18 (0·07–0·47)	<0·0001	14·2 (9·7–19·7)
200–350	2	121·2	1·7	27	225	12·0	0·12 (0·03–0·53)	<0·0001	10·6 (6·8–15·9)
>350	2	100·1	2·0	14	388·3	3·6	0·36 (0·1–1·74)	0·78	2·3 (1·1–4·4)
WHO stage									
1 or 2	1	219	0·5	36	657·4	5·5	0·08 (0·01–0·57)	0·01	5·1 (3·45–7·1)
3 or 4	8	172·75	4·6	46	190·8	24·1	0·22 (0·09–0·41)	0·03	18·8 (13·2–26·1)
Socioeconomic status									
Low	6	166·21	3·6	65	514·34	10·9	0·21 (0·09–0·49)	<0·0001	8·6 (6·2–11·5)
High	3	208·89	1·44	17	333·86	5·09	0·17 (0·05–0·57)	<0·0001	4·2 (2·3–7·0)

HAART=highly active antiretroviral therapy. *Per 100 patient-years.

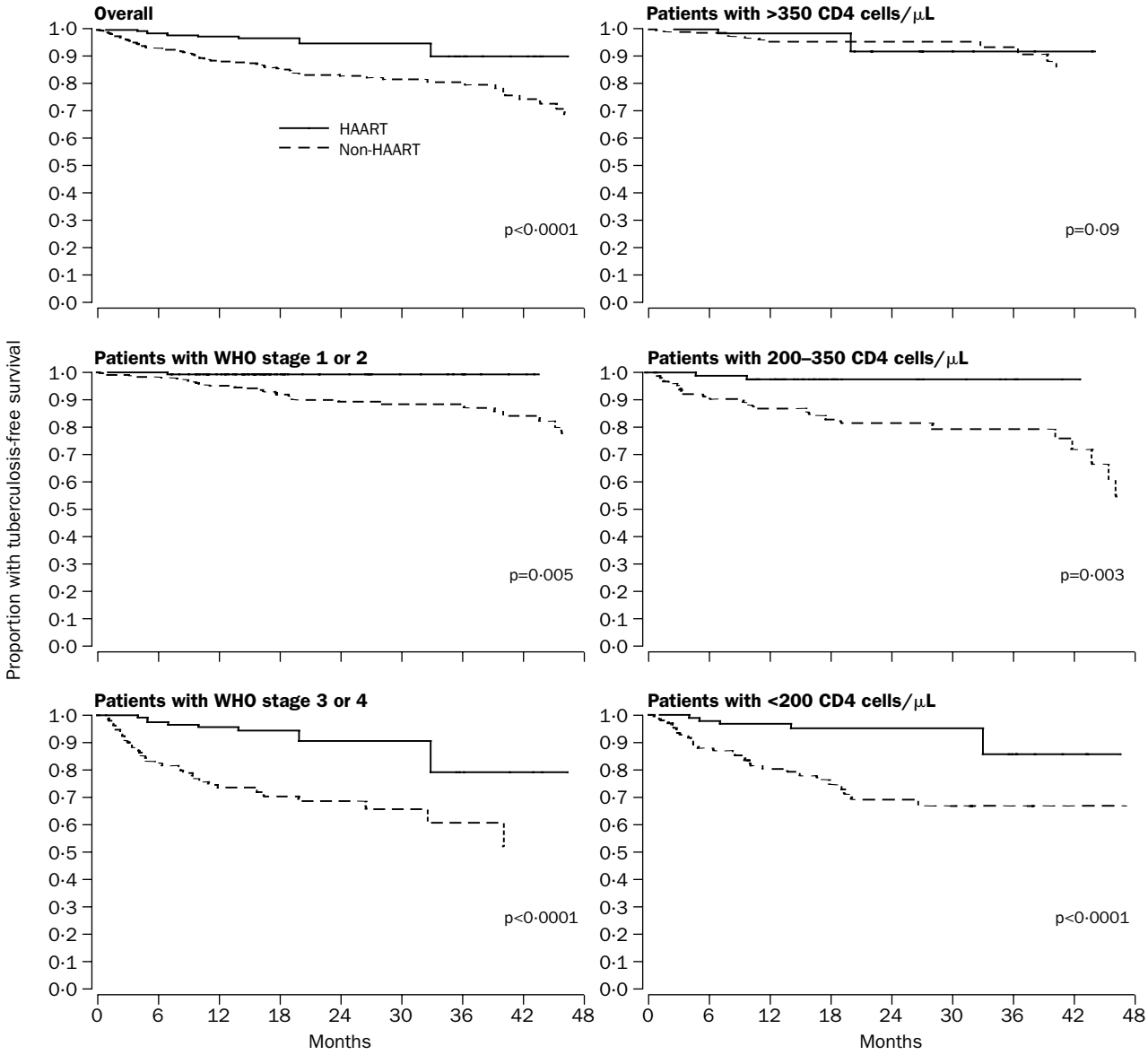
Table 2: **Tuberculosis incidence and cases averted, stratified by baseline CD4 count, WHO stage, and socioeconomic status**

The Kaplan-Meier technique and the generalised log-rank test were used to construct and compare the tuberculosis-free survival probabilities curves of the two groups. Tuberculosis-free survival was defined as the time from inclusion to the date of tuberculosis diagnosis, to death from any cause, or to the last follow-up visit. Patients who were switched over from the non-HAART to the HAART cohort contributed survival time to both cohorts: for the non-HAART cohort from their initial clinic visit to the date they started HAART, and to the HAART cohort from date of starting HAART until the date of tuberculosis diagnosis, death, or the last follow-up visit. To compare survival in the two cohorts by baseline immunological and clinical status, the Kaplan-Meier analysis was further stratified by baseline CD4 count (<200, 200–350, and >350 cells/μL) and WHO clinical stage (1 or 2, 3 or 4).

Univariate and multivariate Poisson regression models were fitted to determine risk of tuberculosis, which was expressed as a rate ratio. Sex, socioeconomic status, baseline age, year of presentation, CD4 count, and clinical WHO stage were considered for inclusion into the multivariate analysis as potential confounding variables if they were significantly associated with the risk of tuberculosis in the univariate analyses. Age was modelled as a categorical variable (less or greater than the mean age of the patient's cohort). Female sex and WHO stage 1 or 2 were modelled as baseline risk for sex and clinical WHO stage. To validate our results, we did further analyses on the subsets of patients with baseline WHO stage 1 or 2, and stage 3 or 4 separately. CD4 count was tested for normality using the Shapiro-Wilks' *W* test and was later log-transformed when found to be non-normally distributed. EpiInfo (version 6.0; CDC, Atlanta, GA, USA), STATISTICA (release 6.6, Tulsa, KA, USA), and STATA (version 6.0, College Station, TX, USA) software were used for data analysis.

Role of the funding source

The funding source had no role in the data collection, analysis, or interpretation, or the decision to submit the study for publication.



Kaplan-Meier probabilities of tuberculosis-free survival

	Rate ratio (95% CI)			
	Univariate analysis	p	Multivariate analysis	p
General cohort				
HAART	0·25 (0·13–0·50)	0·0001	0·19 (0·09–0·38)	<0·0001
CD4 count (log_{10} baseline)	0·45 (0·11–0·62)	<0·0001	0·67 (0·47–0·99)	0·03
WHO stage (3 or 4)	3·48 (1·17–5·29)	<0·0001	4·28 (2·64–6·95)	<0·0001
Low socioeconomic status	1·67 (1·02–2·59)	0·02	1·59 (1·01–2·50)	<0·0001
WHO stage 1 and 2				
HAART	0·10 (0·01–0·74)	0·02	0·07 (0·009–0·55)	0·01
CD4 count (log_{10} baseline)	0·28 (0·13–0·59)	0·001	0·18 (0·08–0·43)	<0·0001
Low socioeconomic status	1·56 (0·77–3·16)	0·22	1·39 (0·69–2·84)	0·35
WHO stage 3 and 4				
HAART	0·19 (0·09–0·42)	<0·0001	0·21 (0·10–0·46)	0·039
CD4 count (log_{10} baseline)	0·89 (0·56–1·45)	0·66	0·89 (0·57–1·42)	0·65
Low socioeconomic status	2·17 (1·23–3·81)	0·008	1·83 (1·03–3·24)	0·03

HAART=highly active antiretroviral therapy.

Table 3: **Poisson regression analyses for predictors of tuberculosis**

Results

1085 patients in the non-HAART cohort and 270 patients in the HAART cohort were studied. 315 patients were excluded from the non-HAART cohort: 79 were on antiretroviral monotherapy or dual therapy, isoniazid prophylaxis, or both; 222 presented with tuberculosis at their initial clinic visit; and 14 incident cases received tuberculosis chemotherapy but did not meet the tuberculosis case definition. The remaining 770 patients were included in the analysis. Of the 270 patients recruited in the HAART trials, two patients who presented with tuberculosis at their initial clinic visit, and four who started tuberculosis chemotherapy but did not meet tuberculosis case definition were excluded from the study. The remaining 264 patients included in the analysis received HAART. 40 patients who started off in the non-HAART cohort switched to the HAART cohort.

The baseline demographic and clinical characteristics of both cohorts are shown in table 1. Mean age in the two groups did not differ significantly, but the proportion of women in the non-HAART cohort was significantly higher than in HAART cohort, probably due to the systematic exclusion of pregnant or lactating women in the HAART cohort. At baseline, the HAART cohort had more clinical advanced HIV-1 disease and lower CD4 counts than the non-HAART cohort. Baseline CD4 count was not available for 38 patients in the non-HAART cohort.

Mean follow-up in the HAART cohort was significantly greater than in the non-HAART cohort (16·8 months [SD 8·3] *vs* 13·2 months [15·5]). During follow-up, nine cases of tuberculosis (four probable and five definite) were reported in the HAART cohort compared with 82 cases (48 probable and 34 definite) in the non-HAART cohort (unadjusted rate ratio 0·15 [95% CI 0·08–0·32]; p<0·0001, table 2). The rate ratio remained significant when patients were stratified by baseline WHO stage or CD4 count, except in the stratum of patients with CD4 count of more than 350 cells/μL. The greatest number of tuberculosis cases averted by HAART was in the subset of patients with baseline WHO stage 3 or 4 (table 2).

A similar trend to that reported in the above stratified incidence analysis was seen in the tuberculosis-free survival proportions in the stratified Kaplan-Meier analysis of the two cohorts shown in the figure. Overall median tuberculosis-free survival in the HAART cohort was significantly greater than that of the non-HAART cohort, and across all strata of WHO stages and CD4 counts, but not in the stratum of more than 350 CD4 cells/μL.

We did a separate analysis to ascertain the outcome of the 38 patients with missing baseline CD4 count in the non-HAART group. The proportion of tuberculosis cases occurring in this group (five of 38 [13%]) was not significantly different from that of patients in the non-HAART cohort for whom baseline values were available (82 of 770 [11%]; p=0·8). Tuberculosis-free survival was also similar in the two groups (p=0·42).

Poisson multivariate regression analysis revealed that, after controlling simultaneously for baseline differences, HAART conferred an independent protective benefit against risk of tuberculosis (table 3). Other predictors of tuberculosis were WHO stage 3 or 4, low socioeconomic status, and baseline CD4 count (table 3). In the univariate analyses, sex (female, rate ratio 1·45 [95% CI 0·93–2·28]; p=0·07) and age (greater or less than mean age, 0·78 [0·51–1·20]; p=0·09), and year of presentation (0·99 [0·91–1·08]; p=0·87) were not significantly associated with the risk of tuberculosis and were thus not included in the multivariate analysis.

In a separate subset, an independent and consistent protective benefit of HAART was seen in multivariate analyses of patients with baseline WHO stage 1 or 2 or stage 3 or 4 (table 3). The adjusted risk of tuberculosis associated with CD4 count (log_{10} baseline) was significant in the multivariate analysis of patients with baseline WHO stage 1 or 2, but not in patients with baseline WHO stage 3 or 4. Conversely, low socioeconomic status was associated with increased risk of tuberculosis in the subset analysis of WHO stage 3 or 4 but not of WHO stage 1 or 2 (table 3).

Discussion

We have shown a substantial reduction in tuberculosis incidence attributable to HAART in HIV-1-infected individuals in sub-Saharan Africa. This study differs from previous reports because the high frequency of tuberculosis in our cohort allowed quantification of the protective effect of HAART at the different stages of HIV-1 disease. The effect of HAART was significant across all the baseline immunological, clinical, and socioeconomic variables in our cohort, except in patients with CD4 counts of more than 350 cells/μL. The greatest number of tuberculosis cases averted by HAART was in patients with baseline WHO clinical stage 3 or 4 and those with CD4 counts of less than 200 cells/μL.

The overall tuberculosis risk reduction estimate of 81% (95% CI 62–91) associated with use of HAART in this study is similar to that reported in two studies from the USA and Italy (80% and 92%, respectively).[16,17] Brodt and colleagues[18] found no significant tuberculosis

reduction during a 5-year period in which HAART use in a German cohort increased from 5·7% to 87·3%. Moreover, although there was a tendency towards a lower risk of tuberculosis with HAART use in a study by Santoro-Lopes and colleagues from Brazil,[19] the adjusted estimate was not significant. However, only 41 individuals received HAART in that study.

The number of tuberculosis cases averted is a function of both risk reduction due to HAART and tuberculosis incidence. The overall tuberculosis incidences in the studies from the USA and Italy were low (0·5 and 0·79 per 100 patient-years, respectively);[16,17] rates were higher in the studies by Brodt and colleagues (2·1 per 100 patient-years)[18] and Santoro-Lopes and colleagues (8·4 per 100 patient-years)[19] because only patients with advanced HIV-1 disease (CD4 counts <200 cells/μL and <15%, respectively) were enrolled. Although the overall tuberculosis incidence in our study was 7·4 per 100 patient-years, patients with CD4 counts of less than 200 cells/μL had a tuberculosis incidence of 12 per 100 patient-years, which is a substantially higher rate than those reported in these studies.

Owing to current international funding initiatives and decreasing cost, access to HAART is expected to increase in resource-constrained countries. Our results are of particular relevance to the recently proposed WHO guidelines for the scaling up of antiretroviral therapy in resource-limited settings. These guidelines recommend starting antiretroviral therapy in adult and adolescent HIV-1-infected patients with WHO stage 4 disease or a CD4 count of 200 cells or fewer per μL.[20] In the light of these recommendations, our analyses suggest that starting HAART in these two groups will result in prevention of 14–20 cases of tuberculosis per 100 patient-years of treatment. However, tuberculosis incidence remained high in these groups and in individuals with CD4 counts of between 200 and 350 cells/μL, despite the substantial numbers of tuberculosis cases averted by HAART.

Initiation of HAART in patients with CD4 counts of less than 350 cells/μL will have large cost implications, particularly in resource-constrained settings. Therefore, tuberculosis preventive therapy, which has been reported to reduce the risk of tuberculosis in HIV-1-infected patients with a tuberculin-positive skin test (PPD) by more than 40%,[23,24] might be a more attractive alternative for reducing risk of tuberculosis in patients with CD4 counts between 200 and 350 cells/μL.

In multivariate analysis, low socioeconomic status was independently associated with increased risk of tuberculosis in the general cohort and in patients with baseline WHO stage 3 or 4, but not in those with baseline WHO stage 1 or 2. 56% of our cohort were socially deprived and lived in areas characterised by high rates of tuberculosis infection and poor living conditions. These factors, compounded with advanced HIV-1 disease, resulted in extremely high tuberculosis rates.

Our study has some limitations. Tuberculosis prophylaxis of PPD-positive individuals was not part of the national tuberculosis control programme during the study period, and PPD test results were not available in our cohort. Latent tuberculosis infection is, however, prevalent in our local population. In more than 900 antiretroviral-therapy-naive patients with confirmed HIV-1 infection at a voluntary counselling centre in Cape Town, PPD positivity was 55%.[25] We have adjusted in our multivariate analysis for factors known to be associated with overt tuberculosis disease in our setting.[26]

The observational design of our study is a further limitation, but because of the recognised survival benefits of HAART, a randomised placebo-controlled trial in patients with advanced HIV-1-disease at high risk of tuberculosis would not be ethically justifiable. The two cohorts in our study were largely self-selected and the HAART cohort was under trial-determined conditions with fairly intense follow-up that might lead to greater opportunity to diagnose tuberculosis. Unmeasured factors such as viral load, which was not available for the non-HAART cohort, could account for some of the higher tuberculosis incidence in this group. The two cohorts were not strictly contemporaneous, but year of presentation was not a significant factor for the risk of tuberculosis in our analysis. Data on baseline CD4 count were not available for 38 patients in the non-HAART cohort. However, survival and tuberculosis incidence in this group was not different from that of patients in whom baseline CD4 counts were available. The median follow-up in our cohort was limited; however, the number of tuberculosis events was higher than that reported in all previous studies.

In conclusion, our study has quantified the added benefit of tuberculosis reduction that would result from expanded access to HAART, as proposed by WHO, in a setting of high tuberculosis and HIV-1 prevalence. The decrease in tuberculosis incidence with HAART was substantial, but immune-compromised and symptomatic individuals were still at unacceptably high risk of developing active tuberculosis. Tuberculosis preventive therapy remains an important strategy for patients with early HIV-1 disease. However, because social deprivation was shown to be a significant risk factor for tuberculosis in this group, medical interventions cannot be separated from the need for social improvement. Our findings suggest that HIV-1 control is required for effective tuberculosis control, and that HAART can have a critical role in addressing the therapeutic nihilism surrounding the HIV-1 and tuberculosis co-epidemic in South Africa and other African countries.

Contributors

All authors contributed to conceptualisation, design, data collection, and revision of the final draft of the study, which was written by M Badri. R Wood contributed to the design of the statistical analysis. M Badri designed and carried out the statistical analysis.

Conflict of interest statement

None declared.

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