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Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention

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Abstract

Objectives: We piloted an intervention to determine if support from a case-manager would assist adults being investigated for TB to link into TB and HIV care.

Design: Pilot interventional cohort study.

Participants and setting: Patients identified by primary healthcare clinic staff in South Africa as needing TB investigations were enrolled.

Intervention: Participants were supported for three months by case-managers who facilitated the care pathway by promoting HIV testing, getting laboratory results, calling patients to return for results, and facilitating treatment initiation.

Outcomes measured: Linkage to TB care was defined as starting TB treatment within 28 days in those with a positive test result; linkage to HIV care, for HIV-positives, was defined as having blood taken for CD4 count and, for those eligible, starting antiretroviral therapy within three months. Intervention implementation was measured by number of attempts to contact participants.

Results: Among 562 participants [307 (54.6%) female, median age 36 years (interquartile range [IQR] 29-44)], most 477 (84.8%) had previously tested for HIV; of these, 328 (69.0%) self-reported being HIV-positive. Overall, 189/562 (33.6%) participants needed linkage to care [132 HIV care linkage only; 35 TB treatment linkage only; 22 both]. Of 555 attempts to contact these 189 participants, 407 were to facilitate HIV care linkage, 78 for TB treatment linkage and 70 for both. At end of three months' follow-up, 40 participants had not linked to care [29 of the 132 (21.9%) participants needing linkage to HIV care only, 4 of the 35 (11.4%) needing to start on TB treatment only and 7 of the 22 (31.8%) needing both].

Conclusion: Many people testing for TB need linkage to care. Despite case-manager support, non-linkage into HIV care remained higher than desirable, suggesting a need to modify this intervention before implementation. Innovative strategies to enable linkage to care are needed.

Strengths and limitations of the study

- The study had a representative sample of adults being investigated for TB from five clinics in two provinces with diverse living conditions and representative of urban as well as peri-urban setting.
- The intervention was well implemented with 555 contact attempts made to participants needing linkage to care.
- The lack of a "standard of care" comparison group meant we could not formally determine if the strategy made a difference or not.

Background

Linkage to HIV care for people being investigated for TB is suboptimal. Studies done in South Africa have shown that 11-25% people with positive sputum results have "pre-treatment loss to follow-up", defined as not starting on TB treatment either at all, or within a month of sputum submission.[1, 2, 3] More recently the XTEND trial, a pragmatic cluster-randomized controlled trial comparing smear microscopy versus Xpert MTB/RIF (a rapid and more sensitive assay) amongst adults being investigated for TB, showed pre-treatment loss to follow-up of 17%, not reduced by use of Xpert MTB/RIF.[4] Mortality at three and six months of sending sputum for microbiological investigation was 3.2% and 5.0% respectively.[4, 5] South Africa's guidelines recommend that all patients with a positive diagnosis for TB as well as those being investigated for TB be tested for HIV.[6] The XTEND trial also showed that not being on ART and not knowing one's HIV status were associated with an increased risk of death,[4] suggesting that for persons being investigated for TB and not already on antiretroviral treatment (ART), linkage to HIV care is a priority.

Linking people with a positive HIV test result into HIV care has traditionally involved multiple steps, including undertaking a CD4 count to determine eligibility for ART initiation, with losses at each step. [7] Furthermore, TB and HIV care are not fully integrated, making it difficult for patients needing treatment for TB and HIV to access care for both conditions. In an attempt to improve linkage into HIV care among HIV-positive patients, strategies such as case management or health system navigation, using strengths-based case management, where patients identify their strengths and use them to improve their circumstances, have been evaluated.[8, 9, 10] One such study, a randomized control trial in the United States of America among recently-diagnosed HIV-positive people supported by a case manager, showed that 78% in the intervention arm linked into care successfully compared to the 60% in the control arm.[8] Task-shifting of duties such as TB counselling, HIV counselling and testing and ART adherence counselling to lay counsellors has been used as a strategy to relieve short-staffed and overwhelmed health care workers in primary health care clinics.[11] In

this study, we pilot tested an intervention using lay counsellors to provide support to adults being investigated for TB by following up with patients to ensure that they returned to clinic 1) to receive their TB and HIV-related test results; 2) to do follow-up tests and 3) to start appropriate treatment. This was intended to overcome obstacles such as nurses not having enough time to follow-up patients and the difficulties of making contact with patients. The study objectives were to determine feasibility of implementing the intervention, (determined by number of interactions made), acceptability of the intervention (determined by a qualitative study, reported separately) and to estimate linkage to TB and HIV care.

Methods

Study design

An interventional cohort study was designed to pilot-test case manager support at primary health care clinics (PHCs) for adults being investigated for TB, to link them into HIV care and initiate TB treatment where these were clinically indicated. The study was conducted from September 2014 – April 2015 in six PHCs in Mpumalanga and Gauteng provinces, South Africa which had previously participated in the XTEND trial. At the time of implementing the case manager study, South Africa's criteria for ART initiation were a CD4 count of ≤350 cells/mm^3 or active TB at any CD4 count. Guidelines also suggested that following a TB diagnosis, ART should be initiated in HIV-positive persons within two weeks after TB treatment initiation.

Description of case manager intervention

Case managers were lay counsellors, trained by investigators on basic TB and HIV education, according to national guidelines at the time. One case manager was placed at each of the six clinics. The role of the case managers was 1) to follow up on sputum test results from the laboratory; 2) to call all patients to return to the clinic for their results; 3) to facilitate TB treatment start in patients with a positive sputum test result; 4) to encourage those with unknown HIV status or negative HIV

test results older than three months at enrolment to test for HIV; and 5) for those who tested HIV-positive or knew themselves to be HIV-positive but did not know their CD4 count at enrolment, to facilitate CD4 count testing, follow up on CD4 results from laboratory and to facilitate ART initiation if eligible. A study algorithm, based on the national TB and ART guidelines, was developed to assist the study staff in guiding patients through the health system in seeking appropriate care (Figure 1). Case managers attempted to contact participants at least once a week and continued with contact attempts until linkage to care was complete, or the end of study follow-up, three months after enrolment. Contact attempts were made to inform participants of the availability of their results as soon as they were received at the clinics, to remind participants of clinic appointments and to check if patients had returned to clinic for appropriate care. These attempts included in-person meetings at the clinic or telephonic calls. Contacts were categorized as successful if the case manager was able to meet with the participant or speak to the participant telephonically. All decisions about clinical management of participants were made by PHC staff according to their routine practice. Case managers were not actively involved in arranging any additional investigations for TB after enrolment.

Study population and data collection

Participants were eligible for inclusion in the study, based on criteria previously used in the XTEND trial, if they were aged ≥18 years, identified by PHC staff as needing investigation for TB, provided a sputum specimen for TB investigation, able to give informed consent, likely to remain in the study catchment area for eight months and able to provide adequate locator information. Case managers recruited participants who met the inclusion criteria. Data on demographics, current TB symptoms, TB and HIV history and health care-seeking behaviour was collected at enrolment. Contact attempts and participants' progress in linkage into appropriate care was recorded on log forms.

At the end of the follow-up period, the case managers conducted a telephonic or clinic interview with the participant to ascertain if linkage into appropriate care had taken place by collecting self-reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and current TB symptoms. Additional data were collected by professional nurses abstracting from clinic records HIV data (such as HIV testing, CD4 count testing and ART start dates) and TB data (TB testing and treatment start dates). Case report forms were completed on a study-specific smart phone application and data submitted in an encrypted format to a central database.[4]

Description of outcomes and analysis

Linkage into HIV care was defined as, at three months after enrolment, i) if HIV status unknown at enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4 count ≤ 350 cells/mm^3 or testing Xpert MTB/RIF positive); ii) if HIV-positive with an unknown CD4 count and not on ART at enrolment: having done a CD4 count test; and being started on ART if eligible; iii) if last CD4 count done more than six months previously and not on ART at enrolment: having a CD4 count done; and being started on ART if eligible. Failure to initiate ART after three months when ART eligible at initial assessment was defined as non-linkage to HIV care.

Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of sputum submission among patients with a positive sputum test result. Non-linkage to TB treatment (pre-treatment loss to follow up) was defined as not starting TB treatment within 28 days of sputum collection among people with a positive TB test result, consistent with definitions in previous studies.[2, 4]

Linkage to HIV care or TB treatment initiation was confirmed by record of ART or TB treatment start date as reported by the participant and documented in study documents or from patient clinic files. Mortality was ascertained by reports by close relatives or friends indicating the death of a

participant. Participants were defined as lost to follow-up if at three months, linkage status was unknown and the participant could not be contacted by case managers.

Contacts attempts were defined as any effort (successful or unsuccessful), done either telephonically or in-person meeting, made by case managers to interact with a patient. The total number of contact attempts per patients was counted and median attempts needed for linkage into TB and HIV care or both were calculated.

Sample size calculation

This was a pilot study aiming to determine feasibility of implementing the intervention, and to estimate linkage to TB and HIV care. The sample size calculation was based on two binary outcomes: 1) uptake of ART among those who were HIV positive and ART eligible; 2) pre-treatment loss to follow-up among those who tested TB positive. We had planned to enrol 1200 participants (200 per clinic as in XTEND) with the assumption that 96 (8%) of those tested for TB would test TB positive and need to initiate TB treatment.[4] We also assumed that 20 (21%) of people with a sputum testing positive for TB would experience pre-treatment loss to follow-up.[4] For patients needing linkage to HIV care, the assumption was that 240 (20%) of patients enrolled would not know their HIV status. It was also assumed that 576 (60%) of patients who knew their HIV status would self-report being HIV positive. [4] Two hundred and eighty-eight (50%) of those who were HIV positive would not know their CD4 count and would be ART eligible once a CD4 count test was done.[4]

Risk factor analysis for mortality

Univariable logistic regression analysis was used to assess risk factors for mortality. Due to the small proportion of participants who died by end of three months follow-up, categories per predictor variable in the univariable model were restricted to three and a multivariable logistic regression model was not built as a minimum of 10 events per predictor variable is required.[12] All statistical analyses were done using Stata version 14 (Stata Corp LP, College Station, Texas).

Results

Baseline characteristics

From September to December 2014, 800 adults having a sputum taken for TB investigations in six PHCs were screened and 585 were enrolled. Of these 585, 23 from one site were excluded from analysis because ill health prevented the case manager from undertaking study procedures correctly, leaving 562 from five clinics for analysis. Of the 562 participants, 307 (54.6%) were female and the median age was 36 years (interquartile range (IQR) 29-44) (Table 1). The majority of participants (477, 84.8%) self-reported having had an HIV test in the past and of these 328 (69.0%) reported being HIV-positive. Of the 328 HIV-positive participants, 156/327 (47.7%) reported having a CD4 count done within the previous six months and self-reported median CD4 count was 315 cells/mm^3 (IQR 164-471). Over half of the HIV-positive participants (209 [63.9%]) had never received ART. Five hundred and fourteen (94.6%) participants reported having at least one TB symptom to the study team and the majority 452 (88.1%) reported having cough (Table 1).

Table 1: Baseline characteristics of the study population

Variable	**n (%)** **N= 562**
Gender	
Female	307 (54.6)
Age (Median, IQR)	36 (29-44)
Country of birth	
South Africa	447 (79.5)
Ethnic group	
Black	556 (98.9)
Highest education completed	
No schooling	23 (4.0)
Pre-school – Grade 7	124 (22.0)
Grade 8 - 12	377 (67.1)
University/technical qualification	38 (7.0)
Marital Status	
Single never married	250 (44.5)
Married	108 (19.2)
Cohabitating	159 (28.3)
Divorced/widowed/separated	45 (8.0)
Main income source	
Formal-employment	250 (44.3)
Self-employment/ Odd jobs	134 (23.8)
No income	88 (15.7)
Grant/dependence	90 (16.0)
Average monthly income	
< ZAR 600	34 (6.0)
ZAR 601-1000	73 (12.9)
ZAR 1001-2000	120 (21.4)
ZAR 2001-4000	167 (29.7)
Greater than ZAR 4000	58 (10.3)
Don't know	110 (19.6)
Ever had HIV test	
Yes	477 (84.8)
Self-reported HIV status (n=475)	
Negative	143 (29.8)
Positive	328 (69.1)
Unknown	4 (1.0)
CD4 count known (n=327)[#]	
Yes	156 (47.7)
Self-reported CD4 count, median (IQR)	315 (164 - 471)
Ever been on ART (n=327)	
Never	209 (63.9)
Currently	116 (35.5)
Previously	2 (0.6)
Time on ART in years, median (IQR) n=118	2 (0 - 4)
Ever treated for TB	
Yes	96 (17.1)
TB symptoms reported (n=543)*	
Yes	514 (94.6)

Symptoms reported (n=514)	
Cough	452 (88.1)
Unintentional weight loss	311 (60.6)
Night sweats	218 (42.5)
Fever	186 (6.3)

Abbreviations: ART antiretroviral treatment, *TB* tuberculosis
*data missing for 19 participants
data missing for 1 participant

Implementation of the intervention

Overall 189/562 (33.6%) participants required linkage into HIV care or TB treatment initiation or both. Of the 189, 132 (69.8%) participants required linkage into HIV care only, 35 (18.5%) TB treatment initiation only and 22 (11.6%) required both TB treatment initiation and linkage to HIV care. A total of 555 contact attempts were made by the case managers to these participants: 310 (55.9%) were telephonic, 243 (43.8%) were contacts at clinic and 2 (0.4%) were home visits. Of the 310 telephonic contacts, 211 (68.1%) were successful. Of the 99 unsuccessful telephone contact attempts, 98 were due to numbers ringing without an answer and in one the call went to voicemail.

Linkage to HIV care only: of the 132 people needing linkage to HIV care only, 407 contact attempts in total were made to these individuals with a median of 3 (IQR 2-4) attempts per individual. At the end of the follow-up, 29 (21.9%) people had still not linked into HIV care and a total of 111 contact attempts, with a median of four attempts (IQR 2- 4) per individual, had been made to these individuals.

Linkage to TB care only: for people needing to initiate TB treatment only (35), 78 contact attempts with a median two (IQR 1-3) attempts were made. Four (11.4%) of the participants did not initiate TB treatment by end of follow-up period. Ten contact attempts with median of one (IQR 1-4) were made to these individuals.

Linkage to TB and HIV care: 70 contact attempts with median of three (IQR 2-4) attempts were made to the 22 participants that needed both to initiate TB treatment and link into HIV care. At end of

follow-up, seven (31.8%) people had not completely linked into care as they had started on TB treatment but had not initiated ART. Twenty-seven contact attempts with a median of two attempts (IQR 4-5) per individual were made to these seven individuals.

Linkage into HIV care

Participant flow through the steps of linkage to HIV care is shown in figure 2. Amongst 94 who needed an HIV test, 26 (27.6%) declined to test. Of those who tested, 26 (38.2%) were HIV positive. A total of 132 (26 newly-tested HIV positive and 106 not on ART with unknown CD4 count) needed a CD4 count, of whom 119 (90.1%) had blood taken for a CD4 count by the end of the study. Of the 135 with a CD4 count result (119 who had a new CD4 count and 16 who already knew their CD4 count), 91 (67.4%) were ART eligible and 67 (73.6%) of those initiated for ART. Of those needing a CD4 count, 13/132 (9.8%) did not have a CD4 count done and 24/91 (26.3%) ART eligible did not initiate ART. The highest proportion of HIV positive patients were lost at the ART initiation stage (Figure 2).

TB treatment initiation

A total of 57/562 (10.1%) participants had a positive index Xpert MTB/RIF result. Of the 57, 53 (92.9%) started TB treatment within 28 days of testing positive for TB with median time to TB treatment initiation of five days (IQR 2-7). Of the four that were not initiated on TB treatment, two died before starting TB treatment and two started TB treatment more than 28 days after sputum was taken. An additional 22 participants were started on TB treatment after being diagnosed by follow-up tests.

We could not do a risk factor analysis for non-linkage into care because of the complexity of differing denominators at different stages of HIV linkage into care and the low numbers for those who did not initiate TB treatment.

Mortality and loss to follow-up

At the end of three months follow-up, 27/562 (4.8%) participants had died and loss to follow-up was 49/535 (9.2%). Of 27 participants who died, 18 had self-reported being HIV positive and 14 (77.8%) of them were on ART. Only four of the deceased participants had a TB positive index Xpert MTB/RIF result.

Risk factors of mortality at three months after enrolment

Univariable analysis for mortality (Table 2) showed weak evidence for an association between having more than one TB symptom (OR 2.4, 95% CI 0.89-6.45) and increased risk of death, but a chance finding cannot be excluded.

Table 2: Univariate analysis for risk factors for mortality

Variable	Proportion died (%)	OR (95% CI)	P value
Gender			
Male	10/255 (3.9)	1	
Female	17/307 (6.9)	1.43 (0.65 - 3.19)	0.37
Age group			
>30	5/144 (3.5)	1	
30-39.9	14/210 (6.6)	1.99 (0.69 - 5.64)	
≤40	8/208 (3.8)	1.11 (0.36 - 3.47)	0.29
Self-reported HIV status			
Negative	5/130 (3.9)	1	
HIV-positive on ART	4/120 (3.3)	0.86 (0.23 - 3.28)	
HIV-positive not on ART	14/205 (6.8)	1.83 (0.64 - 5.21)	0.29
Number of TB symptoms			
≤1	5/194 (2.6)	1	
2 and more	22/368 (5.9)	2.4 (0.89 - 6.45)	0.05
BMI			
<18.5	4/78 (5.1)	0.88 (0.29 - 2.68)	
18.5-24.9	18/311 (5.8)	1	
25+	5/173 (2.9)	0.48 (0.18 - 1.32)	0.33

Abbreviations: ART antiretroviral treatment, *HIV* human immunodeficiency virus, *TB* tuberculosis, *BMI* body mass index

Discussion

In our study, 33.6% of people being investigated for TB at PHCs in South Africa required linkage into HIV care or TB treatment initiation. A high proportion of people with positive TB test results started

TB treatment with 78 contact attempts made to them. However, despite support with 477 contact attempts from a case manager, a total of 21.9% of those needing HIV care only and 31.8% needing TB and HIV care did not link into HIV care at the end of the three months follow-up period with the highest proportion lost at the ART initiation step. By piloting this intervention, we had hoped to overcome obstacles such as nurses not having enough time to follow up patients and difficulties of making contact with the patients such as clinic phones not working or people having not given their contact numbers. The processes of the intervention largely worked as intended, with multiple contacts to people needing linkage into care. However, HIV linkage care was still suboptimal, suggesting that this intervention as implemented for HIV was insufficient. It also suggests that linkage to HIV care compared to initiation of TB treatment is harder to achieve. This is probably due to the larger number of steps that were necessary for a person to start ART at the time of the study which included CD4 count testing for ART eligibility assessments, attendance at ART adherence classes and baseline blood tests for assessment of contraindications to specific antiretroviral drugs. This resulted in patients needing to visit the clinic multiple times. South African guidelines now recommend ART for all HIV positive people regardless of CD4 count. This may reduce losses along the linkage pathway by reducing the number of visits needed.

Some of our study participants refused HIV testing but the proportions (27.6%) in our study were lower than that found in a South African study done in 2007 comparing uptake of HIV test between provider initiated testing and counselling and provider referral to voluntary HIV testing amongst patients attending community health centres.[13] The study reported that 45% of patients in the provider initiated testing group, versus 69% of patients in voluntary HIV testing group, refused HIV testing.[13] In a 2012 study amongst HIV non-testers from South Africa, barriers to testing included fear of knowing one's HIV status and fear of what people may say.[14] Linkage to care (HIV and TB) in our study was higher compared to Sizanani, a randomised control trial in South Africa done between 2010 to 2013 using health navigators sending short messaging service (SMS) reminders to newly diagnosed HIV-positive people to link into TB and HIV care.[10]. This difference is probably

because linkage to care was defined differently in Sizanani compared to our study. Standardized definitions of linkage to care would facilitate making comparisons and setting standards.[10]

A number of participants in our study declined to start on ART because they could not get time off work. This could be because the health system is too difficult or time-consuming for working people to navigate; it could also be that participants not wanting to start ART for other reasons gave this as an excuse for not returning to the clinic. A study determining rates and predictors of declining to start ART in treatment-eligible HIV-positive individuals in South Africa in 2009 showed that 20% refused to start ART and 37% of those reported feeling healthy as a reason for non-initiation.[15] Another study, from South Africa in 2010, showed that stigma was the main barrier to initiating ART.[16] The limited information available around the reasons for non-linkage to HIV care suggest that the problem is not simply a failure of clinic staff to communicate results but rather a multifactorial challenge with health system, individual and structural components.[10]

Some interventions have had successes in improving linkage to care. A study in Uganda focusing on improving processes within clinics showed an improvement in ART initiation among HIV-positive patients.[17] Another study done in Zambia and Tanzania that combined clinic-based care plus community support showed a reduction in mortality in HIV-positive patients compared to standard of care.[18] It is hard to know what exactly made these interventions work. Our intervention tried to address challenges of communication between clinic and patients as well as provide support and encouragement to patients.

Our data showed that amongst adults with a positive Xpert MTB/RIF sputum result, 93.0% were started on TB treatment with 148 contact attempts made to them. The median time to TB treatment start in our study was five days which is within the recommended national department of health targets of two to five days.[6] We could not quantify the total number of participants who were diagnosed with TB using follow-up tests in our study, as some may have started TB treatment after our follow-up ended. Pre-treatment loss to follow-up was lower than the 11-25% found in

previous studies in South Africa, although comparisons are limited by the relatively small numbers in our study.[1-4]

Mortality was high in our study at 4.8% by 3 months suggesting that people are presenting with advanced disease or when already severely ill. This underscores the importance of early diagnosis and linkage to care.

Strengths of our study include prospectively enrolling a representative sample of adults being investigated for TB from five clinics in two provinces of the country which are diverse in living conditions and population and likely to be representative of urban and peri-urban practice in South Africa. A limitation of our study is that this was a pilot study and as such had no "standard of care" comparison group, therefore we cannot formally determine if the strategy made a difference or not. Another limitation is that we did not keep record of TB treatment started after the follow-up period.

Conclusion

In our pilot study assessing the potential effect of a case manager to support linkage into HIV care and TB treatment initiation amongst adults being investigated for TB we report a higher than desirable rate of non-linkage into HIV care. This is an indication that the piloted strategy lacks components that are crucial to the successful engagement of patients into HIV care. A qualitative evaluation of the intervention (in progress) may give insights into how this intervention could be improved. This pilot study was planned with the intention to conduct a larger trial afterwards but our findings suggest that further work be done before the intervention is further evaluated. We recommend that more innovative approaches be explored to find strategies that will improve linkage to HIV care and TB treatment initiation in this population to reduce mortality.

Data sharing statement

Data used for this study can be accessed from the London School of Tropical Medicine repository.

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Contributors

NM, AG, VC, KM and GC contributed in the design of the study. NM, AG, VC, KM supervised data collection. NM analysed the data and wrote the first draft of the manuscript. AG, VC, KM and GC provided comments for the revision of the manuscript.

Competing interests

The authors have no competing interests.

Ethics approval and consent to participate

Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand reference number M131143 and the London School of Hygiene & Tropical Medicine, UK reference number 7124. Participants in the study gave written consent, or witnessed oral consent for participants who could not read or write.

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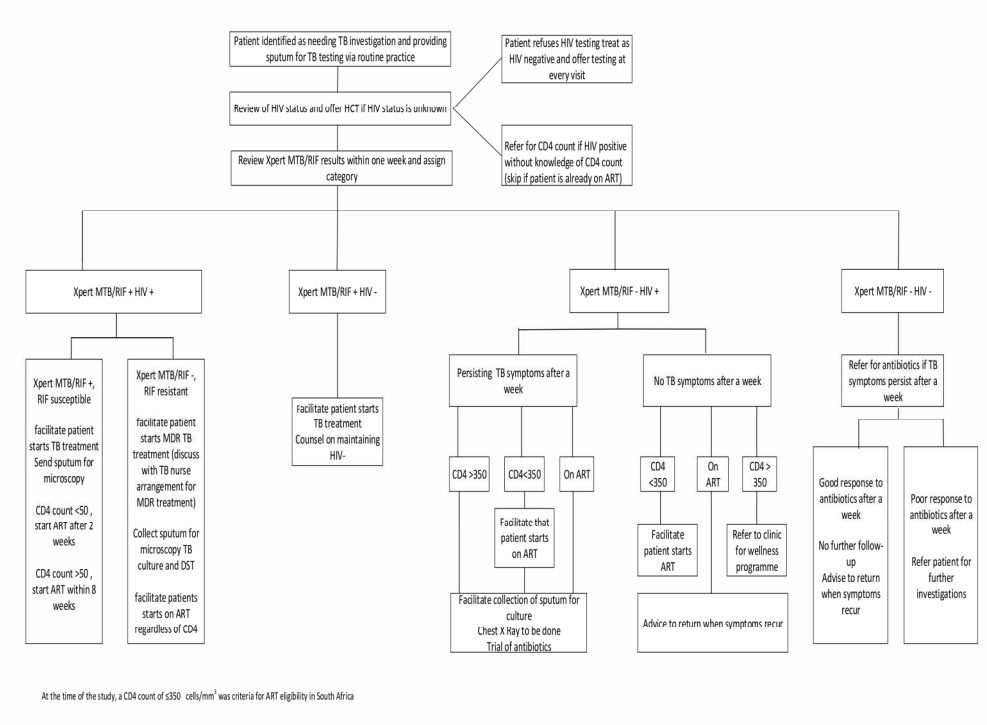
Figure 1: TB and HIV algorithm used to guide case managers.

Figure 2: Flow diagram of linkage into HIV care after three months follow-up.



TB and HIV algorithm used to guide case managers

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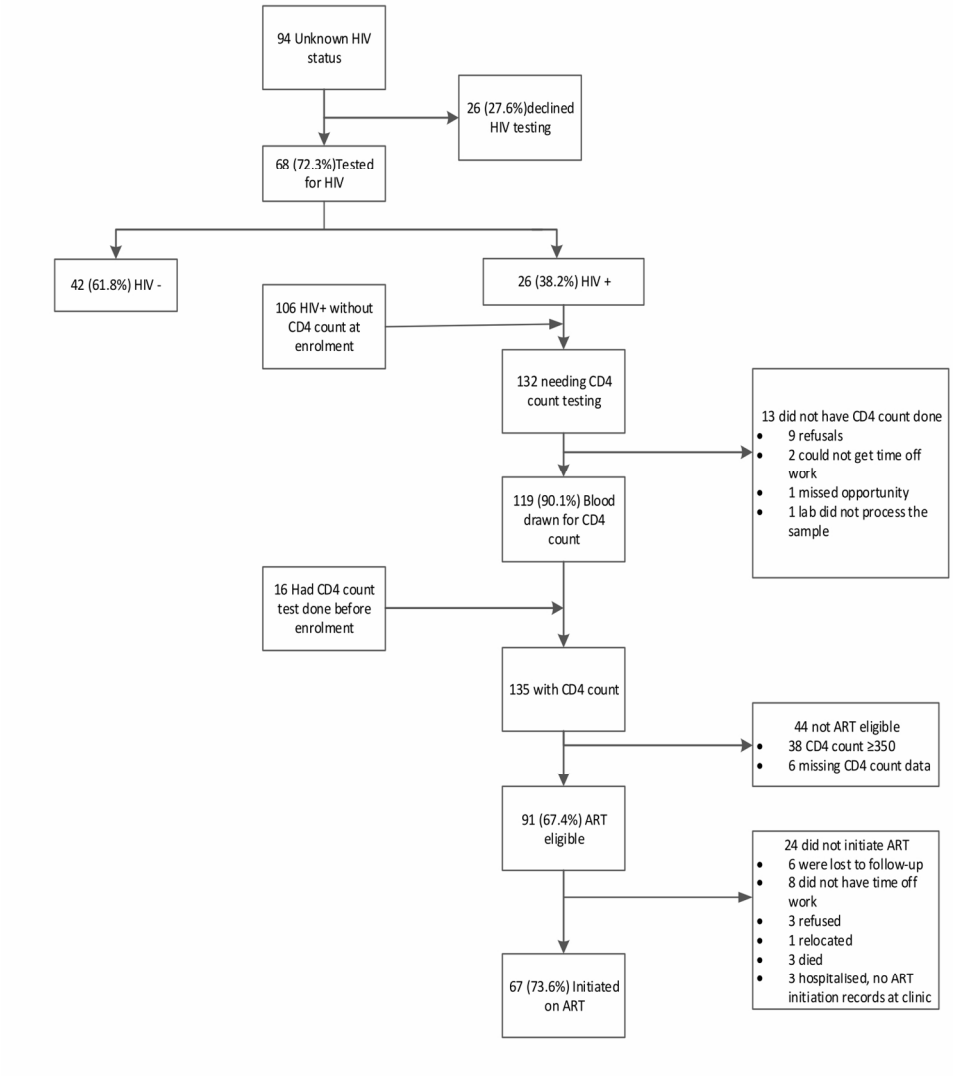

Flow diagram of linkage into HIV care after three months follow-up

137x152mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-13
		(b) Give reasons for non-participation at each stage	23
		(c) Consider use of a flow diagram	23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention

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Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a case manager intervention

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Keywords: HIV infection, tuberculosis, case managers

Abstract

Objectives: We piloted an intervention to determine if support from a case-manager would assist adults being investigated for TB to link into TB and HIV care.

Design: Pilot interventional cohort study.

Participants and setting: Patients identified by primary healthcare clinic staff in South Africa as needing TB investigations were enrolled.

Intervention: Participants were supported for three months by case-managers who facilitated the care pathway by promoting HIV testing, getting laboratory results, calling patients to return for results, and facilitating treatment initiation.

Outcomes measured: Linkage to TB care was defined as starting TB treatment within 28 days in those with a positive test result; linkage to HIV care, for HIV-positives, was defined as having blood taken for CD4 count and, for those eligible, starting antiretroviral therapy within three months. Intervention implementation was measured by number of attempts to contact participants.

Results: Among 562 participants [307 (54.6%) female, median age 36 years (interquartile range [IQR] 29-44)], most 477 (84.8%) had previously tested for HIV; of these, 328/475 (69.1%) self-reported being HIV-positive. Overall, 189/562 (33.6%) participants needed linkage to care [132 HIV care linkage only; 35 TB treatment linkage only; 22 both]. Of 555 attempts to contact these 189 participants, 407 were to facilitate HIV care linkage, 78 for TB treatment linkage and 70 for both. At end of three months' follow-up, 40 participants had not linked to care [29 of the 132 (22.0%) participants needing linkage to HIV care only, 4 of the 35 (11.4%) needing to start on TB treatment only and 7 of the 22 (31.8%) needing both].

Conclusion: Many people testing for TB need linkage to care. Despite case-manager support, non-linkage into HIV care remained higher than desirable, suggesting a need to modify this intervention before implementation. Innovative strategies to enable linkage to care are needed.

Strengths and limitations of the study

- The study had a representative sample of adults being investigated for TB from five clinics in two provinces with diverse living conditions and representative of urban as well as peri-urban setting.
- The intervention was well implemented with 555 contact attempts made to participants needing linkage to care.
- The lack of a "standard of care" comparison group meant we could not formally determine if the strategy made a difference or not.

Background

People being investigated for TB are not linking into TB and HIV care. . Studies done in South Africa have shown that 11-25% people with positive sputum results have "pre-treatment loss to follow-up", defined as not starting on TB treatment either at all, or within a month of sputum submission.[1, 2, 3] More recently the XTEND trial, a pragmatic cluster-randomized controlled trial comparing smear microscopy versus Xpert MTB/RIF (a rapid and more sensitive assay) amongst adults being investigated for TB, showed pre-treatment loss to follow-up of 17%, not reduced by use of Xpert MTB/RIF.[4] Mortality at three and six months of sending sputum for microbiological investigation was 3.2% and 5.0% respectively.[4, 5] South Africa's guidelines recommend that all patients with a positive diagnosis for TB as well as those being investigated for TB be tested for HIV.[6] The XTEND trial also showed that not being on ART and not knowing one's HIV status were associated with an increased risk of death,[4] suggesting that for persons being investigated for TB and not already on antiretroviral treatment (ART), linkage to HIV care is a priority.

Linking people with a positive HIV test result into HIV care has traditionally involved multiple steps, including undertaking a CD4 count to determine eligibility for ART initiation, with losses at each step. [7] Furthermore, TB and HIV care are not fully integrated, making it difficult for patients needing treatment for TB and HIV to access care for both conditions. In an attempt to improve linkage into HIV care among HIV-positive patients, strategies such as case management or health system navigation, using strengths-based case management, where patients identify their strengths and use them to improve their circumstances, have been evaluated.[8, 9, 10] One such study, a randomized control trial in the United States of America among recently-diagnosed HIV-positive people supported by a case manager, showed that 78% in the intervention arm linked into care successfully compared to the 60% in the control arm.[8] Task-shifting of duties such as TB counselling, HIV counselling and testing and ART adherence counselling to lay counsellors has been used as a strategy to relieve short-staffed and overwhelmed health care workers in primary health care clinics.[11] In

this study, we pilot tested an intervention using lay counsellors to provide support to adults being investigated for TB by following up with patients to ensure that they returned to clinic 1) to receive their TB and HIV-related test results; 2) to do follow-up tests and 3) to start appropriate treatment. This was intended to overcome obstacles such as nurses not having enough time to follow-up patients and the difficulties of making contact with patients. The study objectives were to determine feasibility of implementing the intervention, (determined by number of interactions made), acceptability of the intervention (determined by a qualitative study, reported separately) and to estimate linkage to TB and HIV care.

Methods

Study design

An interventional cohort study was designed to pilot-test case manager support at primary health care clinics (PHCs) for adults being investigated for TB, to link them into HIV care and initiate TB treatment where these were clinically indicated. The study was conducted from September 2014 – April 2015 in six PHCs in Mpumalanga and Gauteng provinces, South Africa which had previously participated in the XTEND trial and were selected on the basis of their high proportions of pre-treatment loss to follow-up during that trial. At the time of implementing the case manager study, South Africa's criteria for ART initiation were a CD4 count of ≤350 cells/mm^3 or active TB at any CD4 count. Guidelines also suggested that following a TB diagnosis, ART should be initiated in HIV-positive persons within two weeks after TB treatment initiation.

Description of case manager intervention

Case managers were lay counsellors, trained by investigators on basic TB and HIV education and, national ART and TB management guidelines at the time. One case manager was placed at each of the six clinics. The role of the case managers was 1) to follow up on sputum test results from the laboratory; 2) to call all patients to return to the clinic for their results; 3) to facilitate TB treatment

start in patients with a positive sputum test result; 4) to encourage those with unknown HIV status or negative HIV test results older than three months at enrolment to test for HIV; and 5) for those who tested HIV-positive or knew themselves to be HIV-positive but did not know their CD4 count at enrolment, to facilitate CD4 count testing, follow up on CD4 results from laboratory and to facilitate ART initiation if eligible. A study algorithm, based on the national TB management and ART guidelines, was developed to assist the study staff in guiding patients through the health system in seeking appropriate care (Figure 1). Case managers attempted to contact participants at least once a week and continued with contact attempts until linkage to care was complete, or the end of study follow-up, three months after enrolment. Lists for weekly follow-ups of enrolled participants that needed linkage to care were maintained through the automated release of weekly follow-up case report forms by a smart phone application that was used to collect study data. Contact attempts were made to inform participants of the availability of their results as soon as they were received at the clinics, to remind participants of clinic appointments and to check if patients had returned to clinic for appropriate care. These attempts included in-person meetings at the clinic or telephonic calls. Contacts were categorized as successful if the case manager was able to meet with the participant or speak to the participant telephonically. All decisions about clinical management of participants were made by PHC staff according to their routine practice. Case managers were not actively involved in arranging any additional investigations for TB after enrolment.

Study population and data collection

Participants were eligible for inclusion in the study, based on criteria previously used in the XTEND trial, if they were aged ≥18 years, identified by PHC staff as needing investigation for TB through TB symptom screen as having any of the four TB symptoms, provided a sputum specimen for TB investigation, able to give informed consent, likely to remain in the study catchment area for eight months and able to provide adequate locator information, including an alternative contact number for either a friend of family member. Case managers recruited participants who met the inclusion

criteria. Data on demographics, current TB symptoms, TB and HIV history and health care-seeking behaviour was collected at enrolment. Contact attempts and participants' progress in linkage into appropriate care was recorded on log forms.

At the end of the follow-up period, the case managers conducted a telephonic or clinic interview with the participant to ascertain if linkage into appropriate care had taken place by collecting self-reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and current TB symptoms. Additional data were collected by professional nurses abstracting from clinic records HIV data (such as HIV testing, CD4 count testing and ART start dates) and TB data (TB testing and treatment start dates). Case report forms were completed on a study-specific smart phone application and data submitted in an encrypted format to a central database.[4]

Description of outcomes and analysis

Linkage into HIV care was defined as, at three months after enrolment, i) if HIV status unknown at enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4 count ≤ 350 cells/mm^3 or testing Xpert MTB/RIF positive); ii) if HIV-positive with an unknown CD4 count and not on ART at enrolment: having done a CD4 count test; and being started on ART if eligible; iii) if last CD4 count done more than six months previously and not on ART at enrolment: having a CD4 count done; and being started on ART if eligible. Failure to initiate ART after three months when ART eligible at initial assessment was defined as non-linkage to HIV care.

Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of sputum submission among patients with a positive sputum test result. Non-linkage to TB treatment (pre-treatment loss to follow up) was defined as not starting TB treatment within 28 days of sputum collection among people with a positive TB test result, consistent with definitions in previous studies.[2, 4]

Linkage to HIV care or TB treatment initiation was confirmed by record of ART or TB treatment start date as reported by the participant and documented in study documents or from patient clinic files. Mortality was ascertained by reports by close relatives or friends indicating the death of a participant. Participants were defined as lost to follow-up if at three months, linkage status was unknown and the participant could not be contacted by case managers.

Contacts attempts were defined as any effort (successful or unsuccessful), done either telephonically or in-person meeting, made by case managers to interact with a patient. The total number of contact attempts per patients was counted and median attempts needed for linkage into TB and HIV care or both were calculated.

Sample size calculation

This was a pilot study aiming to determine feasibility of implementing the intervention, and to estimate linkage to TB and HIV care. The sample size calculation was based on two binary outcomes: 1) uptake of ART among those who were HIV positive and ART eligible; 2) pre-treatment loss to follow-up among those who tested TB positive. We had planned to enrol 1200 participants (200 per clinic as in XTEND) with the assumption that 96 (8%) of those tested for TB would test TB positive and need to initiate TB treatment.[4] We also assumed that 20 (21%) of people with a sputum testing positive for TB would experience pre-treatment loss to follow-up.[4] For patients needing linkage to HIV care, the assumption was that 240 (20%) of patients enrolled would not know their HIV status. It was also assumed that 576 (60%) of patients who knew their HIV status would self-report being HIV positive. [4] Two hundred and eighty-eight (50%) of those who were HIV positive would not know their CD4 count and would be ART eligible once a CD4 count test was done.[4]

Risk factor analysis for mortality

Univariable logistic regression analysis was used to assess risk factors for mortality. Due to the small proportion of participants who died by end of three months follow-up, categories per predictor variable in the univariable model were restricted to three and a multivariable logistic regression model was not built as a minimum of 10 events per predictor variable is required.[12] All statistical analyses were done using Stata version 14 (Stata Corp LP, College Station, Texas).

Patient and public involvement

Patients or public were not involved in the development of research question, outcome measures, study design, recruitment to and conduct of the study. Copies of the study report will be send to participants who contact the investigators about an interest to receive the study results.

Results

Baseline characteristics

From September to December 2014, 800 adults having a sputum taken for TB investigations in six PHCs were screened and 585 were enrolled. Of these 585, 23 from one site were excluded from analysis because ill health prevented the case manager from undertaking study procedures correctly, leaving 562 from five clinics for analysis. Of the 562 participants, 307 (54.6%) were female and the median age was 36 years (interquartile range (IQR) 29-44) (Table 1). The majority of participants (477, 84.8%) self-reported having had an HIV test in the past and of these 328/475 (69.1%) reported being HIV-positive. Of the 328 HIV-positive participants, 156/327 (47.7%) reported having a CD4 count done within the previous six months and self-reported median CD4 count was 315 cells/mm^3 (IQR 164-471). Over half of the HIV-positive participants with a known CD4 count (209/327 [63.9%]) had never received ART. Ninety-six/562 (17.1%) of the enrolled participants were previously treated for TB. Five hundred and fourteen/543 (94.7%) participants reported having at least one TB symptom to the study team and the majority 452/514 (87.9%) reported having cough (Table 1).

Table 1: Baseline characteristics of the study population

Variable	n (%) N= 562
Gender	
Female	307 (54.6)
Age (Median, IQR)	36 (29-44)
Country of birth	
South Africa	447 (79.5)
Ethnic group	
Black	556 (98.9)
Highest education completed	
No schooling	23 (4.0)
Pre-school – Grade 7	124 (22.0)
Grade 8 - 12	377 (67.1)
University/technical qualification	38 (6.8)
Marital Status	
Single never married	250 (44.5)
Married	108 (19.2)
Cohabitating	159 (28.3)
Divorced/widowed/separated	45 (8.0)
Main income source	
Formal-employment	250 (44.5)
Self-employment/ Odd jobs	134 (23.8)
No income	88 (15.7)
Grant/dependence	90 (16.0)
Average monthly income	
< ZAR 600	34 (6.0)
ZAR 601-1000	73 (13.0)
ZAR 1001-2000	120 (21.4)
ZAR 2001-4000	167 (29.7)
Greater than ZAR 4000	58 (10.3)
Don't know	110 (19.6)
Ever had HIV test	
Yes	477 (84.9)
Self-reported HIV status (n=475)^	
Negative	143 (30.1)
Positive	328 (69.1)
Unknown	4 (0.8)
CD4 count known (n=327)[#]	
Yes	156 (47.7)
Self-reported CD4 count, median (IQR)	315 (164 - 471)
Ever been on ART (n=327)	
Never	209 (63.9)
Currently	116 (35.5)
Previously	2 (0.6)

Time on ART in years, median (IQR) n=118	2 (0 - 4)
Ever treated for TB	
Yes	96 (17.1)
TB symptoms reported (n=543)*	
Yes	514 (94.7)
Symptoms reported (n=514)	
Cough	452 (87.9)
Unintentional weight loss	311 (60.5)
Night sweats	218 (42.4)
Fever	186 (36.2)

Abbreviations: ART antiretroviral treatment, *TB* tuberculosis
^ 2 participants refused to disclose their HIV status
*data missing for 19 participants
data missing for 1 participant

Implementation of the intervention

Overall 189/562 (33.6%) participants required linkage into HIV care or TB treatment initiation or both. Of the 189, 132/189 (69.8%) participants required linkage into HIV care only, 35/189 (18.5%) TB treatment initiation only and 22/189 (11.6%) required both TB treatment initiation and linkage to HIV care. A total of 555 contact attempts were made by the case managers to these participants: 310/555 (55.9%) were telephonic, 243/555 (43.8%) were contacts at clinic and 2/555 (0.4%) were home visits. Of the 310 telephonic contacts, 211/310 (68.1%) were successful. Of the 99 unsuccessful telephone contact attempts, 98 were due to numbers ringing without an answer and in one the call went to voicemail.

Contact attempts for linkage to HIV care only: of the 132 people needing linkage to HIV care only, 407 contact attempts in total were made to these individuals with a median of 3 (IQR 2-4) attempts per individual. At the end of the follow-up, 29/132 (22.0%) people had still not linked into HIV care and a total of 111 contact attempts, with a median of four attempts (IQR 2- 4) per individual, had been made to these individuals.

Contact attempts for linkage to TB care only: for people needing to initiate TB treatment only (35), 78 contact attempts with a median two (IQR 1-3) attempts were made. Four (11.4%) of the 35

participants did not initiate TB treatment by end of follow-up period. Ten contact attempts with median of one (IQR 1-4) were made to these individuals.

Contact attempts for linkage to TB and HIV care: 70 contact attempts with median of three (IQR 2-4) attempts were made to the 22 participants that needed both to initiate TB treatment and link into HIV care. At end of follow-up, seven (31.8%) of the 22 participants had not completely linked into care as they had started on TB treatment but had not initiated ART. Twenty-seven contact attempts with a median of two attempts (IQR 4-5) per individual were made to these seven individuals.

Linkage into HIV care

Participant flow through the steps of linkage to HIV care is shown in figure 2. At enrolment, 94 participants had unknown HIV status or a negative HIV test results older than three months and were offered an HIV test. Amongst the 94, 26 (27.7%) declined to test. Of those who tested, 26/68 (38.2%) were HIV positive. A total of 132 (26 newly-tested HIV positive and 106 not on ART with unknown CD4 count) needed a CD4 count, of whom 119/132 (90.2%) had blood taken for a CD4 count by the end of the study. Of the 135 with a CD4 count result (119 who had a new CD4 count and 16 who already knew their CD4 count), 91/135 (67.4%) were ART eligible and 67/91 (73.6%) of those initiated for ART. Of those needing a CD4 count, 13/132 (9.8%) did not have a CD4 count done and 24/91 (26.4%) ART eligible did not initiate ART. The highest proportion of HIV positive patients were lost at the ART initiation stage (Figure 2).

TB treatment initiation

A total of 57/562 (10.1%) participants had a positive index Xpert MTB/RIF result. Of the 57, 53 (93.0%) started TB treatment within 28 days of testing positive for TB with median time to TB treatment initiation of five days (IQR 2-7). Of the four that were not initiated on TB treatment, two died before starting TB treatment and two started TB treatment more than 28 days after sputum

was taken. An additional 22 participants were started on TB treatment after being diagnosed by follow-up tests.

We could not do a risk factor analysis for non-linkage into care because of the complexity of differing denominators at different stages of HIV linkage into care and the low numbers for those who did not initiate TB treatment.

Mortality and loss to follow-up

At the end of three months follow-up, 27/562 (4.8%) participants had died and loss to follow-up was 49/535 (9.2%). Of 27 participants who died, 18 had self-reported being HIV positive and 14/18 (77.8%) of them were on ART. Only four of the deceased participants had a TB positive index Xpert MTB/RIF result.

Risk factors of mortality at three months after enrolment

Univariable analysis for mortality (Table 2) showed weak evidence for an association between having more than one TB symptom (OR 2.4, 95% CI 0.89-6.45) and increased risk of death, but a chance finding cannot be excluded.

Table 2: Univariate analysis for risk factors for mortality

Variable	Proportion died (%)	OR (95% CI)	P value
Gender			
Male	10/255 (3.9)	1	
Female	17/307 (5.5)	1.43 (0.65 - 3.19)	0.37
Age group			
>30	5/144 (3.5)	1	
30-39.9	14/210 (6.7)	1.99 (0.69 - 5.64)	
≤40	8/208 (3.8)	1.11 (0.36 - 3.47)	0.29
Self-reported HIV status			
Negative	5/130 (3.8)	1	
HIV-positive on ART	4/120 (3.3)	0.86 (0.23 - 3.28)	
HIV-positive not on ART	14/205 (6.8)	1.83 (0.64 - 5.21)	0.29
Number of TB symptoms			
≤1	5/194 (2.6)	1	
2 and more	22/368 (6.0)	2.4 (0.89 - 6.45)	0.05
BMI			
<18.5	4/78 (5.1)	0.88 (0.29 - 2.68)	
18.5-24.9	18/311 (5.8)	1	
25+	5/173 (2.9)	0.48 (0.18 - 1.32)	0.33

Abbreviations: ART antiretroviral treatment, *HIV* human immunodeficiency virus, *TB* tuberculosis, *BMI* body mass index

Discussion

In our study, 33.6% of people being investigated for TB at PHCs in South Africa required linkage into HIV care or TB treatment initiation. A high proportion of people with positive TB test results started

TB treatment with 78 contact attempts made to them. However, despite support with 477 contact attempts from a case manager, a total of 21.9% of those needing HIV care only and 31.8% needing TB and HIV care did not link into HIV care at the end of the three months follow-up period with the highest proportion lost at the ART initiation step. By piloting this intervention, we had hoped to overcome obstacles such as nurses not having enough time to follow up patients and difficulties of making contact with the patients such as clinic phones not working or people having not given their contact numbers. The processes of the intervention largely worked as intended, with multiple contacts to people needing linkage into care. However, HIV linkage care was still suboptimal, suggesting that this intervention as implemented for HIV was insufficient. It also suggests that linkage to HIV care compared to initiation of TB treatment is harder to achieve. This is probably due to the larger number of steps that were necessary for a person to start ART at the time of the study which included CD4 count testing for ART eligibility assessments, attendance at ART adherence classes and baseline blood tests for assessment of contraindications to specific antiretroviral drugs. This resulted in patients needing to visit the clinic multiple times. South African guidelines now recommend ART for all HIV positive people regardless of CD4 count. This may reduce losses along the linkage pathway by reducing the number of visits needed.

Some of our study participants refused HIV testing but the proportions (27.6%) in our study were lower than that found in a South African study done in 2007 comparing uptake of HIV test between provider initiated testing and counselling and provider referral to voluntary HIV testing amongst patients attending community health centres.[13] The study reported that 45% of patients in the provider initiated testing group, versus 69% of patients in voluntary HIV testing group, refused HIV testing.[13] In a 2012 study amongst HIV non-testers from South Africa, barriers to testing included fear of knowing one's HIV status and fear of what people may say.[14] Linkage to care (HIV and TB) in our study was higher compared to Sizanani, a randomised control trial in South Africa done between 2010 to 2013 using health navigators sending short messaging service (SMS) reminders to newly diagnosed HIV-positive people to link into TB and HIV care.[10]. This difference is probably

because linkage to care was defined differently in Sizanani compared to our study. Standardized definitions of linkage to care would facilitate making comparisons and setting standards.[10]

A number of participants in our study declined to start on ART because they could not get time off work. This could be because the health system is too difficult or time-consuming for working people to navigate; it could also be that participants not wanting to start ART for other reasons gave this as an excuse for not returning to the clinic. A study determining rates and predictors of declining to start ART in treatment-eligible HIV-positive individuals in South Africa in 2009 showed that 20% refused to start ART and 37% of those reported feeling healthy as a reason for non-initiation.[15] Another study, from South Africa in 2010, showed that stigma was the main barrier to initiating ART.[16] The limited information available around the reasons for non-linkage to HIV care suggest that the problem is not simply a failure of clinic staff to communicate results but rather a multifactorial challenge with health system, individual and structural components.[10]

Some interventions have had successes in improving linkage to care. A study in Uganda focusing on improving processes within clinics showed an improvement in ART initiation among HIV-positive patients.[17] Another study done in Zambia and Tanzania that combined clinic-based care plus community support showed a reduction in mortality in HIV-positive patients compared to standard of care.[18] It is hard to know what exactly made these interventions work but the Ugandan study differed from our study in that it targeted multiple number of components within the clinic such as staff training, coaching and facility feedback. On the other-hand the Zambian and Tanzanian study differed in that community support was provided by a lay worker with a higher qualification than a lay counsellor and trained on monitoring of patients for disease progression as well as drug toxicity. Our intervention tried to address challenges of communication between clinic and patients as well as provide support and encouragement to patients.

Our data showed that amongst adults with a positive Xpert MTB/RIF sputum result, 93.0% were started on TB treatment with 148 contact attempts made to them. The median time to TB

treatment start in our study was five days which is within the recommended national department of health targets of two to five days.[6] We could not quantify the total number of participants who were diagnosed with TB using follow-up tests in our study, as some may have started TB treatment after our follow-up ended. Pre-treatment loss to follow-up was lower than the 11-25% found in previous studies in South Africa, although comparisons are limited by the relatively small numbers in our study.[1-4]

Mortality was high in our study at 4.8% by 3 months suggesting that people are presenting with advanced disease or when already severely ill. This underscores the importance of early diagnosis and linkage to care.

Strengths of our study include prospectively enrolling a representative sample of adults being investigated for TB from five clinics in two provinces of the country which are diverse in living conditions and population and likely to be representative of urban and peri-urban practice in South Africa. A limitation of our study is that this was a pilot study and as such had no “standard of care” comparison group, therefore we cannot formally determine if the strategy made a difference or not. Another limitation is that we did not keep record of TB treatment started after the follow-up period.

Conclusion

In our pilot study assessing the potential effect of a case manager to support linkage into HIV care and TB treatment initiation amongst adults being investigated for TB we report a higher than desirable rate of non-linkage into HIV care. This is an indication that the piloted strategy lacks components that are crucial to the successful engagement of patients into HIV care. A qualitative evaluation of the intervention (in progress) may give insights into how this intervention could be improved. This pilot study was planned with the intention to conduct a larger trial afterwards but our findings suggest that further work be done before the intervention is further evaluated. We

recommend that more innovative approaches be explored to find strategies that will improve linkage to HIV care and TB treatment initiation in this population to reduce mortality.

Data sharing statement

Data used for this study can be accessed from the London School of Tropical Medicine repository.

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Contributors

NM, AG, VC, KM and GC contributed in the design of the study. NM, AG, VC, KM supervised data collection. NM analysed the data and wrote the first draft of the manuscript. AG, VC, KM and GC provided comments for the revision of the manuscript.

Competing interests

The authors have no competing interests.

Ethics approval and consent to participate

Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand reference number M131143 and the London School of Hygiene & Tropical Medicine,

UK reference number 7124. Participants in the study gave written consent, or witnessed oral consent for participants who could not read or write.

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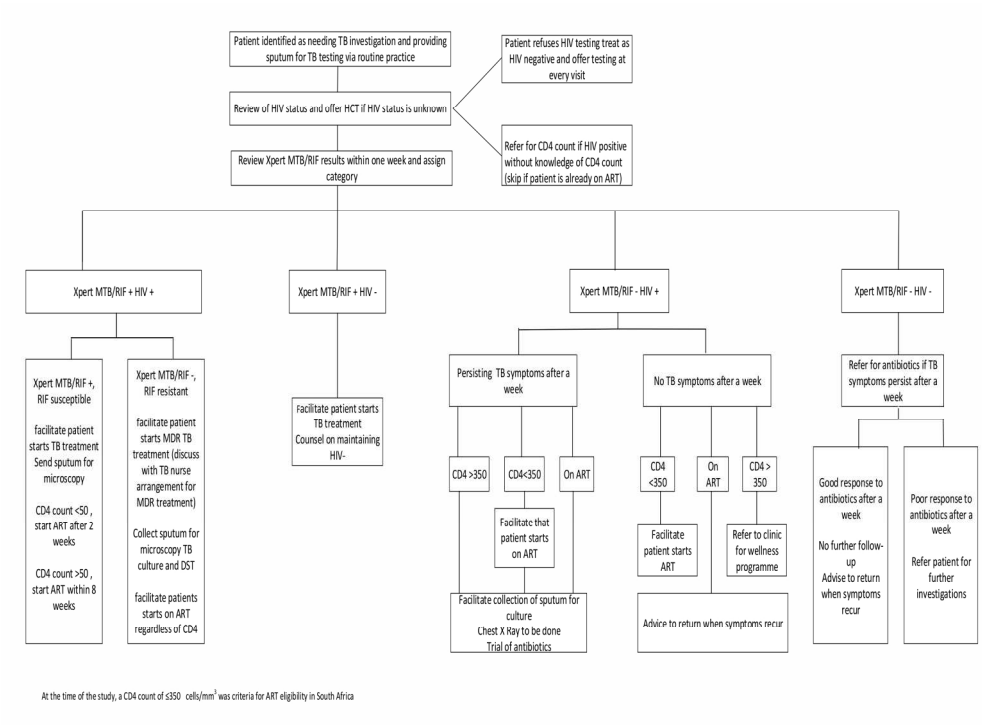
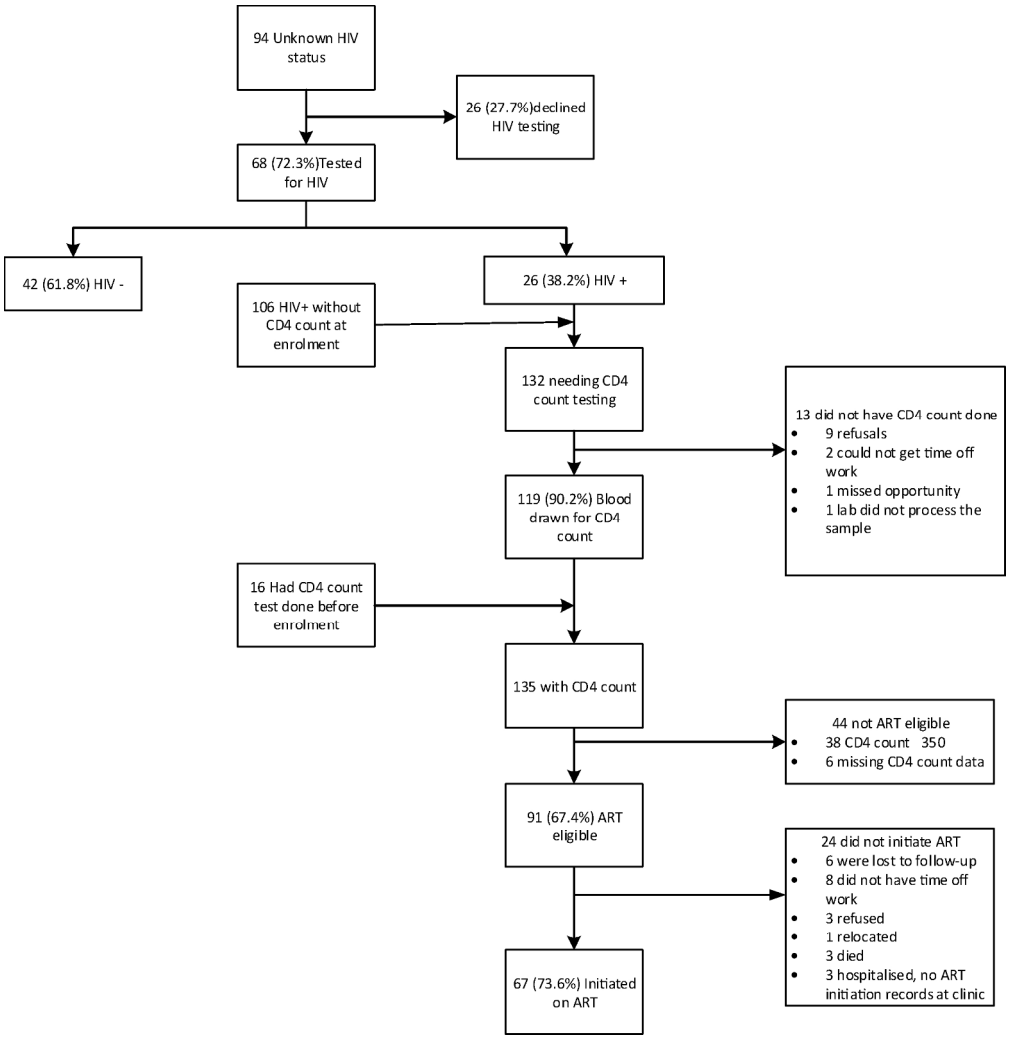
Figure 1: TB and HIV algorithm used to guide case managers.

Figure 2: Flow diagram of linkage into HIV care after three months follow-up.



TB and HIV algorithm used to guide case managers

180x131mm (300 x 300 DPI)



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CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	1
Authors *	Contact details for the corresponding author	13-18
Trial design	Description of pilot trial design (eg, parallel, cluster)	26
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	27
Interventions	Interventions intended for each group	29
Objective	Specific objectives of the pilot trial	24
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	32-35
Randomization	How participants were allocated to interventions	N/A
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	N/A
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	36
Recruitment	Trial status†	N/A
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	36-38
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	38-43
Harms	Important adverse events or side effects	N/A
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	44-46
Trial registration	Registration number for pilot trial and name of trial register	N/A
Funding	Source of funding for pilot trial	N/A

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

**this item is specific to conference abstracts*

***Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those that are a priori agreed as the most important to the decision to proceed with the future definitive RCT.*

†For conference abstracts.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2 & 3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	4 & 5
	2b	Specific objectives or research questions for pilot trial	5
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
	4c	How participants were identified and consented	6 & 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 & 6
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	7 & 8
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	7-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	9 &11
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10 &11
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	11&12
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	11&12
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	13 &14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	17
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	15-17
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	16
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	17
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	N/A
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18
	26	Ethical approval or approval by research review committee, confirmed with reference number	18 &19

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.