Integration of TB and ART services fails to improve TB treatment outcomes: Comparison of ART/TB primary healthcare services in Cape Town, South Africa

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Background. The combined tuberculosis (TB) and HIV epidemics in South Africa (SA) have created enormous operational challenges for a health service that has traditionally run vertical programmes for TB treatment and antiretroviral therapy (ART) in separate facilities. This is particularly problematic for TB/HIV co-infected patients who need to access both services.
Objective. To determine whether integrated TB facilities had better TB treatment outcomes than single-service facilities in Cape Town, SA.
Methods. TB treatment outcomes were determined for newly registered, adult TB patients (aged ≥18 years) at 13 integrated ART/TB primary healthcare (PHC) facilities and four single-service PHC facilities from 1 January 2009 to 30 June 2010. A χ^2 test adjusted for a cluster sample design was used to compare outcomes by type of facility.
Results. Of 13 542 newly registered patients, 10 030 received TB treatment in integrated facilities and 3 512 in single-service facilities. There was no difference in baseline characteristics between the two groups with HIV status determined for 9 351 (93.2%) and 3 227 (91.9%) patients, of whom 6 649 (66.3%) and 2 213 (63%) were HIV-positive in integrated facilities and single-service facilities, respectively. The median CD4$^+$ count of HIV-positive patients was 152 cells/μl (interquartile range (IQR) 71 - 277) for integrated facilities and 148 cells/μl (IQR 67 - 260) for single-service facilities. There was no statistical difference in the TB treatment outcome profile between integrated and single-service facilities for all TB patients (p=0. 56) or for the sub-set of HIV-positive TB patients (p=0.58)
Conclusion. This study did not demonstrate improved TB treatment outcomes in integrated PHC facilities and showed that the provision of ART in the same facility as TB services was not associated with lower TB death and default rates.

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The extent of the combined tuberculosis (TB) and HIV epidemics in South Africa (SA) has created enormous operational challenges for a health service that has traditionally run vertical programmes for TB and HIV, with treatment delivered by different healthcare staff, often in separate facilities. This is particularly problematic for TB/HIV co-infected patients who need to access both services.

In Cape Town, SA, the TB prevalence in HIV-positive patients initiating antiretroviral therapy (ART) has been reported to be as high as 25%,[1] while 51% of TB patients enrolled in the primary healthcare (PHC) TB treatment programme were recorded as co-infected with HIV in 2009.[2] In the developing world, TB is known to be the leading cause of death in HIV-positive patients[3,4] and in 2008 - 2009, a TB-case fatality of 6% was reported in the Cape Town PHC TB programme for HIV-positive TB patients.[5]

Despite the 2010 SA national ART guideline recommendations that ART should be initiated between 2 and 8 weeks after the initiation of TB treatment,[6] long referral delays have been reported between TB and ART facilities.[7,8] These delays could negatively influence TB treatment outcomes, particularly for co-infected patients with low CD4$^+$ counts as the CAMELIA, STRIDE and SAPiT studies have documented. In these studies, death rates were significantly reduced for HIV/TB co-infected patients receiving TB treatment with CD4$^+$ counts <50 cells/μl who initiated ART within 2 weeks after initiating TB treatment.[9-11]

In recent years, the SA National Department of Health (NDoH) has promoted the integration of TB and HIV services to facilitate easy access to healthcare services for TB/HIV co-infected patients and to rationalise resources.[12]

While the introduction of ART in facilities that provide TB treatment could be expected to decrease time from the initiation of TB treatment to the initiation of ART for co-infected patients and therefore impact favourably on TB death and default rates on an individual level, there are few reported data at healthcare facility level comparing TB treatment outcomes between integrated facilities that offer both TB treatment and ART and single-service facilities that only offer TB treatment.

This study evaluated the association of the integration of TB treatment and ART with TB treatment outcomes to determine whether integrated TB facilities, providing both TB and ART, had lower death and default rates than single TB service facilities that

referred patients off-site for ART. As the integration of facilities has been accompanied by the allocation of extra resources and staff, it was envisaged that integration could improve the general standard of care and, in turn, influence outcomes for both HIV-negative and -positive patients.

We investigated the hypothesis that TB treatment outcomes would be better for all TB patients and for TB/HIV co-infected cases in facilities providing TB treatment and ART in one facility than in facilities that only provided TB treatment and required co-infected patients to access ART at a separate facility.

Methods

Population and sample

The target population for this study comprised adult TB patients, aged ≥18 years, who were registered in the national electronic TB register (ETR.net) in all PHC facilities that provided TB treatment in Cape Town over an 18-month period from 1 January 2009 to 30 June 2010.

Setting

During the study period, the Cape Town City Health Directorate and the Western Cape Department of Health provided TB treatment in 99 PHC facilities in eight sub-districts in Cape Town, SA. Of these, 68 provided TB treatment but not ART, while 31 provided integrated ART and TB treatment. All ART and TB services were provided free of charge. The TB treatment regimens during the study period were in accordance with the 2009 SA national TB management guideline.[13] New TB patients received fixed-dose combination tablets consisting of rifampicin, isoniazid, pyrazinamide and ethambutol for a 2-month intensive phase followed by rifampicin and isoniazid for a 4-month continuation phase. Treatment was received 7 days per week. Retreatment TB patients received 2 months of streptomycin 5 days a week plus fixed-dose combination tablets consisting of rifampicin, isoniazid, pyrazinamide and ethambutol 7 days a week for a 3-month intensive phase followed by rifampicin, isoniazid and ethambutol 7 days a week for a 5-month continuation phase.

All TB patients were routinely offered HIV testing. Eligibility for ART was determined for HIV-positive patients through $CD4^+$ count testing and World Health Organization (WHO) disease staging. Consistent with the SA national ART guideline at the time of our study, patients were eligible for ART if they had a $CD4^+$ count <200 cells/μl or WHO stage 4 disease.[14] These patients were offered ART in the same facility, if available, and if not, were referred to another facility to access ART. The recommended ART first-line treatment regimen for co-infected patients during the initial period of the study was stavudine or zidovudine, lamivudine and efavirenz.[14] In March 2010, near the end of the study period, this was changed to tenofovir, lamivudine and efavirenz.[6]

For the purpose of this study, integrated facilities were defined as facilities that provided both ART and TB treatment in the same building. Included in this definition were both partially integrated services that provided ART and TB treatment in different consulting rooms, and fully integrated services where both treatments were provided by the same clinician in the same consulting room.

Single-service facilities only provided TB treatment with patients being referred off-site for ART.

As this study aimed to examine the effect of integration of HIV and TB services, only high-burden TB facilities with a high HIV prevalence were included in the analysis. These were defined as facilities with a TB caseload >400 adult TB patients per year and a HIV prevalence >50% in all TB patients. Facilities were only included in the study if they had been either integrated or single service for the full study period. Patients who were initiated on treatment in hospital and were referred to a PHC clinic to continue their treatment were included in the analysis. However, to avoid possible duplication of cases, patients who were transferred between PHC clinics were excluded. Also excluded were patients with drug-resistant TB.

Study design

This was a retrospective cohort study using routine TB programme data. Facilities were considered as clusters with patients, linked to the facility over the period of sampling, as the individual-level data.

Data sources and management

Out of the 99 TB treatment facilities in Cape Town, 17 were either integrated or single service for the entire study period and met the inclusion criteria for high-burden facilities based on aggregated data for the 18-month period. Of these facilities, 13 were integrated and four were single-service facilities.

Individual patient data from these 17 facilities were extracted for this analysis from the ETR.net for Cape Town. This is a customised computer software program developed for the NDoH National TB Control Programme for the collection of individual patient information for routine monitoring and evaluation of the performance of the programme. TB cases are routinely recorded in a paper-based TB treatment register at PHC-facility level. These data are then captured in the ETR.net. For this study, data were extracted from ETR.net and all unique patient identifiers removed prior to analysis; the facility code was retained to ensure that individuals could be linked to facilities for the cluster analysis.

Data on ART uptake were recorded in ETR.net, but since we were comparing sites that provided ART with sites that did not, the potential for bias in how ART uptake was recorded was high and these data were not considered reliable for comparative purposes. This prohibited an analysis of the direct association of TB treatment outcomes with ART uptake.

Definitions

HIV status

HIV-positive patients were defined as those with positive HIV tests recorded in ETR.net, or with unrecorded test results but were recorded to be receiving ART or co-trimoxazole or had $CD4^+$ test results in ETR.net. HIV-negative patients were defined by recorded HIV-negative test results and no indication of ART or co-trimoxazole treatment in the ETR.net. All other patients were considered to be of unknown HIV status.

TB treatment outcomes

TB treatment outcomes used in this study were the outcomes recorded in ETR.net according to the internationally recommended WHO definitions of cure, completion, failure, death, default, transferred out and not evaluated.[15]

Statistical analysis

Descriptive features of the facilities by integration type were compared. The χ^2 test, adjusted for a cluster sample design, was used to compare categorical variables such as the TB treatment outcome by type of facility. For continuous variables the median value was calculated for each facility and a two-sample Student's *t*-test was used to compare these values between the two types of facilities (analysis at facility level).

Ethics approval

During collection of data for ETR.net, TB patients are not requested to provide informed consent for the collection of data. For this

analysis, the Cape Town City Health TB programme approved the use of an anonymised database of routinely collected TB data for research purposes. Ethics approval for the use of these data was obtained from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease who were requested to waive the requirement for informed consent as the analysis was to be carried out on routinely collected programmatic data with all patient identifiers removed. This study was also approved by the University of Cape Town Research Ethics Committee.

Results

A total of 16 885 patients were registered at the 17 facilities during the study period. Of these, 3 343 patients were excluded from the analysis as they were either <18 years of age or had been transferred between PHC TB facilities. The remaining 13 542 TB patients were included in this analysis.

Baseline characteristics

All patients

The baseline demographics for all 13 542 patients were similar for patients in integrated facilities and single-service facilities (Table 1). The median age was 34 years (interquartile range (IQR) 28 - 42) and 6 331 (46.7%) of the patients were female. HIV status was ascertained for 12 578 (92.9%) patients; 8 862 (65.4%) patients were HIV-positive, 3 716 (27.4%) were HIV-negative and the HIV status was unknown for 964 (7.1%) patients. Of the total, 4 059 (30%) patients were classified as retreatment cases after a previous TB episode. A total of 10 879 (80.3%) patients had pulmonary TB (PTB), 330 (2.4%) had both extrapulmonary (EPTB) and PTB, while 2 333 (17.2%) patients had EPTB. Of the 11 209 patients who had PTB or both PTB and EPTB, 5 557 (49.6%) were smear-positive, 5 019 (44.8%) were smear-negative and 633 (5.6%) had no smear result recorded.

HIV-positive patients

The baseline demographics of the 8 862 HIV-positive patients were similar for patients in integrated facilities and single-service facilities (Table 2). Of all the HIV-positive patients, 4 855 (54.8%) were female and $CD4^+$ counts were recorded for 8 411 (94.9%). The median $CD4^+$ count was 151 cells/μl (IQR 70 - 273) and 5 291 (59.7%) had a $CD4^+$ count <200 cells/μl. There was no difference in $CD4^+$ count distribution between the two groups. Co-trimoxazole was provided to 8 466 (95.5%) of the HIV-positive patients.

TB treatment outcomes

All patients

Fig. 1 compares the TB treatment outcome profile between integrated facilities and single-service facilities for all patients. The aggregated death and default rate for patients treated in all facilities was 16.4%. When compared across the two types of services, aggregated death and default rates were 17.2% (death 6.4%; default 10.8%) for integrated facilities and 14% (death 5.2%; default 8.8%) for single-service facilities.

The treatment success rate (aggregated cured and completion rates) was 74.1% for integrated facilities and 81.7% for single-service facilities. The treatment failure rate was similar for integrated facilities and single-service facilities (1.6% v. 1.7%, respectively). The transfer-out rate was 4.7% at integrated facilities and 1.9% at single-service facilities. There was no statistical difference in the treatment outcome profile between integrated and single-service facilities (p=0.56).

HIV-positive patients

Fig. 2 compares the treatment outcome profile between integrated facilities and single-service facilities for the sub-group of HIV-positive patients. Aggregated death and default rates were 17.2% (death 7.3%; default 9.9%) for integrated facilities and 14.1% (death

Table 1. Baseline characteristics of all TB patients aged ≥18 years registered at 13 integrated and four single-service facilities

	Patients in PHC facilities			
Characteristic	**Total**	**Integrated**	**Single-service**	***p*-value**
Receiving TB treatment, *n*	13 542	10 030	3 512	
Age (years), median (IQR)	34 (28 - 42)	33 (28 - 41)	34 (27 - 42)	0.45
Gender (female), *n* (%)	6 331 (46.7)	4 674 (46.6)	1 657 (47.2)	0.68
HIV status, *n* (%)				
Positive	8 862 (65.4)	6 649 (66.3)	2 213 (63.0)	0.58
Negative	3 716 (27.4)	2 702 (26.9)	1 014 (28.9)	
Unknown	964 (7.1)	679 (6.7)	285 (8.1)	
Classification, *n* (%)				
PTB	10 879 (80.3)	8 030 (80.0)	2 849 (81.1)	0.33
EPTB	2 333 (17.2)	1 721 (17.2)	612 (17.4)	
PTB/EPTB	330 (2.4)	279 (2.8)	51 (1.5)	
New	9 483 (70.0)	7 059 (70.4)	2 424 (69.0)	
Retreatment	4 059 (30.0)	2 971 (29.6)	1 088 (31)	0.58
PTB and PTB/EPTB, *n* (%)				
Smear-positive	5 557 (49.6)	4 110 (49.5)	1 447 (49.9)	0.72
Smear-negative	5 019 (44.8)	3 706 (44.6)	1 313 (45.3)	
No smear	633 (5.6)	493 (5.9)	140 (4.8)	

PHC = primary healthcare; TB = tuberculosis; IQR = interquartile range; PTB = pulmonary tuberculosis; EPTB = extrapulmonary tuberculosis.

Table 2. Baseline characteristics of HIV-positive TB patients aged ≥18 years registered at 13 integrated and four single-service facilities

	Patients in PHC facilities			
Characteristic	**Total**	**Integrated**	**Single-service**	***p*-value**
Receiving TB treatment, *n* (%)	8 862	6 649	2 213	
Age (years), median (IQR)	34 (28 - 40)	33 (28 - 40)	34 (28 - 40)	0.32
Gender (female), *n* (%)	4 855 (54.8)	3 629 (54.6)	1 226 (55.4)	0.40
$CD4^+$ count (cells/μl), *n* (%)				
Median (IQR)	151 (70 - 273)	152 (71 - 277)	148 (67 - 260)	0.96
≤50	1 504 (17)	1 117 (16.8)	387 (17.5)	0.70
51 - 100	1 441 (16.3)	1 083 (16.3)	358 (16.1)	
101 - 200	2 346 (26.5)	1 779 (26.8)	567 (25.6)	
201 - 350	1 809 (20.4)	1 355 (20.4)	454 (20.5)	
>350	1 311 (14.8)	1 025 (15.4)	286 (12.9)	
Missing	451 (5.1)	290 (4.4)	161 (7.3)	
Classification, *n* (%)				
PTB	6 725 (75.9)	5 017 (75.4)	1 708 (77.2)	0.37
EPTB	1 846 (20.8)	1 387 (20.9)	459 (20.7)	
PTB/EPTB	291 (3.3)	245 (3.7)	46 (2.1)	
New	6 138 (69.3)	4 639 (69.8)	1 499 (67.7)	0.39
Retreatment	2 724 (30.7)	2 010 (30.2)	714 (32.3)	
PTB and PTB/EPTB, *n* (%)				
Smear-positive	2 796 (39.9)	2 099 (39.7)	697 (39.7)	0.76
Smear-negative	3 747 (53.4)	2 790 (53)	957 (54.6)	
No smear	473 (6.7)	373 (7.1)	100 (5.7)	
Receiving co-trimoxazole, *n* (%)				
Yes	8 446 (95.5)	6 349 (95.5)	2 117 (95.7)	0.84
No	396 (4.5)	300 (4.5)	96 (4.3)	

PHC = primary healthcare; TB = tuberculosis; IQR = interquartile range; PTB = pulmonary tuberculosis; EPTB = extrapulmonary tuberculosis.

5.8%; default 8.3%) for single-service facilities. The treatment success rate was 73.2% for integrated facilities and 81.2% for single-service facilities. Treatment failure rates were similar for integrated facilities and single-service facilities (1.8% v. 1.6%, respectively). The transfer-out rates was 5.1% at integrated facilities and 2.3% at single-service facilities. There was no statistical difference in the treatment outcome profile between integrated and single-service facilities (p=0.58).

Discussion

The results of this study, involving a large cohort of patients (N=13 542) who received TB treatment according to programmatic standards, reflect actual operational TB treatment outcomes in Cape Town. The study showed high unfavourable outcomes (aggregated death and a default rate of 16.4%) among all TB patients in high-TB/HIV-burden PHC facilities. There was no significant difference in these outcomes between integrated facilities and single-service facilities. Overall single-service facilities had slightly better treatment outcomes with greater treatment success rates and lower death and default rates. However, there were more patients whose outcomes were not evaluated in the integrated facilities.

Our results are similar to those of a much smaller study, which showed a decrease in time between the initiation of TB treatment and that of ART for TB/HIV co-infected patients when ART was introduced into routine TB services in Khayelitsha, Cape Town, but did not show an impact on TB treatment outcomes.[16] Other studies in Uganda and Kenya[17,18] have shown improvements in TB treatment success rates and a marked reduction in death and default rates after the integration of TB and ART services. However, both these studies reported higher death and default rates after integration of services than were observed in either the integrated or single-service facilities in our study. In Uganda, death and default rates were decreased from 33% to 25% after the integration of services and in Kenya, the lost to follow-up rate decreased from 36% to 12.5% and death rates were reduced from 20% to 5.4% over a 5-year period after integration of services. While this shows an impressive improvement in outcomes, aggregated death and default rates remain high, ranging from 17.2% to 25% in the Cape Town, Kenyan and Ugandan studies despite integration of services.

In this study, the HIV prevalence in TB patients was very high (65.4%); almost 60% of patients had a $CD4^+$ count <200 cells/μl and would have been eligible for ART under the 2004 SA national HIV treatment guideline.

Study limitations

A limitation of the study is that data on ART uptake and ART initiation dates were not uniformly collected in the TB services. We could, therefore, not perform a comparative study of ART uptake or determine whether the integration of services reduced the time

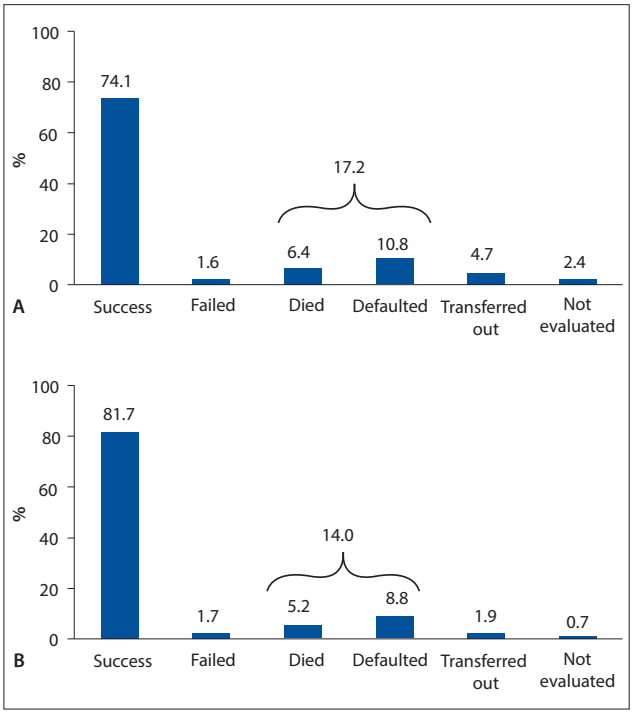

Fig. 1. Comparison of the treatment outcome profiles of all TB patients aged ≥18 years registered at (A) 13 integrated and (B) four single-service facilities (p=0.56).

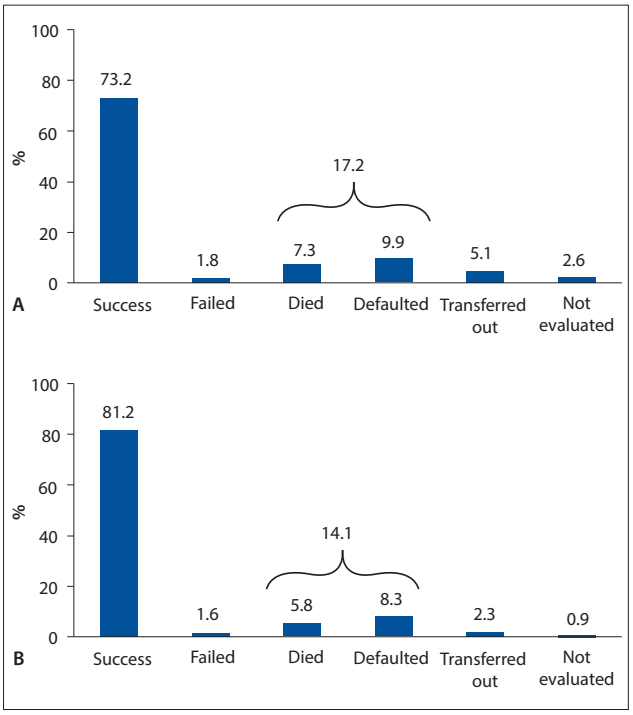

Fig. 2. Comparison of treatment outcome profiles of HIV-positive TB patients aged ≥18 years registered at (A) 13 integrated and (B) four single-service facilities (p=0.58).

between initiation of TB treatment and that of ART. Therefore this study could not determine the direct influence of ART on TB treatment outcomes.

Other studies in Cape Town have shown poor uptake of ART and long delays in time from initiation of TB treatment to that of ART in both integrated and single-service facilities. Pepper *et al.*[19] noted that 34/100 TB patients who were eligible for ART did not initiate treatment in an integrated TB and ART facility in Cape Town and reported a median time of 58 days from initiation of TB treatment to initiation of ART for co-infected patients. Nglazi *et al.*[20] reported that 19.7% of ART-eligible TB patients did not initiate ART during their TB treatment in a large facility in Cape Town that had both ART and TB services on-site and recorded a median delay of 51 days between initiation of TB treatment and that of ART.

A further limitation of our study was that many of the single-service facilities were excluded from the analysis due to either a small annual TB caseload or low co-infection rate. The study therefore compared four single-service facilities with a combined caseload of 3 152 patients with 13 integrated facilities with a combined caseload of 10 030 patients. While this limited the power of the analysis to determine a statistically significant difference in outcomes, the trend of the analysis was for improved outcomes in the single-service facilities and not the integrated facilities.

This study could also not determine the long-term influence of integrated services on mortality, as the analysis was restricted to the period of TB treatment. It is possible that integrated services would be better able to retain HIV-positive patients in care after TB treatment and therefore ensure better long-term outcomes for co-infected patients.

Conclusion

While the scale-up of ART in Cape Town has improved access to HIV treatment for TB/HIV co-infected patients, the high HIV prevalence, low median CD4$^+$ counts and high death and default rates remain serious problems within the health services. This study has shown that in itself, the provision of ART in the same facility as TB services was not associated with improved TB treatment outcomes in the routine TB services. The exact reasons why the integration of services was not associated with better programmatic outcomes are not clear and warrant further operational research to inform services on how to improve integration. It is possible that an accurate recording of ART uptake and time taken to initiate ART, as part of routine indicators, would assist in assessing whether the provision of ART in TB facilities has actually improved access to ART.

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