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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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Complete List of Authors:	Maraba, Noriah; The Aurum Institute; University of Witwatersrand , School of Public Health, Faculty of Health Science Chihota, Violet ; The Aurum Institute, Queens Road, Parktown, Johannesburg ; University of Witwatersrand , School of Public health, Faculty of Health Sciences McCarthy, Kerrigan; National Institute for Communicable Diseases, Outbreak Response Unit; University of Witwatersrand, School of Public Health, Faculty of Health Sciences Churchyard, Gavin; The Aurum Institute ; London School of Hygiene and Tropical Medicine, Department of Infectious Diseases Epidemiology Grant, Alison; London School of Hygiene and Tropical Medicine, Infectious and Tropical Diseases; University of Witwatersrand, School of Public Health, Faculty of Health Sciences
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3 **1 Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a**  
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5 **2 case manager intervention**  
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11 **4 Authors:** N Maraba<sup>1,2</sup>, V Chihota<sup>1,2,3</sup>, K McCarthy<sup>2,4</sup>, GJ Churchyard<sup>1,2, 5,6</sup> and AD Grant<sup>2,7,8</sup>  
12

13 **5 Authors' Institutions**  
14

15  
16 <sup>1</sup> The Aurum Institute, Queens Road Parktown, Johannesburg, South Africa; <sup>2</sup>School of Public Health,  
17 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;  
18

19  
20 <sup>3</sup>Foundation for Innovative New Diagnostics; <sup>4</sup>National Institute of Communicable Disease,  
21 Sandringham, South Africa; <sup>5</sup>Advancing Treatment and Care for TB and HIV, South African Medical  
22

23 Research Council Collaborating Centre for HIV/TB; <sup>6</sup>London School of Hygiene & Tropical Medicine,  
24

25 London, UK; <sup>7</sup>TB Centre, London School of Hygiene & Tropical Medicine, London, UK; <sup>8</sup>Africa Health  
26

27 Research Institute, School of Nursing and Public Health, University of Kwazulu-Natal, South Africa.  
28

29  
30  
31

32 **13 Corresponding author:**  
33

34  
35 **14 Name:** Noriah Maraba  
36

37  
38 **15 Postal Address:** Postnet Suite 300  
39

40 Private Bag X30500, Houghton 2041, South Africa  
41

42  
43 **17 Telephone:** +2710 590 1446  
44

45  
46 **18 Email address:** [nmaraba@auruminstitute.org](mailto:nmaraba@auruminstitute.org)  
47

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3 **Abstract**  
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6 **Objectives:** We piloted an intervention to determine if support from a case-manager would assist  
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8 adults being investigated for TB to link into TB and HIV care.  
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11 **Design:** Pilot interventional cohort study.  
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14 **Participants and setting:** Patients identified by primary healthcare clinic staff in South Africa as  
15  
16 needing TB investigations were enrolled.  
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18  
19 **Intervention:** Participants were supported for three months by case-managers who facilitated the  
20  
21 care pathway by promoting HIV testing, getting laboratory results, calling patients to return for  
22  
23 results, and facilitating treatment initiation.  
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25  
26 **Outcomes measured:** Linkage to TB care was defined as starting TB treatment within 28 days in  
27  
28 those with a positive test result; linkage to HIV care, for HIV-positives, was defined as having blood  
29  
30 taken for CD4 count and, for those eligible, starting antiretroviral therapy within three months.  
31  
32 Intervention implementation was measured by number of attempts to contact participants.  
33

34  
35 **Results:** Among 562 participants [307 (54.6%) female, median age 36 years (interquartile range [IQR]  
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37 29-44)], most 477 (84.8%) had previously tested for HIV; of these, 328 (69.0%) self-reported being  
38  
39 HIV-positive. Overall, 189/562 (33.6%) participants needed linkage to care [132 HIV care linkage  
40  
41 only; 35 TB treatment linkage only; 22 both]. Of 555 attempts to contact these 189 participants, 407  
42  
43 were to facilitate HIV care linkage, 78 for TB treatment linkage and 70 for both. At end of three  
44  
45 months' follow-up, 40 participants had not linked to care [29 of the 132 (21.9%) participants needing  
46  
47 linkage to HIV care only, 4 of the 35 (11.4%) needing to start on TB treatment only and 7 of the 22  
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49 (31.8%) needing both].  
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3 44 **Conclusion:** Many people testing for TB need linkage to care. Despite case-manager support, non-  
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5 45 linkage into HIV care remained higher than desirable, suggesting a need to modify this intervention  
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7 46 before implementation. Innovative strategies to enable linkage to care are needed.  
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9

10 47 **Strengths and limitations of the study**  
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- 12  
13 48 • The study had a representative sample of adults being investigated for TB from five clinics in  
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15 49 two provinces with diverse living conditions and representative of urban as well as peri-  
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17 50 urban setting.  
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19 51 • The intervention was well implemented with 555 contact attempts made to participants  
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21 52 needing linkage to care.  
22  
23 53 • The lack of a “standard of care” comparison group meant we could not formally determine if  
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25 54 the strategy made a difference or not.  
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## 57 **Background**

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

70 Linking people with a positive HIV test result into HIV care has traditionally involved multiple steps,  
71 including undertaking a CD4 count to determine eligibility for ART initiation, with losses at each step.  
72 [7] Furthermore, TB and HIV care are not fully integrated, making it difficult for patients needing  
73 treatment for TB and HIV to access care for both conditions. In an attempt to improve linkage into  
74 HIV care among HIV-positive patients, strategies such as case management or health system  
75 navigation, using strengths-based case management, where patients identify their strengths and use  
76 them to improve their circumstances, have been evaluated.[8, 9, 10] One such study, a randomized  
77 control trial in the United States of America among recently-diagnosed HIV-positive people  
78 supported by a case manager, showed that 78% in the intervention arm linked into care successfully  
79 compared to the 60% in the control arm.[8] Task-shifting of duties such as TB counselling, HIV  
80 counselling and testing and ART adherence counselling to lay counsellors has been used as a strategy  
81 to relieve short-staffed and overwhelmed health care workers in primary health care clinics.[11] In

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2  
3 82 this study, we pilot tested an intervention using lay counsellors to provide support to adults being  
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5 83 investigated for TB by following up with patients to ensure that they returned to clinic 1) to receive  
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7 84 their TB and HIV-related test results; 2) to do follow-up tests and 3) to start appropriate treatment.  
8  
9 85 This was intended to overcome obstacles such as nurses not having enough time to follow-up  
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11 86 patients and the difficulties of making contact with patients. The study objectives were to determine  
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13 87 feasibility of implementing the intervention, (determined by number of interactions made),  
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15 88 acceptability of the intervention (determined by a qualitative study, reported separately) and to  
16  
17 89 estimate linkage to TB and HIV care.

## 90 **Methods**

### 91 *Study design*

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

100

### 101 *Description of case manager intervention*

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

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3 107 test results older than three months at enrolment to test for HIV; and 5) for those who tested HIV-  
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5 108 positive or knew themselves to be HIV-positive but did not know their CD4 count at enrolment, to  
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7 109 facilitate CD4 count testing, follow up on CD4 results from laboratory and to facilitate ART initiation  
8  
9 110 if eligible. A study algorithm, based on the national TB and ART guidelines, was developed to assist  
10  
11 111 the study staff in guiding patients through the health system in seeking appropriate care (Figure 1).  
12  
13 112 Case managers attempted to contact participants at least once a week and continued with contact  
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15 113 attempts until linkage to care was complete, or the end of study follow-up, three months after  
16  
17 114 enrolment. Contact attempts were made to inform participants of the availability of their results as  
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19 115 soon as they were received at the clinics, to remind participants of clinic appointments and to check  
20  
21 116 if patients had returned to clinic for appropriate care. These attempts included in-person meetings  
22  
23 117 at the clinic or telephonic calls. Contacts were categorized as successful if the case manager was able  
24  
25 118 to meet with the participant or speak to the participant telephonically. All decisions about clinical  
26  
27 119 management of participants were made by PHC staff according to their routine practice. Case  
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29 120 managers were not actively involved in arranging any additional investigations for TB after  
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31 121 enrolment.  
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### 36 123 *Study population and data collection*

38 124 Participants were eligible for inclusion in the study, based on criteria previously used in the XTEND  
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40 125 trial, if they were aged  $\geq 18$  years, identified by PHC staff as needing investigation for TB, provided a  
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42 126 sputum specimen for TB investigation, able to give informed consent, likely to remain in the study  
43  
44 127 catchment area for eight months and able to provide adequate locator information. Case managers  
45  
46 128 recruited participants who met the inclusion criteria. Data on demographics, current TB symptoms,  
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48 129 TB and HIV history and health care-seeking behaviour was collected at enrolment. Contact attempts  
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50 130 and participants' progress in linkage into appropriate care was recorded on log forms.  
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3 132 At the end of the follow-up period, the case managers conducted a telephonic or clinic interview  
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5 133 with the participant to ascertain if linkage into appropriate care had taken place by collecting self-  
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7 134 reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and  
8  
9 135 current TB symptoms. Additional data were collected by professional nurses abstracting from clinic  
10  
11 136 records HIV data (such as HIV testing, CD4 count testing and ART start dates) and TB data (TB testing  
12  
13 137 and treatment start dates). Case report forms were completed on a study-specific smart phone  
14  
15 138 application and data submitted in an encrypted format to a central database.[4]

17  
18 139 *Description of outcomes and analysis*

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21 140 Linkage into HIV care was defined as, at three months after enrolment, i) if HIV status unknown at  
22  
23 141 enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4  
24  
25 142 count  $\leq 350$  cells/mm<sup>3</sup> or testing Xpert MTB/RIF positive); ii) if HIV-positive with an unknown CD4  
26  
27 143 count and not on ART at enrolment: having done a CD4 count test; and being started on ART if  
28  
29 144 eligible; iii) if last CD4 count done more than six months previously and not on ART at enrolment:  
30  
31 145 having a CD4 count done; and being started on ART if eligible. Failure to initiate ART after three  
32  
33 146 months when ART eligible at initial assessment was defined as non-linkage to HIV care.

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36 147 Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of  
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38 148 sputum submission among patients with a positive sputum test result. Non-linkage to TB treatment  
39  
40 149 (pre-treatment loss to follow up) was defined as not starting TB treatment within 28 days of sputum  
41  
42 150 collection among people with a positive TB test result, consistent with definitions in previous  
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44 151 studies.[2, 4]

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48 152 Linkage to HIV care or TB treatment initiation was confirmed by record of ART or TB treatment start  
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50 153 date as reported by the participant and documented in study documents or from patient clinic files.

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52 154 Mortality was ascertained by reports by close relatives or friends indicating the death of a  
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3 155 participant. Participants were defined as lost to follow-up if at three months, linkage status was  
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5 156 unknown and the participant could not be contacted by case managers.  
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8 157 Contacts attempts were defined as any effort (successful or unsuccessful), done either telephonically  
9  
10 158 or in-person meeting, made by case managers to interact with a patient. The total number of  
11  
12 159 contact attempts per patients was counted and median attempts needed for linkage into TB and HIV  
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14 160 care or both were calculated.  
15

### 161 *Sample size calculation*

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

### 173 *Risk factor analysis for mortality*

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

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3 179 **Results**

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6 180 *Baseline characteristics*

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8 181 From September to December 2014, 800 adults having a sputum taken for TB investigations in six  
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10 182 PHCs were screened and 585 were enrolled. Of these 585, 23 from one site were excluded from  
11  
12 183 analysis because ill health prevented the case manager from undertaking study procedures  
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14 184 correctly, leaving 562 from five clinics for analysis. Of the 562 participants, 307 (54.6%) were female  
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16 185 and the median age was 36 years (interquartile range (IQR) 29-44) (Table 1). The majority of  
17  
18 186 participants (477, 84.8%) self-reported having had an HIV test in the past and of these 328 (69.0%)  
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20 187 reported being HIV-positive. Of the 328 HIV-positive participants, 156/327 (47.7%) reported having a  
21  
22 188 CD4 count done within the previous six months and self-reported median CD4 count was 315  
23  
24 189 cells/mm<sup>3</sup> (IQR 164-471). Over half of the HIV-positive participants (209 [63.9%]) had never received  
25  
26 190 ART. Five hundred and fourteen (94.6%) participants reported having at least one TB symptom to  
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28 191 the study team and the majority 452 (88.1%) reported having cough (Table 1).  
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201 Table 1: Baseline characteristics of the study population

Variable	n (%)
	<b>N= 562</b>
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)
Cohabiting	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) <sup>#</sup>	
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) <sup>*</sup>	
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)

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202 *Abbreviations: ART antiretroviral treatment, TB tuberculosis*

203 \*data missing for 19 participants

204 # data missing for 1 participant

205

206 *Implementation of the intervention*

207 Overall 189/562 (33.6%) participants required linkage into HIV care or TB treatment initiation or

208 both. Of the 189, 132 (69.8%) participants required linkage into HIV care only, 35 (18.5%) TB

209 treatment initiation only and 22 (11.6%) required both TB treatment initiation and linkage to HIV

210 care. A total of 555 contact attempts were made by the case managers to these participants: 310

211 (55.9%) were telephonic, 243 (43.8%) were contacts at clinic and 2 (0.4%) were home visits. Of the

212 310 telephonic contacts, 211 (68.1%) were successful. Of the 99 unsuccessful telephone contact

213 attempts, 98 were due to numbers ringing without an answer and in one the call went to voicemail.

214 *Linkage to HIV care only:* of the 132 people needing linkage to HIV care only, 407 contact attempts in

215 total were made to these individuals with a median of 3 (IQR 2-4) attempts per individual. At the end

216 of the follow-up, 29 (21.9%) people had still not linked into HIV care and a total of 111 contact

217 attempts, with a median of four attempts (IQR 2- 4) per individual, had been made to these

218 individuals.

219 *Linkage to TB care only:* for people needing to initiate TB treatment only (35), 78 contact attempts

220 with a median two (IQR 1-3) attempts were made. Four (11.4%) of the participants did not initiate TB

221 treatment by end of follow-up period. Ten contact attempts with median of one (IQR 1-4) were

222 made to these individuals.

223 *Linkage to TB and HIV care:* 70 contact attempts with median of three (IQR 2-4) attempts were made

224 to the 22 participants that needed both to initiate TB treatment and link into HIV care. At end of

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3 225 follow-up, seven (31.8%) people had not completely linked into care as they had started on TB  
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5 226 treatment but had not initiated ART. Twenty-seven contact attempts with a median of two attempts  
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7 227 (IQR 4-5) per individual were made to these seven individuals.  
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#### 10 228 *Linkage into HIV care*

11  
12 229 Participant flow through the steps of linkage to HIV care is shown in figure 2. Amongst 94 who  
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14 230 needed an HIV test, 26 (27.6%) declined to test. Of those who tested, 26 (38.2%) were HIV positive.  
15  
16 231 A total of 132 (26 newly-tested HIV positive and 106 not on ART with unknown CD4 count) needed a  
17  
18 232 CD4 count, of whom 119 (90.1%) had blood taken for a CD4 count by the end of the study. Of the  
19  
20 233 135 with a CD4 count result (119 who had a new CD4 count and 16 who already knew their CD4  
21  
22 234 count), 91 (67.4%) were ART eligible and 67 (73.6%) of those initiated for ART. Of those needing a  
23  
24 235 CD4 count, 13/132 (9.8%) did not have a CD4 count done and 24/91 (26.3%) ART eligible did not  
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26 236 initiate ART. The highest proportion of HIV positive patients were lost at the ART initiation stage  
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28 237 (Figure 2).  
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#### 32 238 *TB treatment initiation*

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35 239 A total of 57/562 (10.1%) participants had a positive index Xpert MTB/RIF result. Of the 57, 53  
36  
37 240 (92.9%) started TB treatment within 28 days of testing positive for TB with median time to TB  
38  
39 241 treatment initiation of five days (IQR 2-7). Of the four that were not initiated on TB treatment, two  
40  
41 242 died before starting TB treatment and two started TB treatment more than 28 days after sputum  
42  
43 243 was taken. An additional 22 participants were started on TB treatment after being diagnosed by  
44  
45 244 follow-up tests.  
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48  
49 245 We could not do a risk factor analysis for non-linkage into care because of the complexity of differing  
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51 246 denominators at different stages of HIV linkage into care and the low numbers for those who did not  
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53 247 initiate TB treatment.  
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3 249 *Mortality and loss to follow-up*  
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6 250 At the end of three months follow-up, 27/562 (4.8%) participants had died and loss to follow-up was  
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8 251 49/535 (9.2%). Of 27 participants who died, 18 had self-reported being HIV positive and 14 (77.8%)  
9  
10 252 of them were on ART. Only four of the deceased participants had a TB positive index Xpert MTB/RIF  
11  
12 253 result.  
13

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15 254 *Risk factors of mortality at three months after enrolment*  
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17  
18 255 Univariable analysis for mortality (Table 2) showed weak evidence for an association between  
19  
20 256 having more than one TB symptom (OR 2.4, 95% CI 0.89-6.45) and increased risk of death, but a  
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22 257 chance finding cannot be excluded.  
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259 Table 2: Univariate analysis for risk factors for mortality

Variable	Proportion died (%)	OR (95% CI)	P value
<b>Gender</b>			
Male	10/255 (3.9)	1	
Female	17/307 (6.9)	1.43 (0.65 - 3.19)	0.37
<b>Age group</b>			
>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
<b>Self-reported HIV status</b>			
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
<b>Number of TB symptoms</b>			
≤1	5/194 (2.6)	1	
2 and more	22/368 (5.9)	2.4 (0.89 - 6.45)	0.05
<b>BMI</b>			
<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

260 *Abbreviations: ART antiretroviral treatment, HIV human immunodeficiency virus, TB tuberculosis,*

261 *BMI body mass index*

262

## 263 Discussion

264 In our study, 33.6% of people being investigated for TB at PHCs in South Africa required linkage into

265 HIV care or TB treatment initiation. A high proportion of people with positive TB test results started



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3 266 TB treatment with 78 contact attempts made to them. However, despite support with 477 contact  
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5 267 attempts from a case manager, a total of 21.9% of those needing HIV care only and 31.8% needing  
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7 268 TB and HIV care did not link into HIV care at the end of the three months follow-up period with the  
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9 269 highest proportion lost at the ART initiation step. By piloting this intervention, we had hoped to  
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11 270 overcome obstacles such as nurses not having enough time to follow up patients and difficulties of  
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13 271 making contact with the patients such as clinic phones not working or people having not given their  
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15 272 contact numbers. The processes of the intervention largely worked as intended, with multiple  
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17 273 contacts to people needing linkage into care. However, HIV linkage care was still suboptimal,  
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19 274 suggesting that this intervention as implemented for HIV was insufficient. It also suggests that  
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21 275 linkage to HIV care compared to initiation of TB treatment is harder to achieve. This is probably due  
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23 276 to the larger number of steps that were necessary for a person to start ART at the time of the study  
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25 277 which included CD4 count testing for ART eligibility assessments, attendance at ART adherence  
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27 278 classes and baseline blood tests for assessment of contraindications to specific antiretroviral drugs.  
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29 279 This resulted in patients needing to visit the clinic multiple times. South African guidelines now  
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31 280 recommend ART for all HIV positive people regardless of CD4 count. This may reduce losses along  
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33 281 the linkage pathway by reducing the number of visits needed.  
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37 282 Some of our study participants refused HIV testing but the proportions (27.6%) in our study were  
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39 283 lower than that found in a South African study done in 2007 comparing uptake of HIV test between  
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41 284 provider initiated testing and counselling and provider referral to voluntary HIV testing amongst  
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43 285 patients attending community health centres.[13] The study reported that 45% of patients in the  
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45 286 provider initiated testing group, versus 69% of patients in voluntary HIV testing group, refused HIV  
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47 287 testing.[13] In a 2012 study amongst HIV non-testers from South Africa, barriers to testing included  
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49 288 fear of knowing one's HIV status and fear of what people may say.[14] Linkage to care (HIV and TB)  
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51 289 in our study was higher compared to Sizanani, a randomised control trial in South Africa done  
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53 290 between 2010 to 2013 using health navigators sending short messaging service (SMS) reminders to  
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55 291 newly diagnosed HIV-positive people to link into TB and HIV care.[10]. This difference is probably  
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3 292 because linkage to care was defined differently in Sizanani compared to our study. Standardized  
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5 293 definitions of linkage to care would facilitate making comparisons and setting standards.[10]  
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8 294 A number of participants in our study declined to start on ART because they could not get time off  
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10 295 work. This could be because the health system is too difficult or time-consuming for working people  
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12 296 to navigate; it could also be that participants not wanting to start ART for other reasons gave this as  
13  
14 297 an excuse for not returning to the clinic. A study determining rates and predictors of declining to  
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16 298 start ART in treatment-eligible HIV-positive individuals in South Africa in 2009 showed that 20%  
17  
18 299 refused to start ART and 37% of those reported feeling healthy as a reason for non-initiation.[15]  
19  
20 300 Another study, from South Africa in 2010, showed that stigma was the main barrier to initiating  
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22 301 ART.[16] The limited information available around the reasons for non-linkage to HIV care suggest  
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24 302 that the problem is not simply a failure of clinic staff to communicate results but rather a  
25  
26 303 multifactorial challenge with health system, individual and structural components.[10]  
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29 304 Some interventions have had successes in improving linkage to care. A study in Uganda focusing on  
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31 305 improving processes within clinics showed an improvement in ART initiation among HIV-positive  
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33 306 patients.[17] Another study done in Zambia and Tanzania that combined clinic-based care plus  
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35 307 community support showed a reduction in mortality in HIV-positive patients compared to standard  
36  
37 308 of care.[18] It is hard to know what exactly made these interventions work. Our intervention tried to  
38  
39 309 address challenges of communication between clinic and patients as well as provide support and  
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41 310 encouragement to patients.  
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44  
45 311 Our data showed that amongst adults with a positive Xpert MTB/RIF sputum result, 93.0% were  
46  
47 312 started on TB treatment with 148 contact attempts made to them. The median time to TB  
48  
49 313 treatment start in our study was five days which is within the recommended national department of  
50  
51 314 health targets of two to five days.[6] We could not quantify the total number of participants who  
52  
53 315 were diagnosed with TB using follow-up tests in our study, as some may have started TB treatment  
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55 316 after our follow-up ended. Pre-treatment loss to follow-up was lower than the 11-25% found in

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3 317 previous studies in South Africa, although comparisons are limited by the relatively small numbers in  
4  
5 318 our study.[1-4]  
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8 319 Mortality was high in our study at 4.8% by 3 months suggesting that people are presenting with  
9  
10 320 advanced disease or when already severely ill. This underscores the importance of early diagnosis  
11  
12 321 and linkage to care.  
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14  
15 322 Strengths of our study include prospectively enrolling a representative sample of adults being  
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17 323 investigated for TB from five clinics in two provinces of the country which are diverse in living  
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19 324 conditions and population and likely to be representative of urban and peri-urban practice in South  
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21 325 Africa. A limitation of our study is that this was a pilot study and as such had no “standard of care”  
22  
23 326 comparison group, therefore we cannot formally determine if the strategy made a difference or not.  
24  
25 327 Another limitation is that we did not keep record of TB treatment started after the follow-up period.  
26

### 27 28 328 *Conclusion* 29

30  
31 329 In our pilot study assessing the potential effect of a case manager to support linkage into HIV care  
32  
33 330 and TB treatment initiation amongst adults being investigated for TB we report a higher than  
34  
35 331 desirable rate of non-linkage into HIV care. This is an indication that the piloted strategy lacks  
36  
37 332 components that are crucial to the successful engagement of patients into HIV care. A qualitative  
38  
39 333 evaluation of the intervention (in progress) may give insights into how this intervention could be  
40  
41 334 improved. This pilot study was planned with the intention to conduct a larger trial afterwards but  
42  
43 335 our findings suggest that further work be done before the intervention is further evaluated. We  
44  
45 336 recommend that more innovative approaches be explored to find strategies that will improve  
46  
47 337 linkage to HIV care and TB treatment initiation in this population to reduce mortality.  
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### 50 51 338 *Data sharing statement* 52

53  
54 339 Data used for this study can be accessed from the London School of Tropical Medicine repository.  
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1  
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3 340 *Funding*  
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5  
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7  
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9  
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11  
12  
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14

15  
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17  
18 346 collected the data.

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23 348 *Contributors*  
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25  
26 349 NM, AG, VC, KM and GC contributed in the design of the study. NM, AG, VC, KM supervised data  
27  
28 350 collection. NM analysed the data and wrote the first draft of the manuscript. AG, VC, KM and GC  
29  
30 351 provided comments for the revision of the manuscript.

31  
32  
33 352 *Competing interests*  
34

35  
36 353 The authors have no competing interests.  
37

38  
39 354 *Ethics approval and consent to participate*  
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41  
42 355 Ethical clearance was obtained from the Human Research Ethics Committee of the University of the  
43  
44 356 Witwatersrand reference number M131143 and the London School of Hygiene & Tropical Medicine,  
45  
46 357 UK reference number 7124. Participants in the study gave written consent, or witnessed oral  
47  
48 358 consent for participants who could not read or write.  
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412 Figure 1: TB and HIV algorithm used to guide case managers.

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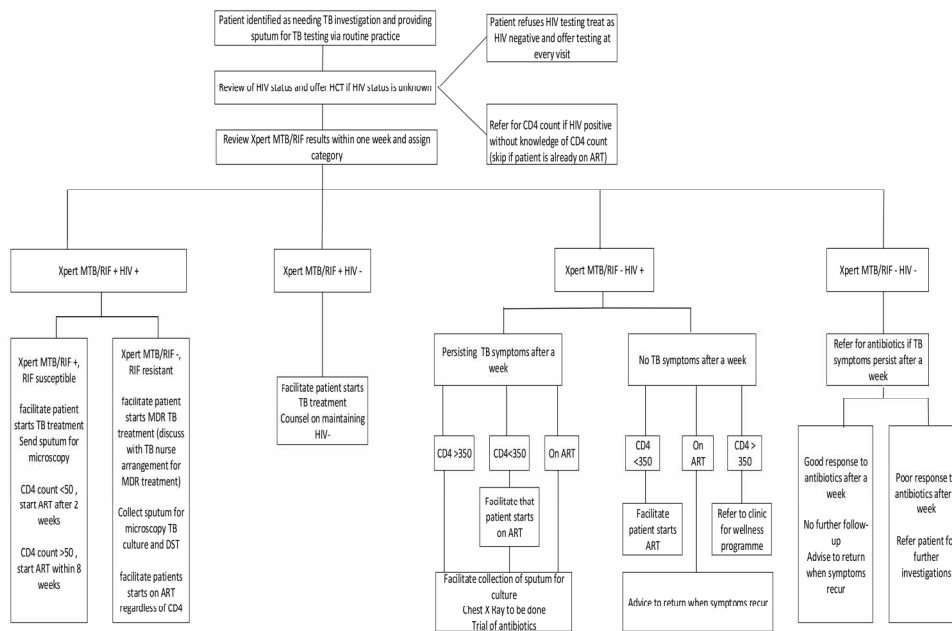
For peer review only

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3 419 Figure 2: Flow diagram of linkage into HIV care after three months follow-up.  
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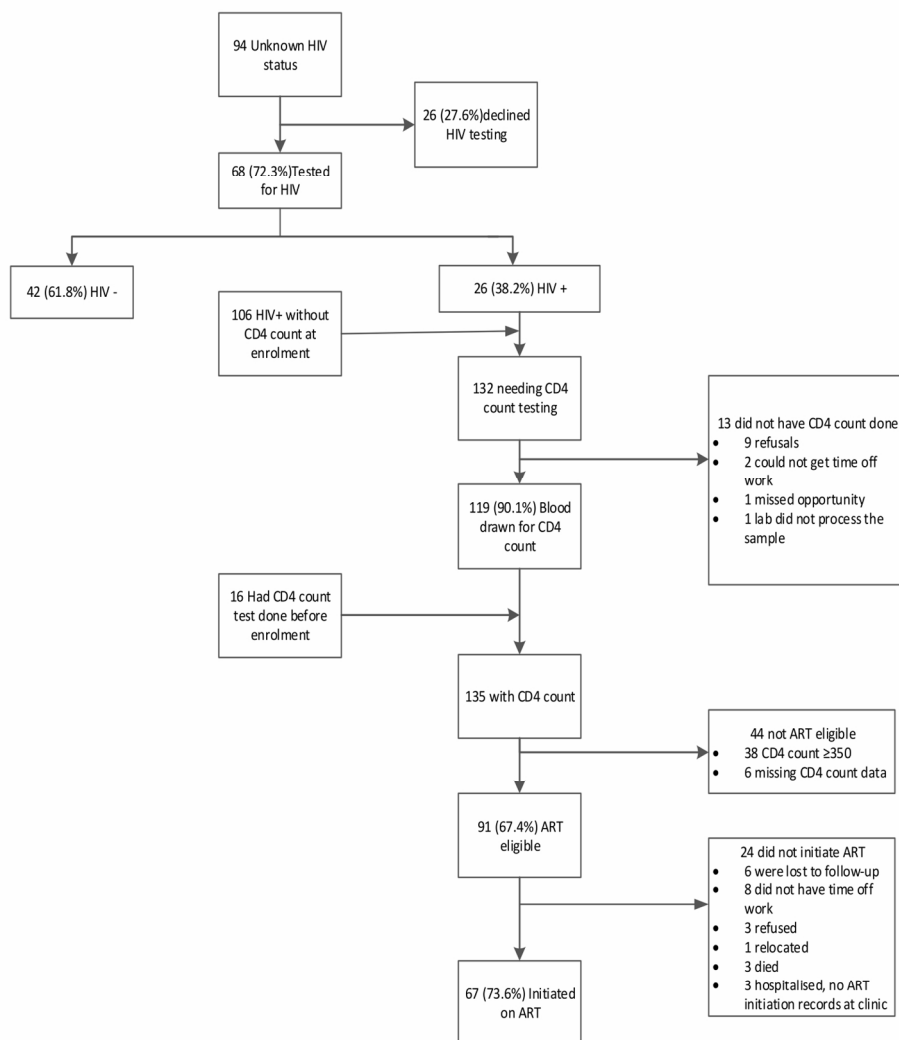


At the time of the study, a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> was criteria for ART eligibility in South Africa

TB and HIV algorithm used to guide case managers

180x131mm (300 x 300 DPI)

Peer review only



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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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Article Type:	Research
Date Submitted by the Author:	26-Mar-2018
Complete List of Authors:	Maraba, Noriah; The Aurum Institute; University of Witwatersrand , School of Public Health, Faculty of Health Science Chihota, Violet ; The Aurum Institute, Queens Road, Parktown, Johannesburg ; University of Witwatersrand , School of Public health, Faculty of Health Sciences McCarthy, Kerrigan; National Institute for Communicable Diseases, Outbreak Response Unit; University of Witwatersrand, School of Public Health, Faculty of Health Sciences Churchyard, Gavin; The Aurum Institute ; London School of Hygiene and Tropical Medicine, Department of Infectious Diseases Epidemiology Grant, Alison; London School of Hygiene and Tropical Medicine, Infectious and Tropical Diseases; University of Witwatersrand, School of Public Health, Faculty of Health Sciences
<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Epidemiology
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, PUBLIC HEALTH

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Manuscripts

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3 1 **Linkage to care among adults being investigated for tuberculosis in South Africa: pilot study of a**  
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5 2 **case manager intervention**

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8 3  
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10 4 **Authors:** N Maraba<sup>1,2</sup>, V Chihota<sup>1,2,3</sup>, K McCarthy<sup>2,4</sup>, GJ Churchyard<sup>1,2, 5,6</sup> and AD Grant<sup>2,7,8</sup>

11  
12  
13 5 **Authors' Institutions**

14  
15  
16 6 <sup>1</sup> The Aurum Institute, Queens Road Parktown, Johannesburg, South Africa; <sup>2</sup>School of Public Health,  
17  
18 7 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;  
19  
20 8 <sup>3</sup>Foundation for Innovative New Diagnostics; <sup>4</sup>National Institute of Communicable Disease,  
21  
22 9 Sandringham, South Africa; <sup>5</sup>Advancing Treatment and Care for TB and HIV, South African Medical  
23  
24 10 Research Council Collaborating Centre for HIV/TB; <sup>6</sup>London School of Hygiene & Tropical Medicine,  
25  
26 11 London, UK; <sup>7</sup>TB Centre, London School of Hygiene & Tropical Medicine, London, UK; <sup>8</sup>Africa Health  
27  
28 12 Research Institute, School of Nursing and Public Health, University of Kwazulu-Natal, South Africa.

29  
30  
31  
32 13 **Corresponding author:**

33  
34  
35 14 **Name:** Noriah Maraba

36  
37  
38 15 **Postal Address:** Postnet Suite 300

39  
40  
41 16 Private Bag X30500, Houghton 2041, South Africa

42  
43  
44 17 **Telephone:** +2710 590 1446

45  
46  
47 18 **Email address:** [nmaraba@auruminstitute.org](mailto:nmaraba@auruminstitute.org)

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50 19 **Current word count:** 4289; **Abstract:** 297

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52 20 **Keywords:** HIV infection, tuberculosis, case managers

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3 **23 Abstract**  
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5 **24 Objectives:** We piloted an intervention to determine if support from a case-manager would assist  
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8 adults being investigated for TB to link into TB and HIV care.  
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10 **26 Design:** Pilot interventional cohort study.  
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13 **27 Participants and setting:** Patients identified by primary healthcare clinic staff in South Africa as  
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16 needing TB investigations were enrolled.  
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18 **29 Intervention:** Participants were supported for three months by case-managers who facilitated the  
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21 care pathway by promoting HIV testing, getting laboratory results, calling patients to return for  
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24 results, and facilitating treatment initiation.  
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26 **32 Outcomes measured:** Linkage to TB care was defined as starting TB treatment within 28 days in  
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29 those with a positive test result; linkage to HIV care, for HIV-positives, was defined as having blood  
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32 taken for CD4 count and, for those eligible, starting antiretroviral therapy within three months.  
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35 Intervention implementation was measured by number of attempts to contact participants.  
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37 **36 Results:** Among 562 participants [307 (54.6%) female, median age 36 years (interquartile range [IQR]  
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40 29-44)], most 477 (84.8%) had previously tested for HIV; of these, 328/475 (69.1%) self-reported  
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43 being HIV-positive. Overall, 189/562 (33.6%) participants needed linkage to care [132 HIV care  
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46 linkage only; 35 TB treatment linkage only; 22 both]. Of 555 attempts to contact these 189  
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49 participants, 407 were to facilitate HIV care linkage, 78 for TB treatment linkage and 70 for both. At  
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52 end of three months' follow-up, 40 participants had not linked to care [29 of the 132 (22.0%)  
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55 participants needing linkage to HIV care only, 4 of the 35 (11.4%) needing to start on TB treatment  
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58 only and 7 of the 22 (31.8%) needing both].  
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3 44 **Conclusion:** Many people testing for TB need linkage to care. Despite case-manager support, non-  
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5 45 linkage into HIV care remained higher than desirable, suggesting a need to modify this intervention  
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7 46 before implementation. Innovative strategies to enable linkage to care are needed.  
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10 47 **Strengths and limitations of the study**

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13 48 • The study had a representative sample of adults being investigated for TB from five clinics in  
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15 49 two provinces with diverse living conditions and representative of urban as well as peri-  
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17 50 urban setting.  
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19 51 • The intervention was well implemented with 555 contact attempts made to participants  
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21 52 needing linkage to care.  
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23 53 • The lack of a “standard of care” comparison group meant we could not formally determine if  
24  
25 54 the strategy made a difference or not.  
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## 57 **Background**

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

70 Linking people with a positive HIV test result into HIV care has traditionally involved multiple steps,  
71 including undertaking a CD4 count to determine eligibility for ART initiation, with losses at each step.  
72 [7] Furthermore, TB and HIV care are not fully integrated, making it difficult for patients needing  
73 treatment for TB and HIV to access care for both conditions. In an attempt to improve linkage into  
74 HIV care among HIV-positive patients, strategies such as case management or health system  
75 navigation, using strengths-based case management, where patients identify their strengths and use  
76 them to improve their circumstances, have been evaluated.[8, 9, 10] One such study, a randomized  
77 control trial in the United States of America among recently-diagnosed HIV-positive people  
78 supported by a case manager, showed that 78% in the intervention arm linked into care successfully  
79 compared to the 60% in the control arm.[8] Task-shifting of duties such as TB counselling, HIV  
80 counselling and testing and ART adherence counselling to lay counsellors has been used as a strategy  
81 to relieve short-staffed and overwhelmed health care workers in primary health care clinics.[11] In

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2  
3 82 this study, we pilot tested an intervention using lay counsellors to provide support to adults being  
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5 83 investigated for TB by following up with patients to ensure that they returned to clinic 1) to receive  
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7 84 their TB and HIV-related test results; 2) to do follow-up tests and 3) to start appropriate treatment.  
8  
9 85 This was intended to overcome obstacles such as nurses not having enough time to follow-up  
10  
11 86 patients and the difficulties of making contact with patients. The study objectives were to determine  
12  
13 87 feasibility of implementing the intervention, (determined by number of interactions made),  
14  
15 88 acceptability of the intervention (determined by a qualitative study, reported separately) and to  
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17 89 estimate linkage to TB and HIV care.  
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## 20 90 **Methods**

### 21 91 *Study design*

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24  
25 92 An interventional cohort study was designed to pilot-test case manager support at primary health  
26  
27 93 care clinics (PHCs) for adults being investigated for TB, to link them into HIV care and initiate TB  
28  
29 94 treatment where these were clinically indicated. The study was conducted from September 2014 –  
30  
31 95 April 2015 in six PHCs in Mpumalanga and Gauteng provinces, South Africa which had previously  
32  
33 96 participated in the XTEND trial and were selected on the basis of their high proportions of pre-  
34  
35 97 treatment loss to follow-up during that trial. At the time of implementing the case manager study,  
36  
37 98 South Africa's criteria for ART initiation were a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> or active TB at any CD4  
38  
39 99 count. Guidelines also suggested that following a TB diagnosis, ART should be initiated in HIV-  
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41  
42 100 positive persons within two weeks after TB treatment initiation.  
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44

45 101

### 46 102 *Description of case manager intervention*

47  
48 103 Case managers were lay counsellors, trained by investigators on basic TB and HIV education and,  
49  
50 104 national ART and TB management guidelines at the time. One case manager was placed at each of  
51  
52 105 the six clinics. The role of the case managers was 1) to follow up on sputum test results from the  
53  
54 106 laboratory; 2) to call all patients to return to the clinic for their results; 3) to facilitate TB treatment  
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3 107 start in patients with a positive sputum test result; 4) to encourage those with unknown HIV status  
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5 108 or negative HIV test results older than three months at enrolment to test for HIV; and 5) for those  
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7 109 who tested HIV-positive or knew themselves to be HIV-positive but did not know their CD4 count at  
8  
9 110 enrolment, to facilitate CD4 count testing, follow up on CD4 results from laboratory and to facilitate  
10  
11 111 ART initiation if eligible. A study algorithm, based on the national TB management and ART  
12  
13 112 guidelines, was developed to assist the study staff in guiding patients through the health system in  
14  
15 113 seeking appropriate care (Figure 1). Case managers attempted to contact participants at least once a  
16  
17 114 week and continued with contact attempts until linkage to care was complete, or the end of study  
18  
19 115 follow-up, three months after enrolment. Lists for weekly follow-ups of enrolled participants that  
20  
21 116 needed linkage to care were maintained through the automated release of weekly follow-up case  
22  
23 117 report forms by a smart phone application that was used to collect study data. Contact attempts  
24  
25 118 were made to inform participants of the availability of their results as soon as they were received at  
26  
27 119 the clinics, to remind participants of clinic appointments and to check if patients had returned to  
28  
29 120 clinic for appropriate care. These attempts included in-person meetings at the clinic or telephonic  
30  
31 121 calls. Contacts were categorized as successful if the case manager was able to meet with the  
32  
33 122 participant or speak to the participant telephonically. All decisions about clinical management of  
34  
35 123 participants were made by PHC staff according to their routine practice. Case managers were not  
36  
37 124 actively involved in arranging any additional investigations for TB after enrolment.  
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#### 42 126 *Study population and data collection*

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45 127 Participants were eligible for inclusion in the study, based on criteria previously used in the XTEND  
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47 128 trial, if they were aged  $\geq 18$  years, identified by PHC staff as needing investigation for TB through TB  
48  
49 129 symptom screen as having any of the four TB symptoms, provided a sputum specimen for TB  
50  
51 130 investigation, able to give informed consent, likely to remain in the study catchment area for eight  
52  
53 131 months and able to provide adequate locator information, including an alternative contact number  
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55 132 for either a friend or family member. Case managers recruited participants who met the inclusion  
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3 133 criteria. Data on demographics, current TB symptoms, TB and HIV history and health care-seeking  
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5 134 behaviour was collected at enrolment. Contact attempts and participants' progress in linkage into  
6  
7 135 appropriate care was recorded on log forms.  
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11 137 At the end of the follow-up period, the case managers conducted a telephonic or clinic interview  
12  
13 138 with the participant to ascertain if linkage into appropriate care had taken place by collecting self-  
14  
15 139 reported data on HIV testing, TB and ART treatment start dates, health-seeking behaviour and  
16  
17 140 current TB symptoms. Additional data were collected by professional nurses abstracting from clinic  
18  
19 141 records HIV data (such as HIV testing, CD4 count testing and ART start dates) and TB data (TB testing  
20  
21 142 and treatment start dates). Case report forms were completed on a study-specific smart phone  
22  
23 143 application and data submitted in an encrypted format to a central database.[4]  
24  
25

26  
27 144 *Description of outcomes and analysis*  
28

29  
30 145 Linkage into HIV care was defined as, at three months after enrolment, i) if HIV status unknown at  
31  
32 146 enrolment: testing HIV-positive, having done a CD4 count and being started on ART if eligible (CD4  
33  
34 147 count  $\leq 350$  cells/mm<sup>3</sup> or testing Xpert MTB/RIF positive); ii) if HIV-positive with an unknown CD4  
35  
36 148 count and not on ART at enrolment: having done a CD4 count test; and being started on ART if  
37  
38 149 eligible; iii) if last CD4 count done more than six months previously and not on ART at enrolment:  
39  
40 150 having a CD4 count done; and being started on ART if eligible. Failure to initiate ART after three  
41  
42 151 months when ART eligible at initial assessment was defined as non-linkage to HIV care.  
43  
44

45 152 Linkage into TB care (TB treatment initiation) was defined as TB treatment start within 28 days of  
46  
47 153 sputum submission among patients with a positive sputum test result. Non-linkage to TB treatment  
48  
49 154 (pre-treatment loss to follow up) was defined as not starting TB treatment within 28 days of sputum  
50  
51 155 collection among people with a positive TB test result, consistent with definitions in previous  
52  
53 156 studies.[2, 4]  
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3 157 Linkage to HIV care or TB treatment initiation was confirmed by record of ART or TB treatment start  
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5 158 date as reported by the participant and documented in study documents or from patient clinic files.  
6  
7 159 Mortality was ascertained by reports by close relatives or friends indicating the death of a  
8  
9 160 participant. Participants were defined as lost to follow-up if at three months, linkage status was  
10  
11 161 unknown and the participant could not be contacted by case managers.

12  
13  
14 162 Contacts attempts were defined as any effort (successful or unsuccessful), done either telephonically  
15  
16 163 or in-person meeting, made by case managers to interact with a patient. The total number of  
17  
18 164 contact attempts per patients was counted and median attempts needed for linkage into TB and HIV  
19  
20 165 care or both were calculated.

#### 21 22 23 166 *Sample size calculation*

24  
25 167 This was a pilot study aiming to determine feasibility of implementing the intervention, and to  
26  
27 168 estimate linkage to TB and HIV care. The sample size calculation was based on two binary outcomes:  
28  
29 169 1) uptake of ART among those who were HIV positive and ART eligible; 2) pre-treatment loss to  
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31 170 follow-up among those who tested TB positive. We had planned to enrol 1200 participants (200 per  
32  
33 171 clinic as in XTEND) with the assumption that 96 (8%) of those tested for TB would test TB positive  
34  
35 172 and need to initiate TB treatment.[4] We also assumed that 20 (21%) of people with a sputum  
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37 173 testing positive for TB would experience pre-treatment loss to follow-up.[4] For patients needing  
38  
39 174 linkage to HIV care, the assumption was that 240 (20%) of patients enrolled would not know their  
40  
41 175 HIV status. It was also assumed that 576 (60%) of patients who knew their HIV status would self-  
42  
43 176 report being HIV positive. [4] Two hundred and eighty-eight (50%) of those who were HIV positive  
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45 177 would not know their CD4 count and would be ART eligible once a CD4 count test was done.[4]

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#### 50 51 52 179 *Risk factor analysis for mortality*

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3 180 Univariable logistic regression analysis was used to assess risk factors for mortality. Due to the small  
4  
5 181 proportion of participants who died by end of three months follow-up, categories per predictor  
6  
7 182 variable in the univariable model were restricted to three and a multivariable logistic regression  
8  
9 183 model was not built as a minimum of 10 events per predictor variable is required.[12] All statistical  
10  
11 184 analyses were done using Stata version 14 (Stata Corp LP, College Station, Texas).

#### 14 185 Patient and public involvement

16  
17 186 Patients or public were not involved in the development of research question, outcome measures,  
18  
19 187 study design, recruitment to and conduct of the study. Copies of the study report will be send to  
20  
21 188 participants who contact the investigators about an interest to receive the study results.

## 24 189 **Results**

### 27 190 *Baseline characteristics*

29  
30 191 From September to December 2014, 800 adults having a sputum taken for TB investigations in six  
31  
32 192 PHCs were screened and 585 were enrolled. Of these 585, 23 from one site were excluded from  
33  
34 193 analysis because ill health prevented the case manager from undertaking study procedures  
35  
36 194 correctly, leaving 562 from five clinics for analysis. Of the 562 participants, 307 (54.6%) were female  
37  
38 195 and the median age was 36 years (interquartile range (IQR) 29-44) (Table 1). The majority of  
39  
40 196 participants (477, 84.8%) self-reported having had an HIV test in the past and of these 328/475  
41  
42 197 (69.1%) reported being HIV-positive. Of the 328 HIV-positive participants, 156/327 (47.7%) reported  
43  
44 198 having a CD4 count done within the previous six months and self-reported median CD4 count was  
45  
46 199 315 cells/mm<sup>3</sup> (IQR 164-471). Over half of the HIV-positive participants with a known CD4 count  
47  
48 200 (209/327 [63.9%]) had never received ART. Ninety-six/562 (17.1%) of the enrolled participants were  
49  
50 201 previously treated for TB. Five hundred and fourteen/543 (94.7%) participants reported having at  
51  
52 202 least one TB symptom to the study team and the majority 452/514 (87.9%) reported having cough  
53  
54  
55 203 (Table 1).

204

205

206 Table 1: Baseline characteristics of the study population

Variable	n (%)
<b>N= 562</b>	
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)
Cohabiting	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)

1		
2		
3	Time on ART in years, median (IQR) n=118	2 (0 - 4)
4	Ever treated for TB	
5	Yes	96 (17.1)
6	TB symptoms reported (n=543)*	
7	Yes	514 ( 94.7)
8	Symptoms reported (n=514)	
9	Cough	452 (87.9)
10	Unintentional weight loss	311 (60.5)
11	Night sweats	218 (42.4)
12	Fever	186 (36.2)

207 *Abbreviations: ART antiretroviral treatment, TB tuberculosis*

208 ^ 2 participants refused to disclose their HIV status

209 \*data missing for 19 participants

210 # data missing for 1 participant

211

### 212 *Implementation of the intervention*

213 Overall 189/562 (33.6%) participants required linkage into HIV care or TB treatment initiation or  
 214 both. Of the 189, 132/189 (69.8%) participants required linkage into HIV care only, 35/189 (18.5%)  
 215 TB treatment initiation only and 22/189 (11.6%) required both TB treatment initiation and linkage to  
 216 HIV care. A total of 555 contact attempts were made by the case managers to these participants:  
 217 310/555 (55.9%) were telephonic, 243/555 (43.8%) were contacts at clinic and 2/555 (0.4%) were  
 218 home visits. Of the 310 telephonic contacts, 211/310 (68.1%) were successful. Of the 99  
 219 unsuccessful telephone contact attempts, 98 were due to numbers ringing without an answer and in  
 220 one the call went to voicemail.

221 *Contact attempts for linkage to HIV care only:* of the 132 people needing linkage to HIV care only,  
 222 407 contact attempts in total were made to these individuals with a median of 3 (IQR 2-4) attempts  
 223 per individual. At the end of the follow-up, 29/132 (22.0%) people had still not linked into HIV care  
 224 and a total of 111 contact attempts, with a median of four attempts (IQR 2- 4) per individual, had  
 225 been made to these individuals.

226 *Contact attempts for linkage to TB care only:* for people needing to initiate TB treatment only (35),  
 227 78 contact attempts with a median two (IQR 1-3) attempts were made. Four (11.4%) of the 35



1  
2  
3 228 participants did not initiate TB treatment by end of follow-up period. Ten contact attempts with  
4  
5 229 median of one (IQR 1-4) were made to these individuals.  
6  
7

8 230 *Contact attempts for linkage to TB and HIV care:* 70 contact attempts with median of three (IQR 2-4)  
9  
10 231 attempts were made to the 22 participants that needed both to initiate TB treatment and link into  
11  
12 232 HIV care. At end of follow-up, seven (31.8%) of the 22 participants had not completely linked into  
13  
14 233 care as they had started on TB treatment but had not initiated ART. Twenty-seven contact attempts  
15  
16 234 with a median of two attempts (IQR 4-5) per individual were made to these seven individuals.  
17  
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### 19 235 *Linkage into HIV care*

20  
21  
22 236 Participant flow through the steps of linkage to HIV care is shown in figure 2. At enrolment, 94  
23  
24 237 participants had unknown HIV status or a negative HIV test results older than three months and  
25  
26 238 were offered an HIV test. Amongst the 94, 26 (27.7%) declined to test. Of those who tested, 26/68  
27  
28 239 (38.2%) were HIV positive. A total of 132 (26 newly-tested HIV positive and 106 not on ART with  
29  
30 240 unknown CD4 count) needed a CD4 count, of whom 119/132 (90.2%) had blood taken for a CD4  
31  
32 241 count by the end of the study. Of the 135 with a CD4 count result (119 who had a new CD4 count  
33  
34 242 and 16 who already knew their CD4 count), 91/135 (67.4%) were ART eligible and 67/91 (73.6%) of  
35  
36 243 those initiated for ART. Of those needing a CD4 count, 13/132 (9.8%) did not have a CD4 count done  
37  
38 244 and 24/91 (26.4%) ART eligible did not initiate ART. The highest proportion of HIV positive patients  
39  
40 245 were lost at the ART initiation stage (Figure 2).  
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43

### 44 246 *TB treatment initiation*

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46  
47 247 A total of 57/562 (10.1%) participants had a positive index Xpert MTB/RIF result. Of the 57, 53  
48  
49 248 (93.0%) started TB treatment within 28 days of testing positive for TB with median time to TB  
50  
51 249 treatment initiation of five days (IQR 2-7). Of the four that were not initiated on TB treatment, two  
52  
53 250 died before starting TB treatment and two started TB treatment more than 28 days after sputum  
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3 251 was taken. An additional 22 participants were started on TB treatment after being diagnosed by  
4  
5 252 follow-up tests.  
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7  
8 253 We could not do a risk factor analysis for non-linkage into care because of the complexity of differing  
9  
10 254 denominators at different stages of HIV linkage into care and the low numbers for those who did not  
11  
12 255 initiate TB treatment.  
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18 257 *Mortality and loss to follow-up*  
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20  
21 258 At the end of three months follow-up, 27/562 (4.8%) participants had died and loss to follow-up was  
22  
23 259 49/535 (9.2%). Of 27 participants who died, 18 had self-reported being HIV positive and 14/18  
24  
25 260 (77.8%) of them were on ART. Only four of the deceased participants had a TB positive index Xpert  
26  
27 261 MTB/RIF result.  
28

29  
30 262 *Risk factors of mortality at three months after enrolment*  
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32  
33 263 Univariable analysis for mortality (Table 2) showed weak evidence for an association between  
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35 264 having more than one TB symptom (OR 2.4, 95% CI 0.89-6.45) and increased risk of death, but a  
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37 265 chance finding cannot be excluded.  
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267 Table 2: Univariate analysis for risk factors for mortality

Variable	Proportion died (%)	OR (95% CI)	P value
<b>Gender</b>			
Male	10/255 (3.9)	1	
Female	17/307 (5.5)	1.43 (0.65 - 3.19)	0.37
<b>Age group</b>			
>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
<b>Self-reported HIV status</b>			
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
<b>Number of TB symptoms</b>			
≤1	5/194 (2.6)	1	
2 and more	22/368 (6.0)	2.4 (0.89 - 6.45)	0.05
<b>BMI</b>			
<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

268 *Abbreviations: ART* antiretroviral treatment, *HIV* human immunodeficiency virus, *TB* tuberculosis,

269 *BMI* body mass index

270

## 271 Discussion

272 In our study, 33.6% of people being investigated for TB at PHCs in South Africa required linkage into

273 HIV care or TB treatment initiation. A high proportion of people with positive TB test results started

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3 274 TB treatment with 78 contact attempts made to them. However, despite support with 477 contact  
4  
5 275 attempts from a case manager, a total of 21.9% of those needing HIV care only and 31.8% needing  
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7 276 TB and HIV care did not link into HIV care at the end of the three months follow-up period with the  
8  
9 277 highest proportion lost at the ART initiation step. By piloting this intervention, we had hoped to  
10  
11 278 overcome obstacles such as nurses not having enough time to follow up patients and difficulties of  
12  
13 279 making contact with the patients such as clinic phones not working or people having not given their  
14  
15 280 contact numbers. The processes of the intervention largely worked as intended, with multiple  
16  
17 281 contacts to people needing linkage into care. However, HIV linkage care was still suboptimal,  
18  
19 282 suggesting that this intervention as implemented for HIV was insufficient. It also suggests that  
20  
21 283 linkage to HIV care compared to initiation of TB treatment is harder to achieve. This is probably due  
22  
23 284 to the larger number of steps that were necessary for a person to start ART at the time of the study  
24  
25 285 which included CD4 count testing for ART eligibility assessments, attendance at ART adherence  
26  
27 286 classes and baseline blood tests for assessment of contraindications to specific antiretroviral drugs.  
28  
29 287 This resulted in patients needing to visit the clinic multiple times. South African guidelines now  
30  
31 288 recommend ART for all HIV positive people regardless of CD4 count. This may reduce losses along  
32  
33 289 the linkage pathway by reducing the number of visits needed.  
34  
35  
36  
37 290 Some of our study participants refused HIV testing but the proportions (27.6%) in our study were  
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39 291 lower than that found in a South African study done in 2007 comparing uptake of HIV test between  
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41 292 provider initiated testing and counselling and provider referral to voluntary HIV testing amongst  
42  
43 293 patients attending community health centres.[13] The study reported that 45% of patients in the  
44  
45 294 provider initiated testing group, versus 69% of patients in voluntary HIV testing group, refused HIV  
46  
47 295 testing.[13] In a 2012 study amongst HIV non-testers from South Africa, barriers to testing included  
48  
49 296 fear of knowing one's HIV status and fear of what people may say.[14] Linkage to care (HIV and TB)  
50  
51 297 in our study was higher compared to Sizanani, a randomised control trial in South Africa done  
52  
53 298 between 2010 to 2013 using health navigators sending short messaging service (SMS) reminders to  
54  
55 299 newly diagnosed HIV-positive people to link into TB and HIV care.[10]. This difference is probably  
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3 300 because linkage to care was defined differently in Sizanani compared to our study. Standardized  
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5 301 definitions of linkage to care would facilitate making comparisons and setting standards.[10]  
6  
7

8 302 A number of participants in our study declined to start on ART because they could not get time off  
9  
10 303 work. This could be because the health system is too difficult or time-consuming for working people  
11  
12 304 to navigate; it could also be that participants not wanting to start ART for other reasons gave this as  
13  
14 305 an excuse for not returning to the clinic. A study determining rates and predictors of declining to  
15  
16 306 start ART in treatment-eligible HIV-positive individuals in South Africa in 2009 showed that 20%  
17  
18 307 refused to start ART and 37% of those reported feeling healthy as a reason for non-initiation.[15]  
19  
20 308 Another study, from South Africa in 2010, showed that stigma was the main barrier to initiating  
21  
22 309 ART.[16] The limited information available around the reasons for non-linkage to HIV care suggest  
23  
24 310 that the problem is not simply a failure of clinic staff to communicate results but rather a  
25  
26 311 multifactorial challenge with health system, individual and structural components.[10]  
27  
28

29 312 Some interventions have had successes in improving linkage to care. A study in Uganda focusing on  
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31 313 improving processes within clinics showed an improvement in ART initiation among HIV-positive  
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33 314 patients.[17] Another study done in Zambia and Tanzania that combined clinic-based care plus  
34  
35 315 community support showed a reduction in mortality in HIV-positive patients compared to standard  
36  
37 316 of care.[18] It is hard to know what exactly made these interventions work but the Ugandan study  
38  
39 317 differed from our study in that it targeted multiple number of components within the clinic such as  
40  
41 318 staff training, coaching and facility feedback. On the other-hand the Zambian and Tanzanian study  
42  
43 319 differed in that community support was provided by a lay worker with a higher qualification than a  
44  
45 320 lay counsellor and trained on monitoring of patients for disease progression as well as drug toxicity.  
46  
47 321 Our intervention tried to address challenges of communication between clinic and patients as well  
48  
49 322 as provide support and encouragement to patients.  
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53 323 Our data showed that amongst adults with a positive Xpert MTB/RIF sputum result, 93.0% were  
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55 324 started on TB treatment with 148 contact attempts made to them. The median time to TB  
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3 325 treatment start in our study was five days which is within the recommended national department of  
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5 326 health targets of two to five days.[6] We could not quantify the total number of participants who  
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7 327 were diagnosed with TB using follow-up tests in our study, as some may have started TB treatment  
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9 328 after our follow-up ended. Pre-treatment loss to follow-up was lower than the 11-25% found in  
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11 329 previous studies in South Africa, although comparisons are limited by the relatively small numbers in  
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13 330 our study.[1-4]

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16 331 Mortality was high in our study at 4.8% by 3 months suggesting that people are presenting with  
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18 332 advanced disease or when already severely ill. This underscores the importance of early diagnosis  
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20 333 and linkage to care.

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23 334 Strengths of our study include prospectively enrolling a representative sample of adults being  
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25 335 investigated for TB from five clinics in two provinces of the country which are diverse in living  
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27 336 conditions and population and likely to be representative of urban and peri-urban practice in South  
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29 337 Africa. A limitation of our study is that this was a pilot study and as such had no “standard of care”  
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31 338 comparison group, therefore we cannot formally determine if the strategy made a difference or not.  
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33 339 Another limitation is that we did not keep record of TB treatment started after the follow-up period.

#### 34 340 *Conclusion*

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39 341 In our pilot study assessing the potential effect of a case manager to support linkage into HIV care  
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41 342 and TB treatment initiation amongst adults being investigated for TB we report a higher than  
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43 343 desirable rate of non-linkage into HIV care. This is an indication that the piloted strategy lacks  
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45 344 components that are crucial to the successful engagement of patients into HIV care. A qualitative  
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47 345 evaluation of the intervention (in progress) may give insights into how this intervention could be  
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49 346 improved. This pilot study was planned with the intention to conduct a larger trial afterwards but  
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51 347 our findings suggest that further work be done before the intervention is further evaluated. We  
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3 348 recommend that more innovative approaches be explored to find strategies that will improve  
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5 349 linkage to HIV care and TB treatment initiation in this population to reduce mortality.  
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8 350 *Data sharing statement*

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10 351 Data used for this study can be accessed from the London School of Tropical Medicine repository.  
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12

13 352 *Funding*

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15  
16 353 The study was funded by the Bill and Melinda Gates foundation grant number [OPP1034523]. The  
17  
18 354 funder did not play a part in the design, collection, analysis or interpretation and the writing of the  
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20 355 manuscript.  
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23 356 *Acknowledgements*

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26 357 We would like to acknowledge all the participants enrolled in the study, the study team collected the  
27  
28 358 data, clinics and clinic staff were the data was collected from.  
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34 360 *Contributors*

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37 361 NM, AG, VC, KM and GC contributed in the design of the study. NM, AG, VC, KM supervised data  
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39 362 collection. NM analysed the data and wrote the first draft of the manuscript. AG, VC, KM and GC  
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41 363 provided comments for the revision of the manuscript.  
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44 364 *Competing interests*

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47 365 The authors have no competing interests.  
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50 366 *Ethics approval and consent to participate*

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53 367 Ethical clearance was obtained from the Human Research Ethics Committee of the University of the  
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55 368 Witwatersrand reference number M131143 and the London School of Hygiene & Tropical Medicine,  
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369 UK reference number 7124. Participants in the study gave written consent, or witnessed oral  
370 consent for participants who could not read or write.

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3 424 Figure 1: TB and HIV algorithm used to guide case managers.  
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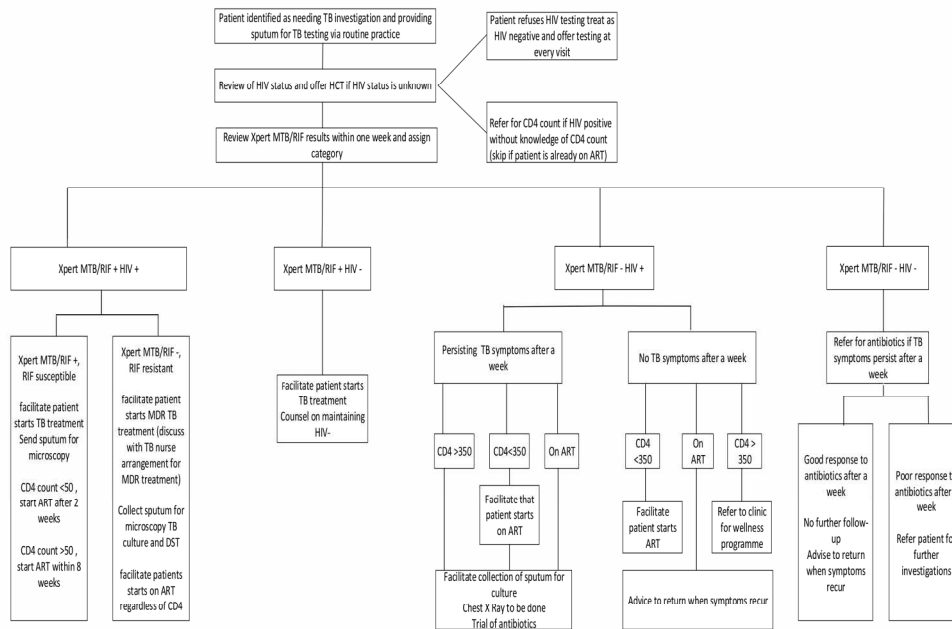
449 Figure 2: Flow diagram of linkage into HIV care after three months follow-up.

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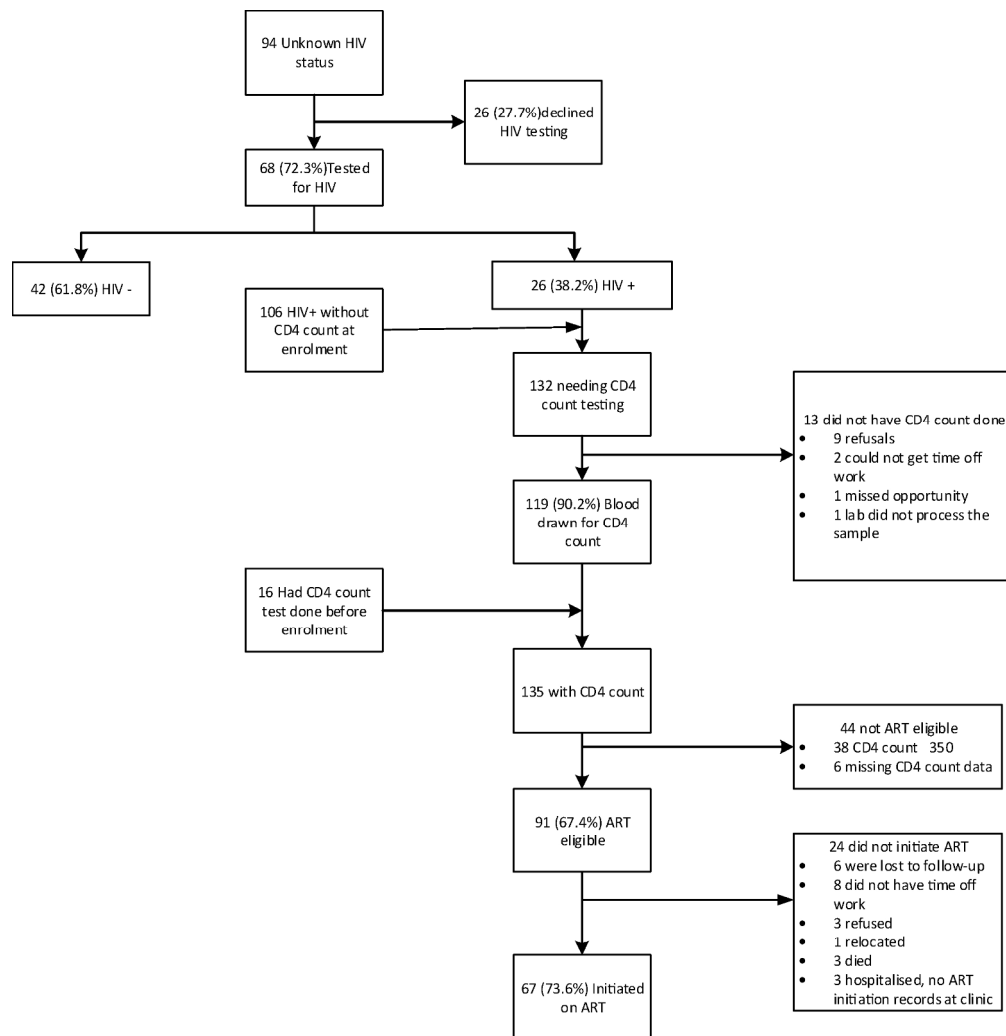


At the time of the study, a CD4 count of  $\leq 350$  cells/mm<sup>3</sup> was criteria for ART eligibility in South Africa

TB and HIV algorithm used to guide case managers

180x131mm (300 x 300 DPI)

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226x233mm (300 x 300 DPI)



## 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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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

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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](http://www.consort-statement.org).

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