An intervention to optimise the delivery of integrated tuberculosis and HIV services at primary care clinics: results of the MERGE cluster randomised trial

Kufa T.[a,b,c,*], Fielding K.L.[d], Hippner P.[a], Kielmann K.[e], Vassall A.[f], Churchyard G.J.[a,b,d], Grant A.D.[b,g,h], Charalambous S.[a,b]

[a] *The Aurum Institute, Johannesburg, South Africa*
[b] *The School of Public Health, University of the Witwatersrand, Johannesburg, South Africa*
[c] *Centre for HIV and STIs, National Institute for Communicable Diseases, Johannesburg, South Africa*
[d] *Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom*
[e] *Institute for Global Health and Development, Queen Margaret University, Edinburgh, United Kingdom*
[f] *Department of Global Health and Development, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom*
[g] *Department of Clinical Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom*
[h] *Africa Health Research Institute, School of Nursing and Public Health, University of KwaZulu-Natal, South Africa*

ARTICLE INFO

ABSTRACT

Objectives: To evaluate the effect of an intervention to optimize TB/HIV integration on patient outcomes.
Methods: Cluster randomised control trial at 18 primary care clinics in South Africa. The intervention was placement of a nurse (TB/HIV integration officer) to facilitate provision of integrated TB/HIV services, and a lay health worker (TB screening officer) to facilitate TB screening for 24 months. Primary outcomes were i) incidence of hospitalisation/death among individuals newly diagnosed with HIV, ii) incidence of hospitalisation/death among individuals newly diagnosed with TB and iii) proportion of HIV-positive individuals newly diagnosed with TB who were retained in HIV care 12 months after enrolment.
Results: Of 3328 individuals enrolled, 3024 were in the HIV cohort, 731 in TB cohort and 427 in TB-HIV cohort. For the HIV cohort, the hospitalisation/death rate was 12.5 per 100 person-years (py) (182/1459py) in the intervention arm vs. 10.4/100py (147/1408 py) in the control arms respectively (Relative Risk (RR) 1.17 [95% CI 0.92–1.49]).For the TB cohort, hospitalisation/ death rate was 17.1/100 py (67/ 392py) vs. 11.1 /100py (32/ 289py) in intervention and control arms respectively (RR 1.37 [95% CI 0.78–2.43]). For the TB-HIV cohort, retention in care at 12 months was 63.0% (213/338) and 55.9% (143/256) in intervention and control arms (RR 1.11 [95% 0.89–1.38]).
Conclusions: The intervention as implemented failed to improve patient outcomes beyond levels at control clinics. Effective strategies are needed to achieve better TB/HIV service integration and improve TB and HIV outcomes in primary care clinics.
Trial registration: South African Register of Clinical Trials (registration number DOH-27-1011-3846).

1. Introduction

South Africa faces a large burden of the dual epidemics of tuberculosis (TB) and HIV. With an HIV prevalence of 12.8% in the general population [1], an estimated TB incidence rate of 781 per 100,000 of the population [2], and HIV positivity of 59% among individuals diagnosed TB in 2016 [2], the country could benefit from improved integration of TB and HIV services. The integration of TB and HIV services refers to co-location and joint delivery of TB and HIV-related services. TB and HIV integration comprise activities to reduce morbidity and mortality from HIV among individuals with TB - HIV counselling and testing, initiation of cotrimoxazole preventive therapy (CPT) and earlier initiation of antiretroviral therapy (ART) as well activities to reduce morbidity and mortality from TB among individuals living with HIV - intensified case finding, isoniazid preventive therapy (IPT), TB infection control and the early initiation of ART [3, 4]

---

* Corresponding author at: Centre for HIV and STIs, National Institutes of Communicable Diseases, 1 Modderfontein Road, Sandringham, United Kingdom.
E-mail addresses: tendesayikc@nicd.ac.za, tendesayik@yahoo.com (T. Kufa).

Different models have been used to deliver integrated TB/HIV services at primary care level [5, 6]. These models range from separate services with referral between them to complete integration where care for both diseases is provided by the same provider in the same consultation [6]. Evidence of the benefits of TB/HIV integration is limited to evidence of improved TB treatment outcomes, increased ART uptake and shorter time to ART initiation among HIV positive individuals treated for TB [7–10]. Information on the effectiveness of interventions to improve integration of TB and HIV services and the effect of such integration on distal outcomes such as mortality, hospitalisations and retention in care is however limited [6, 11–13]. We report on the outcomes of a cluster randomised trial to evaluate the effect of an intervention to optimise integration of TB and HIV-related services on morbidity (hospitalizations), mortality and retention in care among individuals newly diagnosed with TB and individuals newly diagnosed with HIV at primary care clinics in South Africa.

2. Methods

2.1. Study design and setting

The setting and methods of this cluster-randomised trial have been previously reported. [14] Clusters comprised primary care clinics in a sub-district of Ekurhuleni District, Gauteng province, South Africa. At randomization in August 2011, all the participating clinics provided TB and HIV services under the same roof, but these services were run separately with varying levels of cross-referral between them – that is they had co-location of services. This level of integration- co-location of services- was assumed sub-optimal with the one-stop-shop model- a model in which both TB and HIV services are provided by the same provider in the same consultation- considered ideal. [15] In addition, in the sub-district where the trial was implemented, there was an on-going TB/HIV health systems strengthening programme whose main activities were mentoring clinic nurses on ART and training on recording and reporting for TB and HIV. At the time of clinic randomization, South African national HIV treatment guidelines recommended ART for HIV positives with WHO Stage 3 or 4 disease, CD4 count < 200 cells/μl, TB disease or pregnancy with at CD4 counts < 350 cells/μl. [16] These guidelines changed in March 2012 making patients who were HIV positive and had CD4 counts < 350 cells/μl, TB or were pregnant eligible for ART regardless of CD4 count [17]. In 2016, CD4 criteria for ART eligibility were removed, making all positive individuals eligible for ART [18].

2.2. Randomization

Of 32 available clinics, 18 were purposively selected, i) ensuring availability of TB diagnostic and treatment services, ii) at least 40 TB patients registered at the clinic in the preceding year, iii) good geographic spread the sub-district (clinics not too close to one another) and iv) absence of other competing research studies. The selected clinics were stratified into high or low case-fatality clinics (i.e. TB CFR rates > 3.5% OR ≤ 3.5% among smear-positive TB patients diagnosed in 2010), and then randomly assigned within strata to either the intervention or the control arm. Randomization was done by pulling numbers out of bowls. This was done at a meeting with clinic managers and sub-district health management staff and facilitated by the trial statistician.

2.3. Description of the intervention

The intervention was a set of activities to optimise the integration of TB and HIV services beyond the level prevailing at the control clinics and has been described previously. [14] Briefly, the intervention were any activities meant to address clinic level barriers to better delivery and co-location of TB/HIV services at each intervention clinic. These

were tailored to the physical layout, human resources availability and needs and priorities of the clinics with respect to TB/HIV integration. In order to support the implementation of such activities, the trial introduced two new staff cadres – a TB/HIV integration officer (IO) and a TB screening officer (SO). The IOs who were professional nurses with prior TB/HIV experience. Following study specific training, the IOs worked with clinic managers to identify gaps and barriers to effective TB and HIV service integration, to support the clinic with better delivery of TB and HIV collaborative services and to transition towards the single provider model of TB/HIV integration as recommended by the national TB/HIV integration guidelines [19]. At placement, both the IOs and clinic staff were made aware that the IOs were meant to be catalysts for change, that the IOspresence in the clinics was limited to the intervention period (1st September 2011–31st August 2013), and that the clinics were expected to sustain any TB/HIV integration activities initiated by the IOs beyond this intervention period.

The broad function of the SOs was to support the screening of HIV positive individuals for TB, the demand for which was expected to increase with better TB/HIV integration. The TB screening officers were lay workers with previous experience of working in health care settings and their placement was considered task shifting for TB screening- that is use of lay workers in place of nurses to conduct TB screening. The SOs were meant to work with the IOs, clinic staff and managers to identify bottlenecks to TB screening and determine where they would be best located in the clinic in order to maximise the number of HIV positive patients screened for TB. The location of the SOs in the clinics was also allowed to vary depending on the physical layout and the flow of patients in the clinics.Clinics were expected to identify a staff member who would continue with TB screening beyond the intervention period.

2.4. Description of the control clinics

In control clinics, TB and HIV services were provided as recommended by the South African National Department of Health guidelines for TB/HIV integration. At randomization, these guidelines recommended provision of all TB/HIV collaborative services including on-site TB diagnostic services and ART initiations and encouraged the physical integration of the services. [19] However implementation of these guidelines in clinics was variable and sub-optimal with no clinic providing the one-stop-shop model at baseline.

2.5. Baseline assessments and monitoring fidelity to the intervention

At baseline, assessments of participating clinics were conducted to establish clinic characteristics and the extent of co-location of TB and HIV services. Fidelity to the intervention was assessed through bi-monthly monitoring and supervision visits to intervention clinics by the study coordinators and monthly group meetings for IOs and SOs. In addition, the IOs and SOs also completed time sheets in order to document how they spent their time in the clinics. At the end of the intervention period, facility assessments were conducted in order to measure the extent of TB/HIV integration at both intervention and control clinics. During the assessments, quantitative data on clinic level indicators of TB and HIV integration were collected from routine clinic data for the preceding month (May 2013). In addition, assessments of the location of key integrated TB/HIV services (i) TB screening for HIV positive individuals, ii) HIV testing for individuals diagnosed with TB patients and iii) ART treatment and monitoring for individuals diagnosed with both TB and HIV- were conducted. Fig. S1 shows the timing of these activities during the trial.

2.6. Enrolment and follow up of evaluation cohorts

Research assistants placed at each clinic and with assistance from clinic staff, identified and enrolled a consecutive sample of clinic attendees aged ≥18 years and i) newly diagnosed with TB, defined as

having initiated TB treatment in the 60 days preceding enrolment (TB cohort) or ii) newly diagnosed with HIV, defined as having tested HIV positive in the 60 days preceding enrolment (HIV cohort) respectively. Individuals who met inclusion criteria for both TB and HIV cohorts were identified as the TBHIV cohort. At enrolment, baseline questionnaires were administered collecting information on participant demographic and socioeconomic characteristics, TB screening, diagnosis and treatment, HIV testing, care and treatment and on factors related to trial outcomes, as well as contact information for follow-up. Enrolment of participants started at intervention clinics at least three months after the start of the intervention, to allow time for the intervention to have an effect on clinic activity.

Participants were followed up through telephone interviews at six monthly intervals for at least 12 months and up to 18 months for some participants recruited earlier on. During the calls, data on clinic attendance, TB and/or HIV care received were collected. Telephonic interviews were considered necessary to measure outcomes of participants who transferred from or stopped attending care at the clinic of enrolment.Research assistants also conducted medical record review and abstractions. If participants could not be reached through the telephone, their next-of-kin were contacted and information on whether participants had moved, been hospitalised or died obtained. For participants who had a valid South African national identification number, the national vital statistics register was used to determine vital status and date of death if the participant had died. Fig. S1 shows the timing of participant enrolment in relation to the implementation of the intervention.

2.7. Outcomes

The trial had three primary outcomes: i) the incidence of death or hospitalisation in the HIV cohort; ii) the incidence of death or hospitalisation in the TB cohort; and iii) the 12-month retention in care in the TBHIV cohort.Death was defined as any death occurring during the follow-up period as reported by any of next of kin OR detected through the clinic records OR the vital statistics register. Hospitalisations were either self-reported or reported by the next of kin during the follow-up period (excluding those associated with pregnancy). Retention in care among HIV positive individuals newly diagnosed with TB was defined as clinic attendance for routine HIV care with receipt of IPT, CPT, and ART, CD4 or viral load testing which was self - reported or documented on medical record review during the period 305 to 425 days from the date of starting TB treatment. This corresponded to a 12 month visit post ART initiation with a 60 day window around the visit.

The study also had several secondary outcomes. These outcomes were the comparison among intervention and control clinics ofi) Proportion of the TB cohort whoknew their HIV status by the end of TB treatment;ii) median CD4 count at enrolment in the HIV cohort;iii) proportion of HIV cohort who started IPT within 12 months of the HIV test;iv) the proportion of the TB cohort who successfully completed TB treatment during 12 months of follow up;and v) the proportion of the ART-eligible HIV cohortwho initiated ART by 10 weeks after date of CD4 count (based on the current guidelines). These secondary outcomes were selected because they represented steps in the pathway from diagnosis of TB or HIV to primary outcomes and aimed to measure the extent of delivery of integrated TB/HIV services. For both primary and secondary outcomes individuals were considered to enter the cohort on the date of the HIV test and date of starting TB treatment for the HIV and TB cohorts respectively.

2.8. Sample size and statistical analysis

The sample size calculations took into account the clustered design through the coefficient of variation [20–22] and have been outlined previously [14]. Briefly, we assumed nine clinics per arm, a type I error of 5%, a coefficient of variation of 0.25 and 15 months average follow-

up time for the hospitalisation/mortality outcome. We assumed a sample size of 60 patients per clinic for the TB cohort and 165 patients for the HIV cohort per clinic across the 18 clinics taking into account refusals and loss to follow up [14].For the TB cohort, assuming an incidence of hospitalisation or mortality of 20 per 100 person-years (py) in the control clinics, the target sample size cited above gave 92% power to assess a 50% reduction in either mortality or hospitalisation at the intervention clinics [14]. For the HIV cohort, we assumed an incidence of hospitalisation or mortality of 15 per 100 py in the control clinics which gave 86% power to assess a 40% reduction in either mortality or hospitalisation at the intervention clinics. For the retention in care endpoint, we assumed that 70% of TB cohort would be HIV positive and that 30% would not be retained in care over a 12-month period in the control clinics. [14] This gave 90% power to assess a 50% reduction in the proportion not retained over a 12-month period in the intervention clinics.

For the primary outcome person time at risk was measured from date of HIV test or starting TB treatment to the earlier of first hospitalisation, death, or date last known to be alive, for the HIV and TB cohorts, respectively. Date last known to be alive was defined using multiple data sources: date of most recent interview; date of most recent routine clinic visit; date last seen alive as reported by the participant's next of kin (if participant was lost to follow-up); and the vital statistics register (those with a South African identity number).

The analysis of the intervention effect on primary and secondary outcomes was based on comparisons of two arms (intervention vs control) for in the three cohorts (TB, HIV and TBHIV cohorts).The analyses generated cluster-level summaries and took into account the stratified randomization. Briefly, the logs of the cluster-level summaries of the outcomes were used to calculate geometric means in each of the two arms. An approximate standard error for the log (risk or rate) ratio based on geometric means of cluster risks or rates were calculated by two-way analysis of variance on randomization stratum, arm, and the interaction between stratum and arm. The 95% confidence interval (CI) was calculated from this standard error, using a *t*-statistic with 14 degrees of freedom. An adjusted analysis, taking into account baseline imbalances, was also conducted using a two-stage approach recommended for studies with a small number of clusters. [14, 21, 22] Pre-specified subgroup analyses for sex, CD4 count strata (< 350 cells/μl versus 350 or over cells/μl), social –economic status and enrolment period (last year of enrolment versus earlier) were planned for all primary outcomes. Socioeconomic status was measured using the socio-economic position index (defined as the number of assets that theparticipant ownedoutof a list of 16 listed (working electric/gas stove, working vacuum cleaner,working washing machine,working satellite television,working digital videodisc[DVD] player, working motor/car,working mail/ post box/bag,working mail delivery at home,-working radio,working television [TV],working computer,working refrigerator,working landline telephone,working cell phone,working bicycle,working motorcycle/ scooter). The scores were determined for each participants and distribution of the index determined using principal component analysis [23]. Participants who belonged to lower, middle and upper thirds of this distribution were identified.This items included in the index were adapted from a questionnaire used by Statistics South Africa household surveys [24].

2.9. Ethical considerations

Ethical clearance was obtained from the research ethics committees of University of the Witwatersrand and the London School of Hygiene & Tropical Medicine as well as from the Centres for Disease Control (CDC) office of the Associate Director for Science.Permission to conduct the study was also obtained from the Ekurhuleni District Department of Family Health prior to randomization. The trial was registered on the South African Register of Clinical Trials (registration number DOH-27-1011-3846). Participants enrolled in the evaluation cohorts were
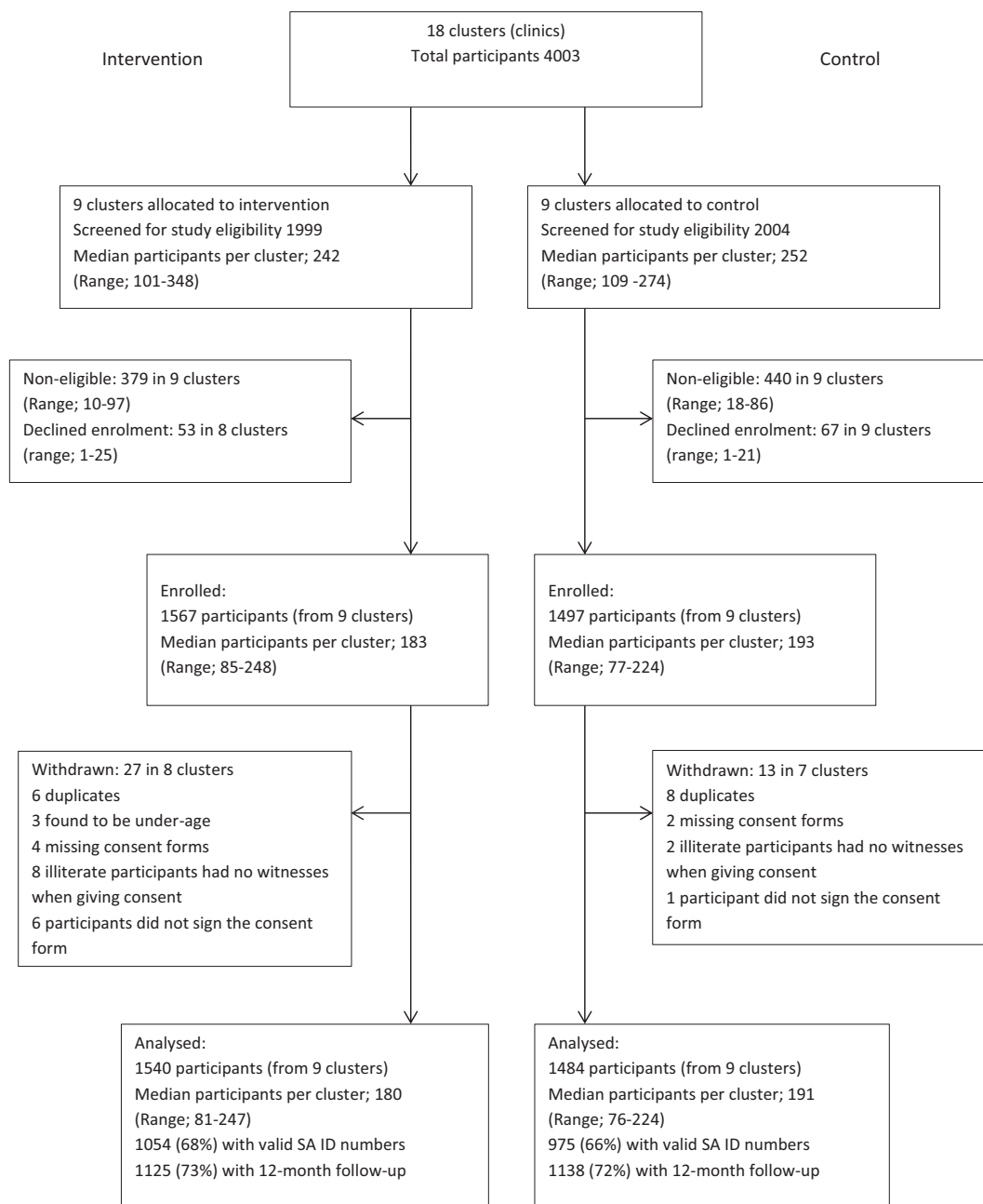
Intervention

Control

```
┌──────────────────────────────────────┐
│        18 clusters (clinics)          │
│        Total participants 4003        │
└──────────────────────────────────────┘
```

```
┌─────────────────────────────────────┐    ┌─────────────────────────────────────┐
│ 9 clusters allocated to intervention │    │ 9 clusters allocated to control     │
│ Screened for study eligibility 1999  │    │ Screened for study eligibility 2004 │
│ Median participants per cluster; 242 │    │ Median participants per cluster; 252│
│ (Range; 101-348)                     │    │ (Range; 109 -274)                   │
└─────────────────────────────────────┘    └─────────────────────────────────────┘
```

```
┌─────────────────────────────────────┐    ┌─────────────────────────────────────┐
│ Non-eligible: 379 in 9 clusters     │    │ Non-eligible: 440 in 9 clusters     │
│ (Range; 10-97)                      │    │ (Range; 18-86)                      │
│ Declined enrolment: 53 in 8 clusters│    │ Declined enrolment: 67 in 9 clusters│
│ (range; 1-25)                       │    │ (range; 1-21)                       │
└─────────────────────────────────────┘    └─────────────────────────────────────┘
```

```
┌─────────────────────────────────────┐    ┌─────────────────────────────────────┐
│ Enrolled:                           │    │ Enrolled:                           │
│ 1567 participants (from 9 clusters) │    │ 1497 participants (from 9 clusters) │
│ Median participants per cluster; 183│    │ Median participants per cluster; 193│
│ (Range; 85-248)                     │    │ (Range; 77-224)                     │
└─────────────────────────────────────┘    └─────────────────────────────────────┘
```

```
┌─────────────────────────────────────┐    ┌─────────────────────────────────────┐
│ Withdrawn: 27 in 8 clusters         │    │ Withdrawn: 13 in 7 clusters         │
│ 6 duplicates                        │    │ 8 duplicates                        │
│ 3 found to be under-age             │    │ 2 missing consent forms             │
│ 4 missing consent forms             │    │ 2 illiterate participants had no    │
│ 8 illiterate participants had no    │    │ witnesses when giving consent       │
│ witnesses when giving consent       │    │ 1 participant did not sign the      │
│ 6 participants did not sign the     │    │ consent form                        │
│ consent form                        │    │                                     │
└─────────────────────────────────────┘    └─────────────────────────────────────┘
```

```
┌─────────────────────────────────────┐    ┌─────────────────────────────────────┐
│ Analysed:                           │    │ Analysed:                           │
│ 1540 participants (from 9 clusters) │    │ 1484 participants (from 9 clusters) │
│ Median participants per cluster; 180│    │ Median participants per cluster; 191│
│ (Range; 81-247)                     │    │ (Range; 76-224)                     │
│ 1054 (68%) with valid SA ID numbers │    │ 975 (66%) with valid SA ID numbers  │
│ 1125 (73%) with 12-month follow-up  │    │ 1138 (72%) with 12-month follow-up  │
└─────────────────────────────────────┘    └─────────────────────────────────────┘
```

Fig. 1. CONSORT diagram for the HIV cohort.

requested to provide written informed consent before enrolment into the study. The study was conducted according to ICH/GCP guidelines and had oversight from a Data Monitoring Committee.

3. Findings

3.1. Description of clinics

At randomization, intervention clinics were comparable to control clinics with respect to opening hours, adult head count per month and the number of TB and HIV services provided (Supplementary Table S1).During the enrolment and follow up periods, no clinics were dropped from the trial (Fig. 1).

3.2. Fidelity to the intervention

The intervention was implemented over a 24-month period as planned. IOs were present at all intervention clinics for 197 person-months (91% of the intervention period), while SOs were present for 191 person-months (88% of the intervention period). From analyses of timesheets and in-depth interviews, the main activities of the TB/HIV integration officers were providing direct care to patients (mean monthly proportion 39.6%), administration duties (mean 32.8%), reporting and recording TB and HIV activities (mean 10.6%), mentoring counsellors and data clerks (mean 3.6%) (See Fig. S2), in contrast to the leadership and coordination role envisaged at intervention design. The main activities of the SOs were screening patients for TB, completing registers and following up individuals with confirmed TB who failed to return to initiate TB treatment as intended at trial conception.
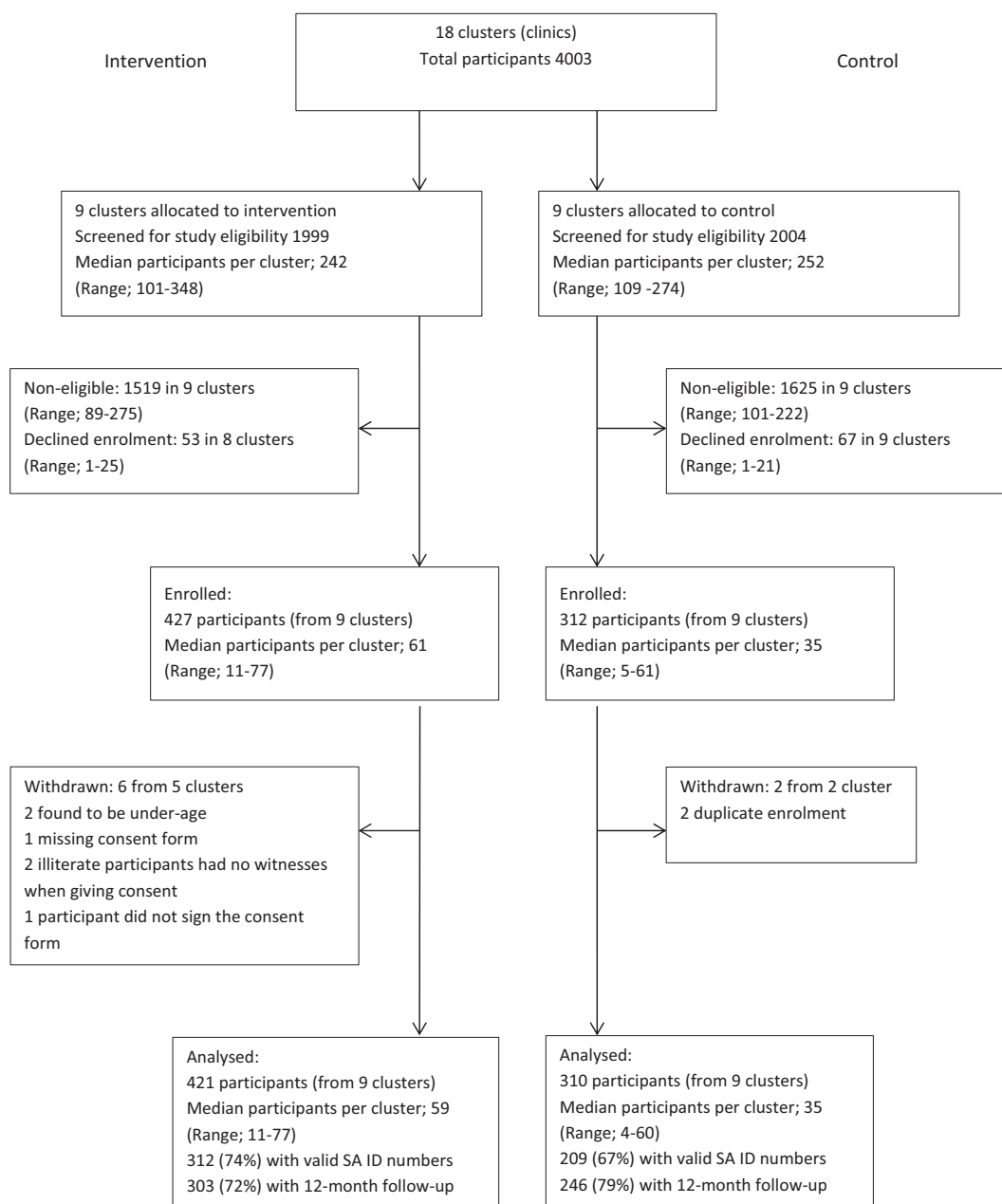
```
                          ┌─────────────────────────────────┐
                          │ 18 clusters (clinics)           │
Intervention              │ Total participants 4003         │            Control
                          └─────────────────────────────────┘
```

Intervention

18 clusters (clinics)
Total participants 4003

Control

9 clusters allocated to intervention
Screened for study eligibility 1999
Median participants per cluster; 242
(Range; 101-348)

9 clusters allocated to control
Screened for study eligibility 2004
Median participants per cluster; 252
(Range; 109 -274)

Non-eligible: 1519 in 9 clusters
(Range; 89-275)
Declined enrolment: 53 in 8 clusters
(Range; 1-25)

Non-eligible: 1625 in 9 clusters
(Range; 101-222)
Declined enrolment: 67 in 9 clusters
(Range; 1-21)

Enrolled:
427 participants (from 9 clusters)
Median participants per cluster; 61
(Range; 11-77)

Enrolled:
312 participants (from 9 clusters)
Median participants per cluster; 35
(Range; 5-61)

Withdrawn: 6 from 5 clusters
2 found to be under-age
1 missing consent form
2 illiterate participants had no witnesses
when giving consent
1 participant did not sign the consent
form

Withdrawn: 2 from 2 cluster
2 duplicate enrolment

Analysed:
421 participants (from 9 clusters)
Median participants per cluster; 59
(Range; 11-77)
312 (74%) with valid SA ID numbers
303 (72%) with 12-month follow-up

Analysed:
310 participants (from 9 clusters)
Median participants per cluster; 35
(Range; 4-60)
209 (67%) with valid SA ID numbers
246 (79%) with 12-month follow-up

Fig. 2. CONSORT diagram for the TB cohort.

3.3. Delivery of integrated TB/HIV service at intervention and control clinics at the end of the intervention period

Overall, there was no difference in location and extent of delivery of TB and HIV collaborative services based on facility assessments and analysis of routine data at the end of the intervention period (see Tables S2 and S3). However, at the end of the intervention period, there was a higher proportion of newly diagnosed HIV positive clinic attendees screened for TB (94.3% vs 39.1%) and a lower proportion of newly diagnosed HIV positive clinic attendees initiated on IPT initiation (29.1% vs 40.2%) at intervention clinics compared to control (see Table S3).

3.4. Description of evaluation cohorts

Between January 2012 to July 2013, 4003 individuals were screened for eligibility and 3393 participants were enrolled for follow up until the end of July 2014 as planned. A total of 3024 participants (1540 in intervention and 1484 in control arm) were eligible for inclusion in the HIV cohort (Fig. 1) and 731 (421 in intervention and 310 in control clinics) were eligible for inclusion in the TB cohort (Fig. 2). There were 427 participants (173 control and 254 intervention clinics) included in both cohorts and therefore made up the TBHIV cohort. Figs. 1 and 2 show CONSORT diagrams for the TB and HIV cohorts.

Participants in both cohorts were comparable with respect to most characteristics at enrolment, by arm (Tables 1 and 2). For the HIV cohort, however, participants in the intervention arm were more likely to be South African born, to be unemployed, to have a lower asset count and to be in the bottom third of the socio-economic position index, to be on CPT at enrolment and less likely to be on ART at enrolment compared to participants in the control arm. For the TB cohort, participants in the intervention arm were also more likely to be South African born and to be in the bottom third of the socio-economic position index compared to those in the control arm.

Table 1
Characteristics of individuals who were newly diagnosed with HIV at enrolment by arm (*n* = 3024).

Characteristic	Intervention (1540)	Control (1484)
Age in years, median (IQR)	34.2 (28.5–40.2)	33.7(28.5–40)
Males, n (%)	608(39.5)	530(35.7)
Married or cohabiting, n (%)[a]	590(38.3)	678(45.7)
South African born, n (%)[a]	1285 (83.4)	1167 (78.6)
Completed grade 12 or higher, n (%)[a]	528(34.3)	606(40.8)
Employed, n (%)[a]	819(53.2)	876(59.0)
Asset count, median (IQR)[a,b]	6 (4–8)	7 (5–9)
In bottom one third of socio-economic position index, n (%)[c]	575 (37.3)	410 (27.6)
Distance from clinic < 5 km, n (%)	1154 (74.9)	1111 (74.9)
Lived alone, n (%)	273(17.8)	303(20.4)
Length of time in town (years),median (IQR), n	7 (1–14)	5(1 − 13)
Ever smoked, n (%)	375 (24.4)	361 (24.3)
Currently drink alcohol, n (%)	345 (22.4)	345 (23.2)
Hospitalized in the last 12 months, n (%)	264 (17.1)	233 (15.7)
Know someone who was ill or died from HIV, n (%)	814 (52.9)	870 (58.6)
Believes that traditional healers can treat HIV, n (%)	99 (6.5)	134 (9.0)
Ever treated for TB	120 (7.8)	100 (6.7)
Newly diagnosedwith TB	254 (16.5)	173 (11.7)
Duration since HIV test (median, IQR)	12 (7–21)	11 (7–20)
On CPT at enrolment, n (%)[a,d]	602(39.1)	472(31.8)
IPT use at or prior to enrolment, n (%)[a,d]	168(10.9)	208(14.5)
Attending usual clinic for HIV care, n (%)	1461 (94.9)	1418 (95.6)
On ART at enrolment, n (%)[a,d]	331 (21.5)	397(26.8)
Pregnant[a,e]	157 (16.9)	236 (24.8)

IQR - interquartile range.

[a] Variables for which there appeared to be some imbalance between arms.

[b] The number of assets the participant owned out 16 assets listed (working electric/gas stove, working vacuum cleaner, working washing machine, working satellite television, working digital video disc (DVD) player, working motor/car, working mail/ post box/bag, working mail delivery at home, working radio, working TV, working computer, working refrigerator, working landline telephone, working cellphone, working bicycle, Working motorcycle/ scooter).

[c] Based on a socio-economic position index with the following elements (assets, water source, type of toilet, type of floors and walls at participants dwelling). Variables to include in the SEP index determined through principal component analysis.

[d] Started Isoniazid preventive therapy (IPT), Cotrimoxazole preventive therapy (CPT) or antiretroviral therapy (ART) prior to or on the day of enrolment.

[e] Out of 931 females at intervention clinics and 953 females at control clinics.

Table 2
Characteristics of individuals who were newly diagnosed with TB at enrolment by arm (*N* = 731).

Characteristic	Intervention(421)	Control (310)
Age in years, median (IQR)	36.6 (29.3–42.7)	35.9(29.6–42.7)
Males, n (%)	225 (53.4)	173(55.8)
Married or cohabiting, n (%)	151(35.9)	125(40.3)
South African born, n (%)[a]	379(90)	249(80.3)
Completed grade 12 or higher, n (%)[a]	152(36.1)	143(46.1)
Employed, n (%)	226(53.7)	179(57.7)
Total asset count, median (IQR),[b]	7 (4–8)	7 (5–9)
In bottom one third of socio-economic position index, n (%)[c]	164 (39.0)	77 (24.8)
Distance from clinic < 5 km, n (%)	324 (77)	234(75.5)
Worked in the mines, n (%)[a]	31(7.4)	11(3.5)
Lived alone, n (%)	71(16.7)	50(16.1)
Length of timein town, median (IQR)	7(1–15)	6 (2–14.5)
Ever smoked, n (%)	133(31.6)	93 (30)
Currently drink alcohol, n (%)	74 (17.6)	71 (22.9)
Previous TB treatment (n, %)	65(15.4)	40(12.9)
Hospitalised in the last 12 months, n (%)	115 (27.3)	82 (26.5)
Know someone who was ill or died from HIV, n (%)[a]	185 (43.9)	187(60.3)
Believes that traditional healers can treat HIV, n (%)	23 (5.5)	14(4.5)
Documented HIV test at enrolment, n (%)	396 (94.1)	288(92.9)
HIV positive at enrolment, n (%)	329(78.1)	254 (81.9)
Duration since HIV test (median, IQR)	20 (7–44)	21 (8–62)
Newly diagnosed HIV positive, n (%)	245 (58.2)	172 (55.5)
On CPT at enrolment, n (%)[a,d,e]	186(56.5)	106(41.7)
On ART at enrolment, n (%)[d,e]	91 (27.7)	79(31.1)
Pregnant, n (%)[f]	8 (4.1)	5 (3.7)

IQR- interquartile range.

[a] Variables for which there appeared to be some imbalance between arms.

[b] The number of assets the participant owned out the 16 listed (working electric/gas stove, working vacuum cleaner, working washing machine, working satellite television, working digital video disc (DVD) player, working motor/ car, working mail/ post box/bag, working mail delivery at home, working radio, working television (TV), working computer, working refrigerator, working landline telephone, working cell phone, working bicycle, Working motorcycle/ scooter).

[c] Based on a socio-economic position index with the following elements based on a socio-economic position index with the following elements (assets, water source, type of toilet, type of floors and walls at participants dwelling). Variables to include in the SEP index determined through principal component analysis.

[d] Denominator is HIV positive TB patients (329 in the intervention arm and 254 in the control arm).

[e] started Cotrimoxazole preventive therapy (CPT) or antiretroviral therapy (ART) prior to or on the day of enrolment.

[f] Out of 196 females at intervention clinics and 136 females at control clinics.

3.5. Effect of the intervention on the co- primary outcomes of hospital admissions and or mortality

The median follow-up for the HIV and TB cohorts was 12.3 and 12.2 months, respectively, and similar by arm.Among individuals in the HIV cohort, the incidence of hospitalisation or death in 12 months of follow up was 12.5 per 100 person-years (py) (182/1459) and 10.4 per 100 py (147/1408) in the intervention and control clinics respectively, giving an incidence rate ratio [IRR] of 1.17 (95% CI 0.92, 1.49), adjusting for randomization strata.After adjusting for age, sex, randomization strata and variables showing baseline imbalance the adjusted IRR was 1.08 (95% CI 0.84–1.38) (Table 3 and Table S4 supplementary appendix). In subgroup analyses, the effects of the intervention were similar by sex, socioeconomic position index (low versus high), and year of enrolment and among those with CD4 counts < 350 cells/μl (Table 4). In the TB cohort, the incidence of hospitalisation or death was 17.1 per 100 py (67/392py) and 11.1 per 100py (32/289py) in the intervention and control clinics respectively, giving an adjusted IRR 1.22 (95% CI 0.70–2.13) in a model adjusting for age, sex,

randomization strata and variables showing baseline imbalance (see Table 3 and Tables S5 in the supplementary appendix). The sample was too small to conduct subgroup analyses for this cohort.

3.6. Effect of the intervention on the co-primary outcome of retention in care

Of 338 individuals in the TB-HIV cohort, 213/338 (63.0%) were retained in care by 12 months in the intervention arm, compared to 143/256 (55.9%) in the control arm, giving an adjusted risk ratio (RR) of 1.11 (95% CI 0.89–1.38) (Table 3), adjusting for randomization strata. A fully-adjusted analysis gave similar results. The sample was too small to conduct subgroup analyses (see Table 3 and Table S5 in the supplementary appendix).

3.7. Effect of the intervention on the secondary outcomes

Table 5 shows the effect of the intervention on the secondary

Table 3
Effect of intervention on the primary outcomes of incidence of hospitalizations and mortality among individuals newly diagnosed with TB and individuals newly diagnosed with HIV and proportion retained in HIV care by 12 months among HIV-positive TB patients.

Primary outcome	Intervention arm		Control arm		Adjusted incidence rate ratio[1] (95% CI)	p-Value[a]	Adjusted incidence rate ratio (95% CI)	p-Value
	N	(Hospitalization or deaths/person-years of follow up) Incidence per 100 person-years	N	(Hospitalisation or deaths/person-years of follow up) Incidence per 100 person-years				
Incidence of morbidity or mortality among individuals newly diagnosed with HIV	1540	(182/1459) 12.5	1484	(147/1408) 10.4	1.17 (0.92, 1.49)	0.18	1.08 (0.84, 1.38)[b]	0.51[b]
Incidence of morbidity or mortality among individuals newly diagnosed with TB[c]	421	(67/392) 17.1	310	(32/289) 11.1	1.37 (0.78, 2.43)	0.25	1.22 (0.70, 2.13)[d]	0.46[d]
	N	% (n)	N	% (n)	Adjusted risk ratio[a]	p-Value[a]	Adjusted risk ratio[e]	p-Value[b]
Proportion of HIV positive individuals with TB retained in care by 12 months	338	63.0% (213)	256	55.9% (143)	1.11 (0.89-1.38)	0.33	1.10 (0.92, 1.31)	0.28

CI – confidence interval.
[a] Adjusted for randomization strata.
[b] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, socio-economic position index, on antiretroviral therapy at enrolment, Cotrimoxazole preventive therapy (CPT) at enrolment and being in the TB cohort.
[c] Two clusters (one intervention and one control) had zero outcomes. For analysis 0.5 events assumed.
[d] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, socio-economic position index, CPT at enrolment and being in the HIV cohort.
[e] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, socio-economic position index, on antiretroviral therapy at enrolment and Cotrimoxazole preventive therapy (CPT) at enrolment.

outcomes. Because of high coverage of HIV testing at enrolment in both arms (94.1% in the intervention arm vs. 92.9% in the control clinics), the outcome of proportion of the TB cohort who knew their HIV status by the end of TB treatment was not determined. There was no difference in the mean CD4 counts at enrolment among those in the HIV cohort between the arms (232 cells/μl [standard deviation (SD) 181 cells/μl] in the intervention arm vs 246 cells/μl [SD 197 cells/μl in the control arms], adjusted mean difference in square root of CD4 count 0.14 (95% CI -0.64, 0.92)]. There wereno significant differencesin the i) proportions of ART eligible individuals in the HIV cohort who initiated ART by 10 weeks after CD4 count testing- a median 10 days after HIV testing (67% vs 70.4%, RR 0.90 [95% CI 0.75–1.10]), ii) ART eligible individuals in the TB cohort who started ART by 10 weeks of HIV testing (39.3% vs 38.8%, RR 1.05 [95% CI0.67–1.63]), iii) individuals in the HIV cohort who started IPT by the end of 12 months (39.8% vs 42.6, RR 0.94 [95% CI 0.64–1.33]) and iv) individuals newly diagnosed with TB who successfully completed TB treatment during 12 months of follow up (76.7% vs 78.4%, RR 0.94 [95% CI 0.83–1.06]), after adjusting for randomization strata (Tables 5 and S7–S11 in the supplementary appendix).

4. Discussion

This cluster-randomised trial evaluated the effect of an intervention to optimise the delivery of integrated TB and HIV care on patient relevant outcomes. The intervention as implemented in the trial did not have an effect on morbidity, mortality and retention in care among individuals newly diagnosed with TB or HIV. This was most likely because the intervention did not succeed in improving coordinated delivery and co-location of TB/HIV services beyond the levels at the control clinics.

This trial intervention was intended to address lack of coordination as a barrier to TB/HIV integration while taking into account variability in other TB/HIV integration-related challenges and clinic-level responses to them. The IO and SO were meant to be catalysts for improved TB/HIV integration while demonstrating that assigning specific health cadres to focus on TB/HIV integration alone could improve delivery of the services. Implementation of the intervention was expected to result in increased proportions of HIV positive individuals tested earlier in the course of the infection, screened for TB and started on IPT as well as increased proportions of individuals diagnosed with TB who are tested for HIV, started on CPT or ART thereby reducing morbidity and mortality.

Although the implementation of this trial intervention was sub-optimal and failed to improve integration, observational studies conducted elsewhere have not consistently demonstrated reductions in mortality with better integration. Most studies that have assessed the effect of improved TB/HIV integration have evaluated the effect of improved co-location of TB and HIV services, comparing vertical services or with the same services before and after implementation. Some of these studies reported more rapid ART start and higher median CD4 counts at ART initiations among HIV positive individuals diagnosed with TB [7–10] while others reported no effect on ART uptake [5, 24–26]. In addition, with respect to TB treatment outcomes among HIV positive individuals, some studies found reduced mortality and better retention [9, 10, 27, 28], where others did not [10, 25, 26, 29–31]. Complex health systems interventions to improve TB/HIV integration have also been evaluated in trials. The PALSA PLUS trial evaluated the effect of a non-didactic, outreach- and case-based training on HIV, sexually transmitted infections, and TB for nurses. This intervention increased TB case detection and CPT uptake among eligible individuals newly diagnosed with HIV but did not reduce mortality [32]. The STRETCH trial added task shifting of ART initiation, further ART training, introduction of ART initiation algorithms and management support to the PALSA PLUS training; this did not reduce mortality among patients eligible but not started ART at enrolment or improve

Table 4

Effect of the intervention among subgroups of sex, socio-economic position (SEP) index, enrolment period and baseline CD4 on incidence of hospitalizations and mortality among individuals newly diagnosed with HIV.

	Intervention arm		Control arm		Adjusted rate ratio[a]	p-Value[a]	Adjusted rate ratio[b]	p-Value[b]
	N	(Hospitalisation or deaths/person-years of follow up) Incidence per 100 person-years	N	(Hospitalisation or deaths/person-years of follow up) Incidence per 100 person-years				
Sex:								
Male	608	(82/571) 14.4	530	(56/498)11.2	1.21 (0.81, 1.79)	0.33	1.1 (0.76, 1.71)	0.51
Female	931	(100/887) 11.3	953	(91/909)10.0	1.15 (0.83, 1.58)	0.37	1.05 (0.76, 1.46)	0.74
SEP index:								
Low	982	(119/926) 12.8	646	(64/620) 10.3	1.11 (0.69, 1.79)	0.64	1.02 (0.65, 1.61)	0.91
High	558	(63/533) 11.8	838	(83/788) 10.5	1.03 (0.61, 1.73)	0.91	0.94 (0.53, 1.66)	0.82
Enrolment period[c]								
Early[d]	358	(48/365) 13.2	281	(41/290) 14.1	N/A		N/A	
Late	1182	(134/1095) 12.2	1203	(106/1118) 9.5	1.37 (0.92, 2.03)	0.11	1.26 (0.84, 1.90)	0.24
Baseline CD4[e]								
< 350	1100	(147/1037) 14.2	1036	(110/988) 11.1	1.25 (0.97, 1.61)	0.09	1.14 (0.88, 1.48)	0.31
≥350[f]	251	(9/253) 3.6	273	(20/263) 7.6	N/A		N/A	

N/A not applicable – analysis not conducted as too few outcomes at the clinic level.

[a] Adjusted for randomization strata.

[b] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, Socioeconomic position index, on antiretroviral therapy (ART) at enrolment, Cotrimoxazole preventive therapy (CPT) at enrolment and in TB cohort.

[c] Early enrolment period defined as being enrolled before 1 September 2012 (≥ 12 months of intervention).

[d] Four clusters in the control arm and three clusters in the control arm have < 10 participants in the early enrolment period. Analysis is not possible for this stratum.

[e] CD4 count measured within 90 days of enrolment. 12% (364/3014) of participants have a missing CD4 count (175/1484 and 189/1540) in the control and interventions arms, respectively).

[f] Two clusters in the intervention and control arms (4/18) have zero outcomes. Analysis was not undertaken for this stratum.

12 month viral suppression rates among those on ART for at least six months at enrolment [32].

Our study had a number of important strengths. Firstly, we used a clustered randomised study design with a large sample size and a reasonable number of clinics. Secondly, because we assumed that the delivery of TB/HIV services was already integrated, to a variable degree, in most clinics, we designed an intervention, which was pragmatic and allowed the activities for optimising integrated TB/HIV care to vary

Table 5

Effect of the intervention on secondary outcomes of CD4 counts at enrolment, time to starting ART among ART eligible individuals, proportion started on Isoniazid preventive therapy (IPT) by the end of 12 months follow up and proportion who successfully completed TB treatment during 12 months of follow up.

	Intervention arm (Overall mean, N)	Control arm (Overall mean, N)	Adjusted mean difference (control-intervention)[a]	p-value[b]	Adjusted mean difference (intervention-control)[c]	p-value
Square root of CD4 counts at enrolment among participants newly diagnosed with HIV[a]	14.0, 1315	14.4, 1309	− 0.28 (− 1.14, 0.58)[a]	0.50	0.14 (− 0.64, 0.92)	0.72

	n/N, (%)	n/N, (%)	Adjusted RR	p-value	Adjusted RR	p-value
Proportion of individuals newly diagnosed with HIV, ART eligible who initiated ART by the end of 10 weeks after CD4 testing	597/891 (67)	626/889 (70.4)	0.90 (0.75–1.10)	0.30	0.91 (0.71–1.10)[d]	0.30
Proportion of HIV positive individuals newly diagnosed with TB who started ART by 10 weeks after HIV testing	88/224 (39.3)	62/160 (38.8)	1.05(0.67–1.63)	0.83	0.99 (0.64–1.54)[d]	0.93
Proportion of individuals newly diagnosed with HIV who started IPT by 12 months after HIV testing	503/1264 (39.8)	552/1295 (42.6)	0.94(0.64–1.33)	0.71	0.96 (0.68–1.35)[e]	0.79
Proportion of individuals newly diagnosed with TB who successfully completed TB treatment during 12 months of follow up	323/421 (76.7)	243/310 (78.4)	0.94 (0.83–1.06)	0.28	0.93(0.82–1.05)[f]	0.23

[a] Untransformed: for the intervention arm overall arithmetic mean is 230.8 (and arithmetic mean of cluster means is 231.5); for the control arm overall arithmetic mean is 245.7 (and arithmetic mean of cluster means is 242.0).

[b] Adjusted for randomization strata.

[c] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, Socioeconomic position (SEP) level, on antiretroviral therapy (ART) at enrolment, Cotrimoxazole preventive therapy (CPT) at enrolment and in TB cohort.

[d] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, SEP level, CPT at enrolment.

[e] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, employment status, SEP level, on ART at enrolment, CPT at enrolment.

[f] Adjusted for randomization strata, sex, age group, country of birth, education level, marital status, SEP level, CPT at enrolment and being in the HIV cohort.

slightly depending on clinic needs. Thirdly, the trial enrolled individuals newly diagnosed with TB, as well as individuals newly diagnosed with HIV, and would have been able to evaluate the potential impact of the intervention on outcomes specific to individuals in both groups. Our trial showed that individuals newly diagnosed with HIV alone did not have worse outcomes where TB/HIV integration was being actively promoted [12].

A number of factors may explain our intervention's apparent lack of effect on both improved TB/HIV integration and patient relevant outcomes. These factors are related to: i) limited implementation of the intervention as intended, ii) differences between arms and, iii) lack of statistical power.

From the facility assessments at the end of the intervention period and process measures (secondary outcomes), the extent to which integrated care was delivered at intervention clinics was not significantly different from that at the control clinics. More robust measurements of TB/HIV integrated service delivery levels were not possible prior to, during or at the end of the trials as there were no validated tools or systems in use.The intervention may also have failed to deliver the expected result because the integration officers did not play the coordination and mentorship role envisaged but instead spent significant amounts of time providing direct care to patients. The integration officers may have focussed on this aspect in order to better 'fit in' to the clinic working routines.As outsiders, the IO may have faced some resistance to changing practice given the prevalent organisational culture within clinics, and hence spent more time on being accepted by contributing to clinic work rather than pushing for change. This can also be partly explained in the context of staff shortages as well as lack of staff training and motivation in both intervention and control clinics that limited the extent to which integrated care at intervention clinics could be improved [33, 34].

As standard of care evolved over time, control clinics may have advanced in the delivery of integrated TB/HIV services more than expected, which may have diluted the effect of the intervention.The IOs and SOs presence in the clinics may also have improved record keeping in the intervention clinics leading to better ascertainment of hospitalizations and other outcomes, although this was unlikely to be a major contributory factor as there were statistically differences in follow up by arm. In addition, participants enrolled into the evaluation cohorts at control clinics were more educated, more likely to be employed, less likely to be in the lower third of the socio-economic position index and more likely to have been on ART at enrolment compared to those at the intervention clinics. On the other hand, intervention clinics may have been able to improve linkage into care for the very ill as indicated by the higher proportion of HIV positive individuals newly diagnosed with TB in that arm. The adjustments for cluster level imbalance at analysis are likely to have minimised the effects of these imbalances.

The trial was also unable to meet the desired sample size and median duration of follow up (expected 15 months follow up) for both cohorts and therefore may not have had adequate power to detect the large differences (40% reduction) between the arms assumed at sample size calculations. However, the small effect sizes for all the primary outcomes and their consistency across a range of sensitivity analyses suggest that that no important differences between the arms would have been observed had the trial been adequately powered.

Despite these limitations, this trial contributed some valuable lessons about the delivery of integrated TB/HIV services and patient outcomes. Firstly, that task shifting for TB screening is feasible at primary care facilities. Secondly, there is a need to strengthen HIV testing and linkage into HIV care at higher CD4 counts. This is because regardless of arm, there were low CD4 counts at HIV testing and linkage into care; 48.5% of individuals in the HIV cohort had CD4 count < 200 cells/ml and 69% had initiated ART 10 weeks after CD4 count testing) despite a national HIV testing campaigns and increased thresholds for ART initiation both introduced during the intervention period. In September 2016, the South African government introduced the test and treat strategy which saw all HIV positive individuals being eligible for ART regardless of CD4 count. [16] The impact of this strategy will be limited by how early HIV positive individuals are identified and initiated on ART.Thirdly, there is a need to scale up interventions that promote the scale-up of IPT in order to prevent TB among HIV positive individuals. In the trial, there were low levels of IPT initiation in 12 months (42% of eligible) following HIV testing.

In conclusion, the trial intervention did not show an effect on patient relevant outcomes, because it had an insufficient effect on integration of care.Alternative strategies are needed to achieve closer integration of TB and HIV care, taking resource constraints and existing organisational culture into account, along with evaluation of the effect on patient-relevant outcomes.

Acknowledgements

Author contribution

TK, KLF, GJC, ADG, SC designed the study.

KK and AV collected the data on the process evaluations including time use (fidelity to intervention).

TK, PH, SC collected the data on the primary and secondary outcomes.

TK, KLF and PH analysed the data.

TK and KLF drafted the manuscript.

TK, KLF, PH, KK, AV, GJC, ADG, SC critically reviewed the manuscript for content.

TK, KLF, PH, KK, AV, GJC, ADG, SC approved the manuscript for submission.

Competing interests

The authors have no competing interests to declare.

Funding source

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2018.07.013.

References

[1] O. Shisana, T. Rehle, L.C. Simbayi, K. Zuma, S. Jooste, N. Zungu, D. Labadarios, D. Onoya, et al., South African National HIV Prevalence, Incidence and Behaviour Survey, 2012, Cape Town (2014).

[2] World Health Organisation. Global Tuberculosis Report 2017. Geneva, Switzerland. WHO/HTM/TB/2017.23.

[3] World Health Organisation, WHO policy on collaborative TB/HIV activities, Guidelines for national programmes and other stakeholders. Geneva, Switzerland, 2012.

[4] World Health Organisation. WHO Three I's meeting: Intensified Case Finding (ICF), Isoniazid Preventive Therapy (IPT) and TB Infection Control (IC) for people living with HIV. 2–4 April 2008. Geneva, Switzerland 2008.

[5] G.A. Ansa, J.D. Walley, K. Siddiqi, X. Wei, Delivering TB/HIV services in Ghana: a comparative study of service delivery models, Trans. R. Soc. Trop. Med. Hyg. (2014 Jul 24) tru110.

[6] H. Legido-Quigley, C.M. Montgomery, P. Khan, R. Atun, A. Fakoya, H. Getahun, A.D. Grant, Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review, Tropical Med. Int. Health 18 (2013) 199–211.

[7] B. Kerschberger, K. Hilderbrand, A.M. Boulle, et al., The effect of complete integration of HIV and TB services on time to initiation of antiretroviral therapy: a before-after study, PLoS One 7 (10) (2012) e46988.

[8] P. Owiti, R. Zachariah, K. Bissell, et al., Integrating tuberculosis and HIV services in rural Kenya: uptake and outcomes, Pub. Health Action 5 (1) (2015) 36–44.

[9] S.M. Hermans, B. Castelnuovo, C. Katabira, et al., Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda, J. Acquir. Immune Defic. Syndr. 60 (2) (2012) e29–e35.

[10] J.M. Ikeda, C.A.L. Tellez, E.S. Hudes, et al., Impact of integrating HIV and TB care and treatment in a regional tuberculosis hospital in rural Guatemala, AIDS Behav. 18 (1) (2014) 96–103.

[11] L.V. Adams, E.A. Talbot, K. Odato, H. Blunt, K.R. Steingart, Interventions to improve delivery of isoniazid preventive therapy: an overview of systematic reviews, BMC Infect. Dis. 14 (2014) 281.

[12] A.B. Suthar, G.W. Rutherford, T. Horvath, M.C. Doherty, E.K. Negussie, Improving antiretroviral therapy scale-up and effectiveness through service integration and decentralization, AIDS (London, England) 28 (Suppl. 2) (2014) S175–S185.

[13] S. Sweeney, C.D. Obure, C.B. Maier, R. Greener, K. Dehne, A. Vassall, Costs and efficiency of integrating HIV/AIDS services with other health services: a systematic review of evidence and experience, Sex. Transm. Infect. 88 (2) (2012) 85–99.

[14] T. Kufa, P. Hippner, S. Charalambous, et al., A cluster randomised trial to evaluate the effect of optimising TB/HIV integration on patient level outcomes: The "merge" trial protocol, Contemp. Clin. Trials 39 (2) (2014) 280–287.

[15] J.C. Chehab, P. Vranken, A. Peters, J.D. Klausner, Current integration of tuberculosis (TB) and HIV services in South Africa, 2011, PLoS One 8 (3) (2013) e5779116.

[16] Department of Health, Republic of South Africa, The South African antiretroviral treatment guidelines, Pretoria South Africa, 2010.

[17] Department of Health, Republic of South Africa, Accelerating Access to ART Services and Uptake (Update on Guidelines) [Press Release], (14 April 2012).

[18] Department of Health, Republic of South Africa, Implementation of the Universal Test and Treat Strategy for HIV Positive Patients and Differentiated Care for Stable Patients (Update on Guidelines), Pretoria, South Africa, 2016.

[19] Department of Health, Republic of South Africa, A Practical Guide for TB and HIV Service Integration at Primary Health Care Facilities, Pretoria, South Africa, 2011.

[20] R.J. Hayes, L.H. Moulton, Cluster Randomised Trials, Chapman & Hall/CRC Taylor Francis Group, 2009.

[21] R.J. Hayes, N.D. Alexander, S. Bennett, S.N. Cousens, Design and analysis issues in cluster-randomized trials of interventions against infectious diseases, Stat. Methods Med. Res. 9 (2) (2000) 95–116.

[22] R.J. Hayes, S. Bennett, Simple sample size calculation for cluster-randomized trials, Int. J. Epidemiol. 28 (2) (1999) 319–326.

[23] S. Vyas, L. Kumaranayake, Constructing socio-economic status indices: how to use principal components analysis, Health Policy Plan. 21 (6) (2006) 459–468.

[24] Statistics South Africa, Community Survey Household Questionairre, Available from, 2007. http://www.statssa.gov.za/questionnaires/CSQuestionnaire.pdf.

[25] R. Kaplan, J. Caldwell, L.G. Bekker, et al., Integration of TB and ART services fails to improve TB treatment outcomes: comparison of ART/TB primary healthcare services in Cape Town, South Africa, S. Afr. Med. J. 104 (3) (2014) 204–209.

[26] A.B. Schwartz, N. Tamuhla, A.P. Steenhoff, et al., Outcomes in HIV-infected adults with tuberculosis at clinics with and without co-located HIV clinics in Botswana, Int. J. Tubercul. Lung Dis. 17 (10) (2013) 1298–1303.

[27] T.D. Ledibane, S.C. Motlhanke, A. Rose, W.H. Kruger, N.R. Ledibane, M.M. Claassens, Antiretroviral treatment among co-infected tuberculosis patients in integrated and non-integrated facilities, Pub. Health Action 5 (2) (2015) 112–115.

[28] S.A. Schulz, H.R. Draper, P. Naidoo, A comparative study of tuberculosis patients initiated on ART and receiving different models of TB/HIV care, Int. J. Tubercul. Lung Dis. 17 (12) (2013) 1558–1563.

[29] J. Uyei, D. Coetzee, J. Macinko, S.L. Weinberg, S. Guttmacher, The influence of integrated tuberculosis and human immunodeficiency virus service delivery on patient outcomes, Int. J. Tubercul. Lung Dis. 18 (3) (2014) 315–321.

[30] A. Ndagijimana, E. Rugigana, C.B. Uwizeye, J. Ntaganira, One-stop TB/HIV services evaluation in Rwanda: comparison of the 2001–2005 and 2006–2010 cohorts, Pub. Health Action 5 (4) (2015) 209–213.

[31] M.D. Nglazi, R. Kaplan, J. Caldwell, et al., Antiretroviral treatment uptake in patients with HIV-associated TB attending co-located TB and ART services, S. Afr. Med. J. 102 (12) (2012) 936–939.

[32] M. Zwarenstein, L.R. Fairall, C. Lombard, et al., Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa: PALSA PLUS pragmatic cluster randomised trial, BMJ 342 (2011) d2022.

[33] L. Fairall, M.O. Bachmann, C. Lombard, et al., Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial, Lancet 380 (9845) (2012) (889–9).

[34] J. Uwimana, D. Jackson, H. Hausler, C. Zarowsky, Health system barriers to implementation of collaborative TB and HIV activities including prevention of mother to child transmission in South Africa, Tropical Med. Int. Health 17 (5) (2012) 658–665.