Outcomes of tuberculosis patients who start antiretroviral therapy under routine programme conditions in Malawi

S. D. Makombe,* A. D. Harries,*†‡ J. K-L. Yu,§ M. Hochgesang,¶ E. Mhango,# R. Weigel,#
O. Pasulani,**†† M. Fitzgerald,**†† E. J. Schouten,‡‡§§ E. Libamba*

* Clinical HIV Unit, Ministry of Health, Lilongwe, † Family Health International, Malawi Country Office, Lilongwe, Malawi; ‡ London School of Hygiene and Tropical Medicine, London, UK; § Taiwan Medical Mission, Mzuzu Central Hospital, Mzuzu, ¶ US Centres for Disease Control and Prevention, Malawi Office, Lilongwe, # Lighthouse Clinic, Lilongwe, Malawi; ** Médecins sans Frontieres, Brussels, Belgium; †† Thyolo District Hospital, Thyolo, ‡‡ Ministry of Health, Lilongwe, §§ Management Sciences for Health, Lilongwe, Malawi

_____ S U M M A R Y

SETTING: Public sector facilities in Malawi providing antiretroviral therapy (ART) to human immunodeficiency virus (HIV) positive patients, including those with tuberculosis (TB).

OBJECTIVES: To compare 6-month and 12-month cohort treatment outcomes of HIV-positive TB patients and HIV-positive non-TB patients treated with ART.

DESIGN: Retrospective data collection using ART patient master cards and ART patient registers.

RESULTS: Between July and September 2005, 7905 patients started ART, 6967 with a non-TB diagnosis and 938 with a diagnosis of active TB. 6-month cohort outcomes of non-TB and TB patients censored on 31 March 2006 showed significantly more TB patients alive and on ART (77%) compared with non-TB patients (71%)

($P < 0.001$). Between January and March 2005, 4580 patients started ART, 4179 with a non-TB diagnosis and 401 with a diagnosis of active TB. 12-month cohort outcomes of non-TB and TB patients censored on 31 March 2006 showed significantly more TB patients alive and on ART (74%) compared with non-TB patients (66%) ($P < 0.001$). Other outcomes of default and transfer out were also significantly less frequent in TB compared with non-TB patients.

CONCLUSION: HIV-positive TB patients on ART in Malawi have generally good treatment outcomes, and more patients need to access this HIV treatment.

KEY WORDS: tuberculosis; antiretroviral therapy; treatment outcomes; Malawi

WITH THE START of the World Health Organization's (WHO's) '3 by 5' initiative, many resource-poor countries have started scaling up antiretroviral therapy (ART) for their human immunodeficiency virus (HIV) infected communities. Although the target was not reached in 2005, excellent progress was made. In Africa, for example, 840 000 patients were started on ART by December 2005.[1]

HIV-positive patients with tuberculosis (TB) are all potentially eligible for ART, because they are in either WHO Clinical Stage 3 (pulmonary tuberculosis [PTB]) or Stage 4 (extra-pulmonary tuberculosis [EPTB]).[2] In principle, HIV-positive TB patients should benefit from ART, which leads to a reduction in HIV-related mortality and HIV-related recurrence of TB disease. Reports on small numbers of patients treated in the UK,[3] Taiwan[4] and Thailand[5] indicate a good outcome in HIV-positive TB patients treated with ART, with the report from Taiwan showing similar responses between HIV-infected TB and non-TB patients.[4] To our knowledge

there have been no reports on outcomes of HIV-infected TB patients treated with ART in the routine health system in sub-Saharan Africa.

Every 3 months, the HIV Unit of the Malawian Ministry of Health and its partners conduct supervisory and monitoring visits to all sites in the country that are delivering ART in the public sector. Data are collected on numbers and characteristics of patients starting ART and their outcomes. We used these structured visits to obtain additional information on outcomes of patients with TB who had been started on ART, and we compared their outcomes with those for non-TB patients.

METHODS

Background of ART and anti-tuberculosis treatment

ART scale-up in Malawi
The process of ART scale-up has already been described in previous articles,[6,7] and only the main elements will

be described below. A standardised, structured approach is used. This includes a focus on the use of one generic, fixed-dose combination treatment with stavudine, lamivudine and nevirapine (NVP) to be delivered free of charge to HIV-positive eligible patients; a standardised system of registration, monitoring and reporting of cases and outcomes; and quarterly supervision and evaluation of all ART sites. Two alternative first-line regimens (for serious side effects of ART drugs) and one second-line regimen (for ART drug failure) have been placed in central hospitals and two district hospitals, and a referral system set up so that patients in need can access appropriate therapy. Between 2004 and the present, health facilities have gradually become accredited and started ART delivery services, and by March 2006, 66 sites were accredited and delivering ART using the national standardised systems.

Referral for ART and start of therapy
When a patient is found to be HIV-positive, he/she is referred to the ART clinic for clinical staging. If the patient is found to be eligible for ART (assessed as WHO Clinical Stage 3 or 4, or with a CD4 lymphocyte count $<200/mm^3$), he/she is asked to attend, with a guardian, a group counselling session conducted by one of the ART clinic staff for education about ART. Following this session the patient is asked to return a few days later for individual counselling and start of ART. Patients are then followed up, first at 2 weeks and thereafter at 4-week intervals, with assessments and drugs distributed from the ART clinic.

Anti-tuberculosis treatment and referral of TB patients for ART
TB patients are diagnosed, registered and treated according to national guidelines, using a standardised approach[8] and following WHO guidelines.[9] New patients are treated with a 2-month initial phase of rifampicin (RMP), isoniazid (INH), and pyrazinamide (PZA) (with additional ethambutol [EMB] for sputum smear-positive patients), followed by a 6-month continuation phase of INH and EMB. Patients with recurrent TB are given a standard retreatment regimen.[8,9] As a patient group earmarked for diagnostic HIV testing and counselling, TB patients should be offered this service, usually during the first 2 weeks of the initial phase of anti-tuberculosis treatment. For patients who are HIV-positive, ART is deferred until the continuation phase of anti-tuberculosis treatment due to concerns about drug-drug interactions with RMP and NVP.[10] HIV-positive TB patients who are started on ART are followed up monthly on the same day, and have to attend the TB clinic for monitoring and anti-tuberculosis medication and the ART clinic for monitoring and ART drugs.

Monitoring and evaluation for ART
During the monthly ART monitoring visits, vital data are recorded using standardised monitoring tools,

Table 1 Standardised treatment outcomes for patients on ART

Outcome	Definition
Alive and on ART	Patient who is alive and on ART at the facility where he/she is registered
Dead	Patient who dies for any reason while on ART
Defaulted	Patient who has not attended the ART clinic for 3 months or longer for no known reason
Stopped	Patient who stops treatment for any reason during the course of treatment
Transferred out	Patient who has been permanently transferred out to another treatment facility

ART = antiretroviral treatment.

particularly the ART patient master cards and ART register, which have been described previously.[7] Standardised treatment outcomes (Table 1) are recorded every month in the master cards and updated in the ART Register. Every 3 months a quarterly cohort analysis is performed on the most recent 3-month cohort of patients started on ART and the cumulative cohort of patients ever started on therapy. Facilities record case-finding characteristics and treatment outcomes at a set point in time, and these are checked and collated by the HIV Unit and its partners during the quarterly supervisory visits. These have also been described previously.[11]

Data collection
By the end of March 2006, there were 66 sites in the public sector delivering ART to patients. They were all visited between April and June 2006. Data for quarterly and cumulative cohort analyses were collected into structured proforma and then entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA, USA) for collation. Sixty sites had started patients on ART between 1 July and 30 September 2005, and their treatment outcomes were censored on 31 March 2006 to provide a 6-month cohort outcome analysis; it is recognised that in effect this means an analysis of patient outcomes 6–9 months after starting ART. Thirty-five sites had started patients on ART between 1 January and 31 March 2005, and their treatment outcomes were also censored on 31 March 2006 to provide a 12-month cohort outcome analysis; it is also recognised that, in effect, this means an analysis of patient outcomes 12–15 months after starting ART. In addition, during these same two quarterly periods, HIV-positive patients with actively treated PTB or EPTB as reasons for starting ART were identified from the ART patient master cards, and their outcomes were censored on 31 March 2006 to provide a 6-month and 12-month outcome analysis for TB patients.

Analysis
Six- and 12-month treatment outcomes were documented for patients who were started on ART because

Table 2   Six-month outcomes in a quarterly cohort of TB patients and non-TB patients started on ART in Malawi between July and September 2005, with outcomes censored on 31 March 2006

	Active PTB patients n (%)	Active EPTB patients n (%)	All types of TB patients n (%)	Non-TB patients n (%)	RR (95%CI)*	P value
Started on ART	673	265	938	6967		
Alive	521 (77)	203 (77)	724 (77)	4979 (71)	1.08 (1.04–1.12)	<0.001
Dead	69 (10)	36 (14)	105 (11)	867 (12)	0.90 (0.74–1.09)	NS
Defaulted	48 (7)	11 (4)	59 (6)	595 (9)	0.74 (0.57–0.95)	<0.05
Stopped	5 (1)	1 (0)	6 (1)	53 (1)	0.84 (0.36–1.95)	NS
Transferred out	30 (5)	14 (5)	44 (5)	473 (7)	0.69 (0.51–0.93)	<0.05

* Treatment outcome relative risks are compared between patients with all types of TB and non-TB patients.
TB = tuberculosis; ART = antiretroviral treatment; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; RR = relative risk; CI = confidence interval; NS = not significant.

of diagnosis with active TB, and data were also disaggregated for those with PTB and EPTB. The numbers of TB patients and their outcome data were subtracted from all patients started on ART during the same time periods, and a calculation was made for survival outcomes for non-tuberculosis patients. Differences in treatment outcomes between groups were compared using the χ^2 test. Relative risks (RR) and 95% confidence intervals (CIs) were obtained, with differences at the level of 0.05 being regarded as significant.

RESULTS

Between 1 July and 30 September 2005, 7905 patients started ART—6967 with a non-TB diagnosis and 938 (12% of all patients on ART) with a diagnosis of active TB (673 PTB and 265 EPTB). The 6-month cohort outcomes of non-TB and TB patients censored on 31 March 2006 are shown in Table 2. At 6 months, significantly more TB patients were alive and significantly fewer TB patients had defaulted or transferred out compared with non-TB patients. Treatment outcomes were not significantly different between patients with active PTB and EPTB.

Between 1 January and 31 March 2005, 4580 patients started ART—4179 with a non-TB diagnosis and 401 (9% of all patients on ART) with a diagnosis of active TB (288 PTB and 113 EPTB). The 12-month

cohort outcomes of non-TB and TB patients censored on 31 March 2006 are shown in Table 3. At 12 months, significantly more TB patients were alive and significantly fewer TB patients had defaulted or transferred out compared with non-TB patients. Treatment outcomes were similar between patients with active PTB and EPTB, except that significantly fewer patients with active PTB had transferred out compared with EPTB (RR 0.34, 95%CI 0.16–0.70, P < 0.01).

DISCUSSION

This is one of the first reports from sub-Saharan Africa that looks at treatment outcomes in the routine setting of HIV-positive patients who have been diagnosed and treated for TB and then started on ART. The treatment outcomes are in general better than for patients without TB. Approximately 75% of HIV-positive TB patients are alive and on ART 6–12 months after starting ART. It is likely, although not yet proven, that patients who transfer out are also alive and taking ART at their new treatment facility. If this is the case, then the proportion of HIV-positive TB patients who are alive at 6 and 12 months after starting ART would increase to approximately 80%. One possible reason for better outcomes in TB patients compared with non-TB patients may be because TB patients have 2 months to stabilise on their anti-tuberculosis treatment before starting ART, giving

Table 3   Twelve-month outcomes in a quarterly cohort of TB patients and non-TB patients started on ART in Malawi between January and March 2005, with outcomes censored on 31 March 2006

	Active PTB patients n (%)	Active EPTB patients n (%)	All types of TB patients n (%)	Non-TB patients n (%)	RR (95%CI)*	P value
Started on ART	288	113	401	4179		
Alive	218 (76)	77 (68)	295 (74)	2678 (66)	1.15 (1.08–1.22)	<0.001
Dead	33 (12)	11 (10)	44 (11)	536 (12)	0.86 (0.64–1.14)	NS
Defaulted	21 (7)	10 (9)	31 (8)	479 (11)	0.67 (0.48–0.96)	<0.05
Stopped	4 (1)	1 (1)	5 (1)	47 (1)	1.11 (0.44–2.77)	NS
Transferred out	12 (4)	14 (12)	26 (5)	439 (10)	0.62 (0.42–0.90)	<0.05

*Treatment outcome relative risks are compared between patients with all types of TB and non-TB patients.
TB = tuberculosis; ART = antiretroviral treatment; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; RR = relative risk; CI = confidence interval; NS = not significant.

them time to stabilise from their opportunistic infection, in contrast to non-TB patients, who are often given a much shorter period in which to stabilise.

It appears from the national quarterly reports on antiretroviral (ARV) scale-up (source: Ministry of Health, Malawi) and from studies conducted in sub-Saharan Africa that there is high early mortality in patients starting ART, which then decreases with time on treatment.[12] This also appears to be the case in TB patients starting ART, as the 6-month and 12-month outcomes of death and default (which might mean undocumented death)[13] are very similar.

This was an operational study conducted within the routine system, and it therefore has all the limitations of this type of research. Data were not extracted on variables such as demographic characteristics of patients, the timing of anti-tuberculosis treatment in patients started on ART, HIV- or drug-related morbidity or causes of death. During the period of observation, very few facilities in Malawi were providing reliable CD4-lymphocyte count measurements, and we therefore have no data on patients' degree of immunodeficiency. However, it was country-wide, the routine systems for monitoring patients using master cards and registers are robust and regularly checked by supervising teams, and we believe that the results are reliable and representative. The use of 6-month and 12-month quarterly cohort analysis is now well-established and enables treatment outcome analyses to be carried out in the routine system. For busy ART facilities and supervising teams with scarce human resources, censoring individual treatment outcomes at a set point in time is too time-consuming, but cohort treatment outcome analysis is quick and reliable, provided the registers are regularly updated.

Several unanswered questions remain. First, although HIV-positive TB patients on ART have a generally good outcome up to 12 months, we do not know how initiation of ART affects TB-specific treatment outcomes. These outcomes are determined by the proportion of TB patients in a cohort who actually start on ART, and the degree of early TB-HIV mortality that occurs before patients are started on ART. In Malawi, we are aware that for various reasons only a small proportion of TB patients access ART,[14] and that there is high early mortality in TB patients during the initial phase of anti-tuberculosis treatment before ART is commenced.[15] Second, according to the recent WHO guidelines, HIV-positive TB patients should be commenced on ART after 2 months of the initiation phase of anti-tuberculosis treatment if a CD4 lymphocyte count is not available to guide decision making.[2] We are following this guidance in Malawi, but if CD4 testing capacity increases in the country it may be possible to start patients earlier. The WHO recommends that TB patients can start ART 2–4 weeks after starting TB treatment if they have low CD4 counts <200 cells/mm^3, and this may improve outcomes.[2] Third, we do not know

whether there is a marked difference in TB-specific treatment outcomes in HIV-positive TB patients started on ART in the continuation phase compared with those not on ART, although we suspect there would be a difference, as a 7-year follow-up study of HIV-positive TB patients in Malawi showed that the long-term outcomes are poor if no HIV intervention is given.[16]

Despite these conundrums, the results of this study provide reassuring evidence that TB patients started on ART during the continuation phase of anti-tuberculosis treatment do well. The climate in which we now work in sub-Saharan Africa has changed, given the arrival of ARV drugs and scale-up programmes in most countries in the region.[17] Our results should further encourage HIV and TB programmes to work together to get more HIV-positive TB patients on this life-saving medication.

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RÉSUMÉ

CONTEXTE : Les services du secteur public du Malawi assurant un traitement antirétroviral (ART) chez les patients séropositifs pour le virus de l'immunodéficience humaine (VIH), y compris ceux atteints de tuberculose (TB).

OBJECTIFS : Comparer les résultats du traitement dans les cohortes de 6 mois et de 12 mois chez les patients séropositifs pour le VIH et tous traités par l'ART, qu'ils soient TB ou non-TB.

SCHÉMA : Collecte rétrospective des données au moyen des cartes maîtresses des malades et des registres des patients sur ART.

RÉSULTATS : Entre juillet et septembre 2005, 7905 patients ont commencé l'ART dont 6967 avec un diagnostic non-TB et 938 avec un diagnostic de TB active. Les résultats de la cohorte de 6 mois chez les patients non-TB et chez les patients TB, clôturés le 31 mars 2006, ont montré que le nombre de patients TB en vie était plus élevé sous traitement ART (77%) par comparaison avec les patients non-TB (71%) (P < 0,001). Entre janvier et mars 2005, 4580 patients ont commencé l'ART (4179 avec un diagnostic non-TB et 401 avec un diagnostic de TB active. Les résultats de la cohorte de 12 mois chez les patients TB et non-TB, clôturés le 31 mars 2006, ont montré qu'un nombre significativement plus élevé de patients TB étaient en vie et sous traitement ART (74%) par comparaison avec les patients non-TB (66%) (P < 0,001). D'autres résultats concernant les abandons et les transferts vers l'extérieur ont été eux aussi significativement moins fréquents chez les patients TB par comparaison avec les non-TB.

CONCLUSION : Au Malawi, les patients TB positifs pour le VIH et sous ART ont généralement de bons résultats du traitement et il y a lieu de veiller à ce qu'un plus grand nombre de patients aient accès à ce traitement du VIH.

RESUMEN

MARCO DE REFERENCIA : Establecimientos del sector público en Malawi que suministran tratamiento antirretrovírico (ART) a pacientes con serología positiva para el virus de la inmunodeficiencia humana (VIH), incluidos los pacientes con tuberculosis (TB).

OBJETIVOS : Comparar el desenlace terapéutico en cohortes de ART de 6 y de 12 meses, en pacientes con TB y VIH positivos y pacientes VIH positivos sin TB.

MÉTODOS : Análisis retrospectivo de datos a partir de las tarjetas de control de tratamiento y de los registros de pacientes en ART.

RESULTADOS : Entre julio y septiembre de 2005, 7905 pacientes comenzaron ART (6967 sin diagnóstico de TB y 938 con TB activa). El desenlace en esta cohorte de pacientes en ART de 6 meses, registrado el 31 de marzo de 2006, demostró que había más pacientes vivos con TB que pacientes vivos sin TB en quienes recibían el ART (77% contra 71% ; P < 0,001). Entre junio y marzo de 2005, 4580 pacientes comenzaron ART (4179 sin diagnóstico de TB y 401 con diagnóstico de TB activa). El desenlace en esta cohorte de pacientes en ART de 12 meses, registrado el 31 de marzo de 2006, demostró que había más pacientes vivos con TB que pacientes vivos sin TB en tratamiento (74% contra 66% ; P < 0,001). Ambas diferencias fueron estadísticamente significativas. Otros desenlaces como abandono y transferencia también fueron significativamente menos frecuentes en pacientes con TB que en pacientes sin TB.

CONCLUSIÓN : En general, el desenlace terapéutico de los pacientes que presentan coinfección por VIH y TB y reciben ART es favorable en Malawi. Es importante ampliar el acceso de los pacientes al tratamiento contra el VIH.