Timing and uptake of ART during treatment for active tuberculosis in HIV co-infected adults in Malawi

M. van Lettow,^{1,2} A. K. Chan,^{1,3} A. S. Ginsburg,⁴ H. Tweya,⁴ D. Gareta,⁴ J. Njala,⁵ H. Kanyerere,⁶ S. Phiri,⁴ I. Idana^{†6}

<http://dx.doi.org/10.5588/pha.11.0003>

Setting: Uptake of antiretroviral therapy (ART) in patients co-infected with tuberculosis (TB) and the human immunodeficiency virus (HIV) has historically been low in Malawi. In response, the National TB Programme piloted the initiation of ART 2 weeks after initiation of TB treatment in 2008–2009, a change from the prior policy of 2 months.

Objective: To determine at programme level if earlier initiation of ART in co-infected patients receiving TB treatment will increase the uptake and continuation of ART.

Design: A prospective observational pilot programme evaluation using routinely collected monitoring data from the first two sites with integrated TB-HIV services in Malawi.

Results: There was wide variability in the ART start time before and after the policy change. Before the policy change, 16% of patients initiated ART by 3 months compared to 24% after the policy change ($P < 0.001$). The proportion of all co-infected patients on ART increased from 32% before the policy change to 39% after ($P < 0.001$). Earlier initiation of ART did not increase the occurrence of side effects and did not reduce adherence to TB treatment.

Conclusion: Earlier initiation of ART in co-infected patients receiving TB treatment improved the uptake and continuation of ART. Malawi ART guidelines in 2011 were changed from initiating ART after 2 months to as soon as possible after starting anti-tuberculosis treatment.

A large proportion of patients with tuberculosis (TB) in sub-Saharan Africa are also living with human immunodeficiency virus (HIV) infection and the acquired immune-deficiency syndrome (AIDS). Co-infected patients have higher TB case fatality and recurrence rates than patients with TB alone.^{1,2} In Malawi, despite effective short-course therapy, routine programme monitoring revealed a 16% case fatality rate in TB patients, with the majority of deaths occurring during the first 2 months of TB treatment.³ With approximately 70% of TB patients in Malawi co-infected with HIV, the high mortality during TB treatment may be attributed to HIV. Simultaneous anti-tuberculosis and antiretroviral therapy (ART) in co-infected patients is associated with improved survival.^{4,5} Recommended programme strategies to reduce early mortality among TB patients include the provision of early HIV diagnosis and timely initiation of ART.^{6–9} Mortality rates rose from 5.4 per 100 person-years (py) to 12.1/100 py when initiation of ART was delayed until the com-

pletion of TB treatment.⁵ As there is no increase in treatment-limiting adverse events associated with the initiation of ART within 2 months of TB diagnosis compared to initiation after 2 months, and immunological and virological responses to ART are comparable in patients receiving concurrent TB treatment, there is support for the early initiation of ART.^{10–12}

In 2008, the national recommendation in Malawi for the timing of ART initiation in co-infected patients on TB treatment was at 2 months after TB treatment initiation.¹³ Routine monitoring data showed that there was wide variability in ART start time following TB treatment initiation as well as low uptake of ART in co-infected patients. After reviewing supportive evidence from research settings that early initiation of ART reduced mortality rates, the National TB Programme (NTP) conducted a pilot study to change the timing of ART initiation from 2 months to 2 weeks after the initiation of TB treatment in the programme setting.

This programme evaluation was designed to determine at programme level if earlier initiation of ART in co-infected patients receiving TB treatment would increase the uptake and continuation of ART. As the standard of care at the time in Malawi for all patients initiated on ART, including those on TB co-treatment, was a nevirapine (NVP) based first-line regimen (stavudine [d4T], lamivudine [3TC], NVP), the programme evaluation was also designed to determine whether earlier introduction of ART would increase mortality and poor clinical outcomes, including unscheduled sick visits and adverse effects as a result of drug-drug interactions, and reduce adherence to TB treatment among TB-HIV co-infected patients.

STUDY POPULATION AND METHODS

A prospective observational pilot programme evaluation of patients registered from 1 October 2008 to 1 July 2009 was carried out using routinely collected monitoring and evaluation (M&E) data comparing the outcomes of earlier (2 weeks to <2 months) vs. later (≥ 2 months) initiation of ART in TB-HIV co-infected patients on TB treatment. Data were collected from the Martin Preuss Centre (MPC) in Lilongwe and from the TB-HIV Integration clinic at Zomba Central Hospital (ZCH) in Zomba, the first two sites in Malawi with co-location of TB-HIV services that have integrated electronic data capture and harmonisation of patient-level information for routine HIV and TB programme data. The MPC is located on the campus of

AFFILIATIONS

- 1 Dignitas International, Zomba, Malawi
 - 2 Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
 - 3 Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
 - 4 The Lighthouse Trust, Lilongwe, Malawi
 - 5 Department of HIV and AIDS, Malawi Ministry of Health, Lilongwe, Malawi
 - 6 National Tuberculosis Programme, Lilongwe, Malawi
- [†]Deceased

CORRESPONDENCE

Monique van Lettow
Dignitas International
c/o PO Box 1071
Zomba, Malawi
Tel: (+265) 888 117 736
Fax: (+265) 152 7558
e-mail: m.vanlettow@dignitasinternational.org

ACKNOWLEDGEMENTS

The authors thank the Dignitas International and Light House Data Management teams for entry, extraction and merging of datasets, as well as the patients, TB officers, clinical officers and nurses at the Martin Preuss Centre and Zomba Central Hospital.

KEY WORDS

TB-HIV co-infection; ART initiation; Malawi

Received 7 March 2011
Accepted 11 July 2011

PHA 2011; 1(1): 6–9
© 2011 The Union

Bwaila Hospital (BH), and is supported by the Lighthouse Trust. The TB-HIV Integration Clinic, located at ZCH, is an expansion of the Ministry of Health (MoH) and Dignitas International collaborative ART Clinic at ZCH. At both sites, a TB officer initiates TB registration and provides TB treatment and monitoring and an HIV/AIDS clinician initiates ART and provides HIV/AIDS care and support. Routine opt-out provider-initiated HIV testing and counselling (HTC) is fully integrated into the TB registration process, and integration of TB-HIV care and NTP infection control guidelines is followed.

From 15 February 2009 onwards, co-infected subjects at both sites were allowed by the NTP to undergo ART from 2 weeks after the initiation of TB treatment and were followed up for the duration of TB treatment, typically 6 months. Two cohorts of TB-HIV co-infected patients were compared: those prior to and those after the policy change date. The pre policy change cohort included all patients registered for TB treatment during a 4.5 month period from 1 October 2008 to 15 February 2009; the post policy change cohort included all those registered during a 4.5 month period between 16 February and 1 July 2009. Cases who had started ART other than at the two pilot sites did not appear in the databases and were thus not included.

Routine M&E data were collected without any additional data

requested. All data were collected from the MoH TB and ART registers and master cards (standard monitoring tool). At both sites, patient level data for TB and ART care were linked. Finally, data from both sites were cleaned and merged for analysis. Data analysis was performed using SPSS 17.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). Standard univariate comparisons of dichotomous outcome, including contingency tables and exact tests, and multivariate logistic regression models were used. Uptake was measured as the proportion of TB-HIV co-infected patients who initiated ART by 3 months, and retention as the proportion who were alive and on ART at 6 months after TB registration. As the initial policy recommended starting ART from 2 months, the majority of subjects would have started by 3 months. The proportion of TB-HIV co-infected patients who initiated ART by 3 months after TB registration and the proportion who remained on ART at 6 months after TB registration were compared between the pre policy change group that was intended to start at the recommended 2 months after TB introduction vs. the post policy change group that was intended to start 2 weeks after commencing TB treatment. Homogeneity between the groups was compared to ensure similarity between groups.

The study received ethical approval from the National Health Science Research Committee in Malawi.

TABLE 1 Characteristics of patients and patient outcomes before and after policy change to start ART as early as 2 weeks after commencing treatment for active TB

	Pre policy change (1 October 2008– 15 February 2009) <i>n</i> (%) or mean $\pm$ SD	Post policy change (16 February 2009– 1 July 2009) <i>n</i> (%) or mean $\pm$ SD	<i>P</i> value
Total patients registered for TB treatment	2155	2041	
Patients registered by age category			
<18 months	15 (1)	15 (1)	0.95
18 months–14 years	128 (6)	124 (6)	
15–24 years	249 (12)	246 (12)	
≥ 25 years	1763 (82)	1656 (81)	
Total TB-HIV + (≥ 15 years of age)	1247	1217	0.6
Adults (aged ≥ 15 years) already on ART at start of TB treatment	136 (11)	145 (12)	0.9
Adults needing to start ART	1111	1072	
Initiated ART by 3 months after TB registration	175 (16)	257 (24)	<0.001
Outcomes at 6 months after TB treatment			
Alive on ART	303 (24)	378 (31)	0.001
Alive, completed TB treatment, not on ART	563 (45)	391 (32)	0.001
Unknown treatment outcome/transferred out	298 (24)	360 (30)	0.01
Dead	83 (7)	87 (7)	0.9
First side effect (any)	174 (14)	144 (12)	0.12
Time of first side effect from concurrent TB treatment and ART, days	48 $\pm$ 33	64 $\pm$ 44	0.001
PN	22 (2)	16 (1)	0.42
Time of onset of PN from concurrent TB treatment and ART, days	65 $\pm$ 48	76 $\pm$ 47	0.5
Skin rash	23 (2)	29 (2)	0.4
Time of onset of rash from concurrent TB treatment and ART, days	30 $\pm$ 25	59 $\pm$ 42	0.006
Hepatitis	7 (1)	4 (0)	0.55
Time of onset of hepatitis from concurrent TB treatment and ART, days	38 $\pm$ 29	14 $\pm$ 7	0.07

ART = antiretroviral therapy; TB = tuberculosis; HIV = human immunodeficiency virus; SD = standard deviation; PN = peripheral neuropathy.

RESULTS

Outcomes of policy change on uptake and continuation of ART in TB-HIV co-infected patients

For the baseline period of 4.5 months prior to policy change, a total of 2155 adults were registered at both sites, while a total of 2041 adults were registered during the 4.5-month period. There was no difference in the proportion of adults already on ART before starting TB treatment between the two groups (12%). Prior to policy change, 16% of adults had initiated ART by 3 months, while 24% had started ART by 3 months after the change ($P < 0.001$, Table 1). When adjusting for sex, age and CD4 count, TB patients registered during the post policy period were 1.6 times more likely to have initiated ART by 3 months after TB registration than those who registered before the policy change (adjusted odds ratio [OR] 1.6, 95%CI 1.1–2.3). Prior to the recommendation to start ART as early as 2 weeks after TB treatment initiation, 3% of patients started within 1 month, 8% by 2 months and 21% by 6 months or on completion of TB treatment. After the recommended policy change, these proportions were respectively 12%, 19% and 29%. The proportion of all TB-HIV co-infected patients on ART, which included those already on ART as well as those who started after TB treatment initiation, increased from 32% before the policy change to 39% after the policy change ($P < 0.001$, Table 2). Prior to the policy change, 24% of adults were alive and on ART 6 months after TB treatment initiation and 31% after ($P = 0.001$). However, when adjusting for sex, age and CD4 count, there was no increased likelihood after the policy change of being alive on ART at 6 months (adjusted OR 1.1, 95%CI 0.7–1.6).

Outcomes of policy change on mortality, adverse events and attrition

There was no difference in mortality before or after the policy change, and no difference in side effects between the two cohorts was reported (Table 1). Side effects occurred in 13% of cases, and the mean time of onset of the first side effect occurred after 56 days (standard deviation [SD] ± 51) from the start of concurrent ART and TB treatment. Peripheral neuropathy occurred in 1.5% (mean 70 days, SD ± 55), rash in 2.1% (mean 47 days, SD ± 39) and hepatitis in 0.5% of cases (mean 30 days, SD ± 26). Univariate comparisons suggested that the mean time of onset of any side effect and rash occurred later in the post policy cohort; however, in multivariate analysis adjusting for age, sex, CD4 count and occurrence of side effects, these differences were no longer evident.

DISCUSSION

Prior to this study, the Malawi Ministry of Health ART guidelines recommended delaying the initiation of ART in TB-HIV co-infected patients until completion of the first 2 months of TB treatment. Evidence from the research setting at the time suggested a clear mortality benefit of earlier initiation of ART treatment in co-infected patients. To rapidly evaluate the operationalisation of a potential policy change, and also to address policy makers' concerns about potential adverse outcomes in a large programme setting using a NVP-based vs. an efavirenz-based first-line regimen for TB-HIV co-treatment, this pilot study was designed to assess the programme impact of earlier initiation of ART (2 weeks vs. 2 months). The results of this evaluation suggested that changing the policy would increase the uptake and continuation of ART among TB-HIV co-infected patients on TB treatment and that earlier initiation did not increase mortality or the occurrence of side effects and did not reduce adherence to TB treatment.

The major strength of this study is that all data were programme-based, collected from operational programme information as part of routine monitoring and evaluation from a national public system. However, study limitations include concerns regarding accuracy and consistency that are associated with using operational data.

Since this study, the CAMELIA (Cambodian Early vs. Late Introduction of Antiretroviral Drugs) randomised superiority trial has clearly demonstrated a mortality benefit in initiating ART at 2 weeks (mortality rate 8.28/100 py) vs. 2 months (13.77/100 py) of TB treatment in patients with newly diagnosed smear-positive pulmonary TB and CD4 count < 200 cells/mm³ ($P = 0.002$) in a research setting,¹⁴ and the current World Health Organization guidelines recommend that ART initiation should follow initiation of TB treatment as soon as possible in resource-limited settings. Based on the mounting evidence from research settings,^{4,5,10–12} the impact at programme level, as demonstrated in this study and, most importantly, changes in WHO guidelines, the Malawi ART guidelines were changed in 2011 with the recommendation to start ART as soon as possible after initiating TB treatment.¹⁵

It is important to note, from the findings of this study, that even with the resulting policy change consistent with these recommendations in the programme setting, large numbers of co-infected patients are still not receiving ART. The findings from this initial pilot study prompted a follow-up operational research study in the same setting that looked at reasons for accepting or declining uptake of HTC and ART by TB and TB-HIV co-infected patients,

TABLE 2 Timing of ART initiation during treatment for active TB (TB treatment) in HIV co-infected patients before and after the policy change to start ART as early as 2 weeks after commencing TB treatment

	Pre policy change (1 October 2008– 15 February 2009) <i>n</i> (%)	Post policy change (16 February 2009– 1 July 2009) <i>n</i> (%)	<i>P</i> value
Total TB-HIV co-infected patients (≥ 15 years of age)	1247	1217	
Adults (aged ≥ 15 years) already on ART	136 (11)	145 (12)	0.9
Adults needing to start ART	1111	1072	
Started within 1 month from TB treatment	36 (3)	127 (12)	< 0.01
Started between 1 and 2 months of TB treatment	57 (5)	71 (7)	0.6
Started between 2 and 6 months of TB treatment	143 (13)	108 (10)	0.6
Total started ART (during TB treatment)	236 (21)	306 (29)	< 0.01
Started after 6 months of TB treatment	33 (3)	21 (2)	0.9
All on ART before, during or after TB treatment	405 (32)	472 (39)	< 0.01

ART = antiretroviral therapy; TB = tuberculosis; HIV = human immunodeficiency virus.

and revealed that anxieties about drug toxicities among both patients and care providers, and the absence of a guardian, contributed to suboptimal ART uptake in TB patients.¹³ Intensified sensitisation of patients and care providers regarding the risks and benefits of early ART in TB-HIV co-infected patients are needed. Further operational research is necessary to open up the bottlenecks to ART uptake in co-infected patients and TB-HIV integration beyond co-location of services in resource-limited settings.

References

- 1 Lawn S D, Myer L, Bekker L G, et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS* 2006; 20: 1605–1612.
- 2 Mukadi Y D, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001; 15: 143–152.
- 3 Zachariah R, Fitzgerald M, Massaquoi M, et al. Does antiretroviral treatment reduce case fatality among HIV-positive patients with tuberculosis in Malawi? *Int J Tuberc Lung Dis* 2007; 11: 848–853.
- 4 Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *J Acquir Immune Defic Syndr* 2009; 1; 50: 148–152.
- 5 Karim S, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; 362: 697–706.
- 6 Harries A D, Zachariah R, Lawn S D. Providing HIV care for co-infected tuberculosis patients: a perspective from sub-Saharan Africa. *Int J Tuberc Lung Dis* 2009; 13: 6–16.
- 7 Lawn S D, Harries A D, Anglaret X, et al. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008; 22: 1897–1908.
- 8 Kumwenda M, Tom S, Chan A K, et al. Reasons for accepting or declining HIV services among TB patients at a TB-HIV integration clinic in Malawi. *Int J Tuberc Lung Dis* 2011; 15 (in press).
- 9 Lawn S D, Wood R. Optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis: there may be more than one right answer. *J Acquir Immune Defic Syndr* 2007; 46: 121–123.
- 10 Breen R A, Miller R F, Gorsuch T, et al. Virological response to highly active antiretroviral therapy is unaffected by antituberculosis therapy. *J Infect Dis* 2006; 193: 1437–1440.
- 11 Lawn S D, Myer L, Bekker L G, et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS* 2006; 20: 1605–1612.
- 12 Breen R A, Miller R F, Gorsuch T, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax* 2006; 61: 791–794.
- 13 Ministry of Health, Malawi. Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi. 3rd ed. Lilongwe, Malawi: Ministry of Health, 2008.
- 14 Blanc F X, Sok T, Laureillard D, et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. Program and abstracts of the XVIII International AIDS Conference, July 18–23, 2010, Vienna, Austria [Abstract THLB106].
- 15 Ministry of Health, Malawi. Guidelines for clinical management of HIV in children and adults (Draft). 1st ed. Lilongwe, Malawi: Ministry of Health, 2011.

Contexte : Dans le passé, au Malawi, la mise en route du traitement antirétroviral (ART) chez les patients co-infectés par la tuberculose (TB) et le virus de l'immunodéficience humaine (VIH) a été peu courante. Comme réponse, le Programme National de la Tuberculose a réalisé en 2008–2009 une modification-pilote du moment de mise en route de l'ART passant à 3 semaines après le début du traitement TB contre la politique antérieure de 2 mois.

Objectif : Déterminer au niveau du programme si un début plus précoce de l'ART chez les patients co-infectés bénéficiant d'un traitement antituberculeux augmentera la mise en route et la poursuite de l'ART.

Schéma : Evaluation prospective observationnelle d'un programme pilote au moyen de données de suivi colligées en routine dans les deux premiers sites où les services TB-VIH avaient été intégrés au Malawi.

Résultats : On a noté d'importantes variabilités dans la période du

début de l'ART à la fois avant et après la modification de politique. Avant la modification, 16% des patients commençaient l'ART dans les 3 mois, et 24% après celle-ci ($P < 0,001$). La proportion de l'ensemble des patients co-infectés mis sous ART est passée de 32% avant la modification de politique à 39% après celle-ci ($P < 0,001$). Une initiation plus précoce de l'ART n'a pas augmenté l'apparition d'effets indésirables et n'a pas diminué l'adhésion au traitement antituberculeux.

Conclusion : Une initiation plus précoce de l'ART chez les patients co-infectés sous traitement antituberculeux a amélioré la mise en route et la poursuite de l'ART. Les directives ART ont changé en 2011 au Malawi, en passant d'un début de l'ART 2 mois après le commencement du traitement antituberculeux vers un début aussi précoce que possible.

Marco de referencia: La aceptación del tratamiento antirretrovírico (ART) por parte de los pacientes que presentan coinfección por el virus de la inmunodeficiencia humana (VIH) y tuberculosis (TB) siempre ha sido baja en Malawi. Como respuesta a esta situación, del 2008 al 2009 en el Programa Nacional contra la Tuberculosis se ensayó una sincronización del comienzo del ART 2 semanas después de la iniciación del tratamiento antituberculoso, con lo cual se modificaba la anterior norma de 2 meses.

Objetivo: Determinar si un comienzo más temprano del ART en los pacientes coinfectados que reciben tratamiento contra la TB mejoraría la aceptación y la continuidad del ART.

Método: Se trató de un programa experimental prospectivo de observación, en el cual se utilizaron los datos de supervisión recogidos de manera ordinaria en los dos primeros centros que integraron los servicios de atención de la TB y del VIH en Malawi.

Resultados: Hubo gran variabilidad en el momento del comienzo del ART antes y después de la modificación de las normas. Antes del cambio de políticas, 16% de los pacientes habían comenzado el ART a los 3 meses de tratamiento antituberculoso y después del cambio esta cifra aumentó a 24% ($P < 0,001$). La proporción de todos los pacientes coinfectados que recibían ART aumentó de 32% antes del programa hasta 39% después del mismo ($P < 0,001$). Un comienzo más temprano de ART no aumentó la aparición de reacciones adversas ni disminuyó el cumplimiento del tratamiento antituberculoso.

Conclusión: Comenzar de manera más temprana la administración de ART en los pacientes coinfectados que reciben tratamiento contra la TB mejoró la aceptación y la continuidad del ART. En el 2011, se modificaron las normas sobre el ART en Malawi y en lugar de comenzarlo 2 meses después, se comienza ahora tan pronto como sea posible después de iniciar el tratamiento antituberculoso.