Antiretroviral treatment among co-infected tuberculosis patients in integrated and non-integrated facilities

T. D. Ledibane,¹ S. C. Motlhanke,² A. Rose,¹ W. H. Kruger,¹ N. R. T. Ledibane,³ M. M. Claassens⁴

<http://dx.doi.org/10.5588/pha.14.0099>

Background: South Africa has the second worst tuberculosis-human immunodeficiency virus (TB-HIV) syndemic in the world: in 2011, the TB-HIV co-infection rate was estimated at 65%. Integration of TB and HIV health-care services was implemented to increase antiretroviral treatment (ART) uptake among eligible patients.

Aim: To evaluate whether integrated TB and HIV facilities had better ART uptake among eligible patients compared to non-integrated facilities.

Methods: A cross-sectional study using routine TB programme data from January to December 2010. ART eligibility was defined as a CD4+ cell count <350 cells/ μ l.

Results: Respectively 2761 (86.8%) and 3611 (84.7%) patients were eligible for ART at integrated and non-integrated facilities ($P < 0.001$). The proportion of patients started on ART at integrated facilities did not differ significantly from that of non-integrated facilities (35.9% vs. 37.1%, $P = 0.340$), but the proportion with unknown HIV status (31.8% vs. 24.5%, $P < 0.001$) and unknown CD4+ cell count (40.9% vs. 30.4%, $P < 0.001$) did.

Conclusion: Integration of TB and HIV services in the Free State (2009–2010) was not associated with improved ART uptake. The reasons why are not clear. Of concern are the high proportions of unknown HIV status and CD4+ cell count results, especially at integrated facilities, and the small proportion of patients on ART, which may indicate poor implementation of integration.

The integration of tuberculosis (TB) and human immunodeficiency virus (HIV) services refers to the simultaneous provision of both TB and HIV services to co-infected patients within the same health-care facility.¹ The integration of TB and HIV services was adopted as a strategy by the South African Department of Health to increase antiretroviral treatment (ART) uptake among eligible TB-HIV co-infected patients.² The aim of integrating TB and HIV services is to reduce TB and/or HIV associated mortality and morbidity and to improve the effectiveness and efficiency of the services.^{2–4}

HIV has been identified as the single most important factor that promotes the progression of latent tuberculous infection to active TB.^{5,6} In the late 1990s, the lifetime risk of developing active TB disease among HIV-negative individuals was estimated at 5–10%,⁷ while the annual risk of developing active TB among HIV-positive individuals was estimated at 10–15%.⁷ In 2009, the burden of TB-HIV co-infection was estimated at 38% in Africa and 15% in high-income

countries.³ In countries with high HIV prevalence, more than 65% of TB disease is associated with HIV infection.⁴ In such countries TB is often the first manifestation of HIV infection and the leading cause of death among HIV-positive patients.^{3,8,9} According to the World Health Organization (WHO) 2013 global tuberculosis report, South Africa had the second worst TB-HIV syndemic in the world, with prevalence of TB-HIV co-infection estimated at 65%.⁴

In studies performed in South Africa and other African countries, the integration of TB and HIV services led to an increase in HIV testing among TB patients.^{1,10–14} Previous studies also revealed that the integration of HIV and TB health care services improves ART uptake among co-infected patients.^{10–13} Added benefits of integration are a reduction in the morbidity and mortality rate among TB-HIV co-infected patients, improved adherence to both ART and anti-tuberculosis treatment and improved clinical management of both diseases.^{15,16} Non-integrated services also pose logistical difficulties for TB patients in accessing centralised HIV services, and may delay the initiation of ART.¹⁷

Prior to January 2010, TB and HIV primary health care services were provided separately in the Free State province of South Africa, with a cross-referral system linking the services. The strategy adopted by the Free State Department of Health to improve ART uptake among eligible TB and HIV co-infected patients was to integrate the HIV and TB services.²

The primary objective of the present study was to evaluate whether the integration of TB and HIV services influences ART uptake among eligible co-infected patients to inform national/provincial policy on clinic integration. The secondary objectives were 1) to describe the TB-HIV co-infection rate among patients in the Electronic Tuberculosis Register (ETR.net), 2) to describe the uptake of HIV testing among TB patients in ETR.net and 3) to describe the uptake of CD4+ cell count testing among TB patients in ETR.net.

METHODS

Study design and population

This was a cross-sectional study of electronic records using routine TB programme data. All 279 primary health care facilities offering TB and HIV services in the Free State province of South Africa were included. The study population included all the TB-HIV co-infected patients registered in ETR.net in Free State province from 1 January 2010 to 31 December 2010.

AFFILIATIONS

- 1 Department of Community Health, University of the Free State, Bloemfontein, South Africa
- 2 Free State Department of Health, Bloemfontein, South Africa
- 3 School of Health Systems and Public Health, University of Pretoria, Pretoria, South Africa
- 4 Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

CORRESPONDENCE

Tladi Ledibane
Department of Community Health
Faculty of Health Science
Room 227, Block E
F Retief Building
University of the Free State
PO Box 339 (G52)
Bloemfontein 9300
South Africa
Tel: (+27) 51 405 3136/72
761 1355
e-mail: drledibane@gmail.com

Conflicts of interest: none declared.

KEY WORDS

HIV; TB; TB-HIV integration; ART uptake

Received 13 November 2015
Accepted 26 April 2015

PHA2015;5(2):112–115
© 2015 The Union

HIV-positive patients with a CD4+ cell count of <350 cells/μl were eligible for ART, according to South African recommendations at the time of the study.¹⁸ All TB patients who were on ART prior to registration in ETR.net and children aged <5 years were excluded. No sampling was done; all eligible patients were included.

The population of 2761 eligible co-infected patients in integrated facilities and 3611 eligible co-infected patients in non-integrated facilities achieved a power of 100% to detect a difference of 20% ART initiation rate between integrated and non-integrated facilities, assuming a 5% level of significance.

Data management and analysis plan

The data source was the ETR.net database. Information about the facility's name and integration status was obtained from the HIV Directorate, which gives accreditation for facilities to qualify for integrated services.

The following variables were exported onto the data sheet: 1) to evaluate whether there was an association between ART uptake among eligible co-infected patients with the integration of TB and HIV services at health care facilities, 2) the demographic profile of the patient, 3) the integration status of each facility (main determinant), 4) the CD4+ count of each patient and 5) whether the patients had been initiated on ART (outcome). ETR.net was used to identify all patients on anti-tuberculosis treatment during the study period and to obtain their HIV status and CD4+ cell count. The facilities were classified according to integration and non-integration status, which was obtained from the HIV Directorate and the District Health Information System.

The data were stored in the computers of the principal investigator and data clerk and were backed up and stored separately in the hard drive by the data clerk on a daily basis. The database was reviewed weekly by the principal investigator.

A descriptive summary table was generated to display the frequencies and percentages of each determinant, classified by the outcome variable. The χ^2 test was used to compare categorical variables such as ART initiation status by the integration status of the facility.

Ethical issues

Written permission to conduct the study was obtained from the Head of Department of the Free State Department of Health. Ethics approval was granted by the Ethics Committee of the Faculty of Health Sciences of the University of the Free State (ECUFS NR 44/2012) and the Ethics Advisory Board of the International Union Against Tuberculosis and Lung Disease (EAF 20/12).

Consent was not needed from patients, as retrospective data from ETR.net was used. Sensitive information obtained during the study was treated as confidential. The principles of safeguarding the dignity and safety of the research participants were observed by ensuring privacy of records and coding of facilities.

RESULTS

A total of 24221 TB patients were registered on ETR.net during the study period. The number of TB patients already on ART prior to admission on ETR.net was 1445 (6%). There were 1524 (6.3%) children aged <5 years. Of the remaining 21252 TB patients, 10028 (47.2%) were treated at integrated health care facilities and 11224 (52.8%) at non-integrated facilities.

Among the patients treated at integrated facilities, 5386 (53.7%) were HIV-positive, 1451 (14.5%) were HIV-negative and

TABLE Demographic and clinical characteristics of TB patients on ETR.net ($n = 21\,252$)

Variables	Integrated $n = 10\,028$ n (%)	Non-integrated $n = 11\,224$ n (%)	<i>P</i> value
Sex			<0.001
Males	5 733 (57.2)	6 052 (53.9)	
Females	4 295 (42.8)	5 172 (46.1)	
Age groups (years)			<0.001
5–14	345 (3.4)	382 (3.4)	
15–24	1 024 (10.2)	1 444 (12.9)	
25–34	2 713 (27.1)	3 214 (28.7)	
35–44	2 824 (28.2)	3 090 (27.6)	
45–54	2 041 (20.6)	1 979 (17.6)	
55–64	793 (7.9)	795 (7.1)	
65–74	215 (2.1)	240 (2.1)	
≥75	73 (0.7)	80 (0.7)	
HIV status			<0.001
Positive	5 386 (53.7)	6 124 (54.6)	
Negative	1 451 (14.5)	2 233 (19.9)	
Unknown	3 191 (31.8)	2 867 (24.5)	
CD4+ cell count result			<0.001
Known	3 181 (59.1)	4 263 (69.6)	
Unknown	2 205 (40.9)	1 861 (30.4)	
CD4+ cell count (cells/μl)			<0.001
≤350	2 761 (86.8)	3 611 (84.7)	
>350	420 (13.2)	652 (15.3)	

TB = tuberculosis; ETR.net = Electronic Tuberculosis Register.

the HIV status of 3191 (31.8%) was unknown (Table). Among the patients in non-integrated facilities, 6124 (54.6%) were HIV-positive, 2233 (19.9%) were HIV-negative and the HIV status of 2867 (24.5%) was unknown. A significantly larger proportion of patients had unknown HIV status at integrated facilities compared to non-integrated facilities (31.8% vs. 24.5%, $P < 0.001$). The CD4+ cell count results of 2205 (40.9%) HIV-positive patients in integrated facilities and 1861 (30.4%) in non-integrated facilities were unknown ($P < 0.001$).

The Figure is a flow chart of the breakdown of TB patients included in the study showing a small proportion of co-infected eligible patients started on ART at both types of facilities (35.9% at integrated facilities and 37.1% at non-integrated facilities).

The TB-HIV co-infection rate for Free Town province was 54.2% ($n = 11\,510$); it was 53.7% ($n = 5386$) at integrated facilities and 54.6% ($n = 6124$) at non-integrated facilities ($P < 0.001$). The proportion of ART-eligible co-infected patients at integrated facilities was 86.8% ($n = 2761$), and 84.7% ($n = 3611$) at non-integrated facilities ($P < 0.001$). There was no significant association between ART uptake among eligible co-infected patients with integrated TB and HIV facilities (35.9%; $n = 991$) vs. non-integrated facilities (37.1%; $n = 1338$, $P = 0.340$).

DISCUSSION

The low uptake of ART among eligible HIV-TB co-infected patients at both integrated and non-integrated facilities indicates a systematic failure to provide quality HIV services for TB patients. Integrating TB and HIV services may therefore not be the only solution for improving ART uptake among eligible co-infected patients. The value of using routine data in operational research to

FIGURE Breakdown of the study participants. TB = tuberculosis; ART = antiretroviral treatment; HIV = human immunodeficiency virus; + = positive; – = negative.

evaluate policy implementation is demonstrated by the study findings: according to our data, the yield of the TB-HIV integration policy seems minimal. Our results are in contrast to the findings of studies elsewhere in Africa and in South Africa that concluded that integrating TB-HIV services can improve ART uptake by up to 68%.^{19,20} The failure of integration to improve ART uptake in the Free State may be attributed to a failure to fully integrate TB-HIV services, the lack of monitoring and evaluation of the integration process at facilities, resistance of staff to offer both services in the same facility due to risk of nosocomial transmission of TB to HIV-positive patients, and poor clinical work-up of TB patients for HIV and ART eligibility. Information about these factors are not included in the ETR.net and were therefore not included in our study, but they should be investigated in future studies, which could include qualitative methodologies to analyse staff knowledge, attitude and practices. Other barriers to ART uptake, such as stigma, drug availability and lack of staff training, were not investigated in this study, but should also be identified and addressed.

The proportion of eligible patients who were not initiated on ART was respectively 64.1% and 62.9% in integrated and non-integrated facilities, which is worse than the findings from a study in the Western Cape, where 34% of ART-eligible patients were not initiated in integrated facilities.²¹ Kaplan et al. also reported that integration failed to improve health outcomes among TB patients.²² It is crucial for the well-being of eligible co-infected patients to be initiated on ART as soon as possible. Policy makers and health-care providers should ensure that ART initiation is a priority for these patients.

The large number of TB patients with unknown HIV and CD4+ cell count results at both types of facilities, but specifically at integrated facilities, could indicate a failure to adhere to the 2010 South African National ART guidelines, challenges and problems with the integration of facilities, or problems with TB and HIV information management. If health care providers are not adhering to the guidelines, they should receive training if their knowledge is inadequate, and be motivated to deliver quality service. The implementation of all aspects of integration, including HIV testing and CD4+ cell count measurement, should be monitored and improved. Focused efforts should be made to make integration effective, and other solutions should be explored if integration proves not to be the answer. TB and HIV information management should be investigated, and problems identified and addressed if necessary.

Limitations of the study

As this was a retrospective record review, there might be errors due to missing or incomplete records when the data were recorded in ETR.net. There might also be discrepancies between actual patient records and ETR.net. Factors that were not investigated may have confounded the results, such as site/area of the patients, co-trimoxazole preventive therapy and treatment outcomes, specifically deaths, which could not be included in the 12-month study. This study could not determine the long-term effect of integrated services on the uptake of ART, as the analysis was restricted to the study period. Finally, the study was limited to the Free State province of South Africa and is therefore not necessarily generalisable to other contexts.

CONCLUSION

While the integration of TB-HIV services has improved ART uptake elsewhere, this study has shown that integration was not associated with improved ART uptake among eligible co-infected patients in the Free State province in 2009–2010. The reasons why the integration of services was not associated with improved ART uptake were not clear and warrant further operational research to inform policy makers on how to improve integration. Of concern are the high proportions of patients with unknown HIV status and CD4+ cell count results, particularly at integrated facilities, and the small proportion of eligible co-infected patients on ART, which may indicate poor implementation of integrated services and should be investigated further.

References

- Legido-Quigley H, Montgomery C M, Khan P, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Trop Med Int Health* 2013; 18: 199–211.
- South Africa Department of Health. National Strategic Plan on HIV, STIs and TB: 2012–2016. Pretoria, South Africa: South Africa Department of Health, 2012. http://www.sahivsoc.org/upload/documents/National_Strategic_Plan_2012.pdf Accessed May 2015.
- World Health Organization. WHO Report 2009. Global tuberculosis control: epidemiology, strategy, financing. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO, 2009. http://whqlibdoc.who.int/publications/2009/9789241563802_eng_doc.pdf Accessed May 2015.
- World Health Organization. Global tuberculosis report 2013. WHO/HTM/TB/2013.11. Geneva, Switzerland: WHO, 2013. http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf Accessed May 2015.
- Rieder H, Cauthen G, Comstock G, Snider D. Epidemiology of tuberculosis in the United States. *Epidemiol Rev* 1989; 11: 79–98.
- Kwan C K, Ernst J D. HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev* 2011; 24: 351–376.
- Von Reyn C F. The significance of bacteremic tuberculosis among persons with HIV infection in developing countries. *AIDS* 1999; 13: 2193–2195.

- 8 Coetzee D, Hilderbrand K, Goemaere E, et al. Integrating tuberculosis and HIV care in the primary care setting in South Africa. *Trop Med Int Health* 2004; 9: A11–A15.
- 9 Corbett E L, Marston B, Churchyard G J, De Cock K M. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. *Lancet* 2006; 367: 926–937.
- 10 Wallrauch C, Heller T, Lessells R, et al. High uptake of HIV testing for tuberculosis patients in an integrated primary health care HIV/TB programme in rural KwaZulu-Natal. *S Afr Med J* 2010; 100: 146–147.
- 11 Harris J B, Hatwiinda S M, Randels K M, et al. Early lessons from the integration of tuberculosis and HIV services in primary care centers in Lusaka, Zambia. *Int J Tuberc Lung Dis* 2008; 12: 773–779.
- 12 Gasana M, Vandebriel G, Kabanda G, et al. Integrating tuberculosis and HIV care in rural Rwanda. *Int J Tuberc Lung Dis* 2008; 12: 39–43.
- 13 Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. *J Infect Dis* 2007; 196 (Suppl 1): S114–S123.
- 14 Howard A A, El-Sadr W M. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis* 2010; 50 (Suppl 3): S238–S244.
- 15 Abdool Karim S S, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011; 365: 1492–1501.
- 16 Sylla L, Bruce R D, Kamarulzaman A, Altice F L. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. *Int J Drug Policy* 2007; 18: 306–312.
- 17 Kumwenda M, Tom S, Chan A K, et al. Reasons for accepting or refusing HIV services among tuberculosis patients at a TB-HIV integration clinic in Malawi. *Int J Tuberc Lung Dis* 2011; 15: 1663–1669.
- 18 South Africa Department of Health. South African antiretroviral treatment guidelines 2010. Pretoria, South Africa: South Africa Department of Health, 2010. <http://www.uj.ac.za/en/CorporateServices/ioha/Documentation/Documents/ART%ROGuideline.pdf> Accessed June 2015.
- 19 Phiri S, Khan P Y, Grant A D, et al. Integrated tuberculosis and HIV care in a resource-limited setting: experience from the Martin Preuss centre, Malawi. *Trop Med Int Health* 2011; 16: 1397–1403.
- 20 Médecins Sans Frontières. Report on the integration of TB and HIV services in Site B Khayelitsha. Cape Town, South Africa: MSF, 2005. http://webdav.uct.ac.za/depts/epi/ideufiles/tb_integration_progress_report_022005.pdf Accessed May 2015.
- 21 Pepper D J, Marais S, Wilkinson R J, et al. Barriers to initiation of antiretrovirals during antituberculosis therapy in Africa. *PLOS ONE* 2011; 6: 2–7.
- 22 Kaplan R, Caldwell J, Bekker L, et al. Integration of TB and ART services fails to improve TB treatment outcomes: Comparison of ART/TB primary health-care services in Cape Town, South Africa. *S Afr Med J* 2014; 104: 204–209.

Contexte : L'Afrique du Sud est au deuxième rang dans le monde de la « syndémie » tuberculose/virus d'immunodéficience humaine (TB-VIH) : en 2011, le taux de coinfection TB-VIH a été estimé à 65%. L'intégration des services de soins de la TB et du VIH a été mise en œuvre pour augmenter la mise sous traitement antirétroviral (ART) chez les patients éligibles.

Objectif : Evaluer si les structures intégrant TB et VIH comparées aux structures non-intégrées ont un meilleur taux de prise d'ART parmi les patients éligibles.

Méthodes : Etude transversale utilisant les données de routine des programmes TB de janvier à décembre 2010. L'éligibilité à l'ART a été définie comme un comptage de CD4+ <350 cellules/μl.

Résultats : Respectivement 2761 (86,8%) et 3611 (84,7%) patients ont été éligibles pour l'ART dans les structures intégrées et non-

intégrées ($P < 0,001$). La proportion de patients mis sous ART dans des structures intégrées comparées aux structures non-intégrées n'a pas été significativement différente (35,9% contre 37,1%; $P = 0,340$) ; par contre, la différence a été significative pour les patients de statut VIH inconnu (31,8% contre 24,5%; $P < 0,001$) et de comptage de CD4+ inconnu (40,9% contre 30,4%; $P < 0,001$).

Conclusion : L'intégration des services de TB et VIH dans le Free State (2009–2010) n'a pas été associée à une amélioration de la prise de l'ART. Les raisons n'en sont pas très claires. Par contre, il est préoccupant de constater la proportion élevée de statut VIH inconnu et d'absence de résultats de comptage des CD4+, surtout dans les structures intégrées, et la faible proportion de patients sous ART, qui témoigne d'une mise en œuvre médiocre de l'intégration.

Marco de referencia: Suráfrica ocupa el segundo puesto de los países con la más alta sindemia de tuberculosis (TB) e infección por el virus de la inmunodeficiencia humana (VIH) en todo el mundo. Se estimó que en el 2011 la tasa de coinfección por el VIH y la TB fue 65%. Se integraron los servicios de atención de la TB y el VIH con el propósito de fomentar la aceptación del tratamiento antirretrovírico (ART) por parte de los pacientes que reúnen las condiciones para recibirlo.

Objetivo: Comparar la utilización del ART en los centros integrados de atención de la TB y VIH y en centros no integrados.

Método: Se llevó a cabo un estudio transversal de los datos sistemáticos del programa contra la TB de enero a diciembre del 2010. El criterio de inclusión al ART fue un recuento de linfocitos CD4+ <350 células/μl.

Resultados: En los centros de atención integrada se encontraron 2761 pacientes aptos al ART (86,8%) y 3611 en los centros no integrados (84,7%) ($P < 0,001$). La diferencia en la proporción de

pacientes que comenzó el tratamiento no fue estadísticamente significativa (35,9% contra 37,1%; $P = 0,340$); se observó una diferencia significativa en el porcentaje de pacientes que desconocía su situación frente al VIH (31,8% en los centros integrados contra 24,5% en los demás centros; $P < 0,001$) y en la proporción de pacientes VIH cuyos resultados del recuento de linfocitos CD4+ se desconocía (40,9% contra 30,4%; $P < 0,001$).

Conclusión: La integración de los servicios de atención de la TB y la VIH en la Provincia del Estado Libre de Suráfrica (del 2009 al 2010) no se asoció con una mayor utilización del ART y las razones de este resultado no son claras. Son fuente de inquietud la alta proporción de pacientes que desconocen su situación frente al VIH y la falta de resultados del recuento de linfocitos CD4+, sobre todo en los centros de atención integrada y la baja proporción de pacientes que recibe ART; esta situación puede obedecer a una deficiencia en la integración de los servicios.