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Eligibility for Isoniazid Preventive Therapy in South African Gold Mines

James J. Lewis1,2, Katherine L. Fielding1, Alison D. Grant1, Violet N. Chihota1, Flora Popane2, Mariette Luttig2, Dorothy Muller2, Leonie Coetzee2, Gavin J. Churchyard1,2

1 London School of Hygiene and Tropical Medicine, London, United Kingdom, 2 The Aurum Institute for Health Research, Johannesburg, South Africa

Abstract

Setting: The “Thibela TB” cluster randomised trial of community-wide isoniazid preventive therapy (IPT) to reduce tuberculosis incidence in the South African gold mines.

Objectives: To determine the proportion of participants eligible for IPT and the reasons and risk factors for ineligibility, to inform the scale-up of IPT.

Design: Cross-sectional survey of participants in intervention clusters (mine shafts) consenting to tuberculosis screening and assessment for eligibility to start IPT.

Results: Among 27,126 consenting participants, 94.7% were male, the median age was 41 years, 12.2% reported previous tuberculosis, 0.6% reported ever taking IPT and 2.5% reported currently taking antiretroviral therapy. There were 24,430 (90.1%) assessed as eligible to start IPT, of whom 23,659 started IPT. The most common reasons for ineligibility were having suspected tuberculosis that was subsequently confirmed by a positive smear and/or culture (n=705), excessive alcohol consumption (n=427) and being on tuberculosis treatment at time of initial screen (n=241). Ineligibility was associated with factors including older age, female gender, prior history of tuberculosis and being in “HIV care”. However, at least 78% were eligible for IPT in all of these sub-groups.

Conclusions: The vast majority of participants in this community-wide intervention were eligible for IPT.

Introduction

Settings with a high prevalence of the human immunodeficiency virus (HIV) have experienced dramatic increases in tuberculosis incidence [1]. Alternative approaches are necessary to reduce the risk of HIV associated tuberculosis in such settings. Approaches promoted by the World Health Organization (WHO) include antiretroviral therapy and its 3Is strategy of isoniazid preventive therapy (IPT), intensified case finding (ICF) and infection control [1]. IPT was provided to almost 450,000 newly enrolled into HIV care in 2011, up from 201,000 in 2010, yet still far lower than the total number newly enrolled in HIV care and potentially eligible for IPT (estimated at 1.5 million in 2010) [1]. In 2011, the WHO released simplified guidelines for IPT and ICF, recommending that all people living with HIV should be regularly screened for tuberculosis using a clinical algorithm of any of cough, night sweats, weight loss and/or fever. Those without any of these symptoms and without further contraindications to IPT should be enrolled on IPT [2].

The Global Plan to Stop TB (2011-2015) has set a target of a 50% reduction in tuberculosis incidence in the South African gold mines. A high prevalence of tuberculosis in the South African gold mines has been reported, with increases in tuberculosis incidence [1]. Alternative approaches promoted by the World Health Organization (WHO) include antiretroviral therapy and its 3Is strategy for isoniazid preventive therapy (IPT), intensified case finding (ICF) and infection control [1]. IPT was provided to almost 450,000 newly enrolled into HIV care in 2011, up from 201,000 in 2010, yet still far lower than the total number newly enrolled in HIV care and potentially eligible for IPT (estimated at 1.5 million in 2010) [1]. In 2011, the WHO released simplified guidelines for IPT and ICF, recommending that all people living with HIV should be regularly screened for tuberculosis using a clinical algorithm of any of cough, night sweats, weight loss and/or fever. Those without any of these symptoms and without further contraindications to IPT should be enrolled on IPT [2]. The Global Plan to Stop TB (2011-2015) has set a target of a 50% reduction in tuberculosis incidence in the South African gold mines. A high prevalence of tuberculosis in the South African gold mines has been reported, with increases in tuberculosis incidence [1]. Alternative approaches promoted by the World Health Organization (WHO) include antiretroviral therapy and its 3Is strategy for isoniazid preventive therapy (IPT), intensified case finding (ICF) and infection control [1]. IPT was provided to almost 450,000 newly enrolled into HIV care in 2011, up from 201,000 in 2010, yet still far lower than the total number newly enrolled in HIV care and potentially eligible for IPT (estimated at 1.5 million in 2010) [1]. In 2011, the WHO released simplified guidelines for IPT and ICF, recommending that all people living with HIV should be regularly screened for tuberculosis using a clinical algorithm of any of cough, night sweats, weight loss and/or fever. Those without any of these symptoms and without further contraindications to IPT should be enrolled on IPT [2].
defined by the AIDS clinical trials group [8]; measured weight
21 units per week for women; note one unit is equivalent to
alcohol use (defined as exceeding 28 units per week for men or
hypersensitivity to isoniazid; chronic liver disease; excessive
neuropathy grade 2 (moderate) or greater; as
defined by the AIDS clinical trials group [8]; measured weight
less than 40 kg; a woman who was pregnant (by self-report or
urine test), or up to 3 months post-partum, or of child bearing
potential and declined to use contraception, or planned to
become pregnant over the next 12 months; receipt of an
investigational drug or product within the previous 30 days; or
contraindicated drugs (defined as any of: carbamazepine and
phenytoin; selective serotonin reuptake inhibitor antidepressants;
disulfiram; warfarin; theophylline; oral ketoconazole or
itraconazole).

Methods

Ethics Statement

"Thibela TB" was approved by the Research Ethics Committees of the University of KwaZulu Natal and the London School of Hygiene and Tropical Medicine. All consenting participants gave written consent or, for illiterate participants, witnessed oral consent. For illiterate participants, there was an impartial witness present during the consenting process, who then signed the relevant witness section of the consent form. Both ethics committees approved the consent form, including the section on the use of witnessed oral consent for illiterate participants, at the beginning of the study.

Setting: Thibela TB study

The Thibela TB study has been described in detail elsewhere [7]; briefly, all consenting workers in the eight intervention clusters were screened for tuberculosis and, if eligible, received nine months of IPT (300mg daily, self-administered, plus pyridoxine 25mg daily). All employees and contractors were invited to take part in the study, regardless of HIV or silicosis status and of previous history of tuberculosis or IPT. The three mining companies taking part in Thibela TB provide free tuberculosis and HIV care to all employees.

Intervention and screening for eligibility

The intervention was designed to be delivered by trained nurses with eligibility determined on clinical grounds as far as possible and laboratory tests only conducted for suspected tuberculosis and suspected hepatitis. Permanent ineligibility criteria (as summarised in Table 1) were: currently on tuberculosis treatment or IPT; known or suspected hypersensitivity to isoniazid; chronic liver disease; excessive alcohol use (defined as exceeding 28 units per week for men or 21 units per week for women; note one unit is equivalent to 10ml of pure alcohol); history of convulsions or psychosis; peripheral neuropathy grade 2 (moderate) or greater, as defined by the AIDS clinical trials group [8]; measured weight less than 40 kg; a woman who was pregnant (by self-report or urine test), or up to 3 months post-partum, or of child bearing potential and declined to use contraception, or planned to

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Thibela TB</th>
<th>World Health Organization 2011</th>
<th>South African Department of Health 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV status</td>
<td>No restriction</td>
<td>Evaluate for TB if any of: cough, fever, weight loss, night sweats, abnormality</td>
<td>Investigate for TB if any of: cough, fever, weight loss, night sweats, abnormality</td>
</tr>
<tr>
<td>TB screen</td>
<td>Investigate for TB if any of: cough &gt; two weeks, night sweats, weight loss, other compatible symptom, compatible chest X-ray radiograph can be done if available</td>
<td>Investigate for TB if any of: cough, fever, weight loss, night sweats, abnormality</td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>No restriction</td>
<td>No restriction</td>
<td>No restriction</td>
</tr>
<tr>
<td>Prior history of TB</td>
<td>No restriction</td>
<td>No restriction</td>
<td>No restriction</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Excluded if any of: pregnant, up to 3 months post-partum, of child bearing potential and declined to use contraception, or planned to become pregnant over the next 12 months</td>
<td>No restriction</td>
<td>No restriction</td>
</tr>
<tr>
<td>TST ¹</td>
<td>Not done</td>
<td>Unnecessary</td>
<td>Unnecessary ²</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Chronic liver disease or hepatitis suspect confirmed by liver function tests</td>
<td>Active hepatitis (acute or chronic)</td>
<td>Active liver disease</td>
</tr>
<tr>
<td>Alcohol</td>
<td>&gt;28 units per week for men, &gt;21 units per week for women</td>
<td>Regular and heavy alcohol consumption</td>
<td>“Actively abusing alcohol”</td>
</tr>
<tr>
<td>Other contra-indications</td>
<td>History of convulsions or psychosis; peripheral neuropathy grade 2 (moderate) or greater; weight &lt;40 kg; receipt of an investigational drug or product within the previous 30 days; or contraindicated drugs</td>
<td>Symptoms of peripheral neuropathy</td>
<td>None specified</td>
</tr>
</tbody>
</table>

1. TST = tuberculin skin test
2. The 2013 South African antiretroviral treatment guidelines state that IPT should be provided regardless of TST result, but contain revised guidance that a TST is now required before offering at least 36 months of IPT [18].

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Table 1. Eligibility criteria for isoniazid preventive therapy, contrasting those for the Thibela TB study to those of the guidelines from the World Health Organization in 2011 [2] and the South African Department of Health in 2010 [12].
Participants with no reasons for permanent ineligibility were classified as temporarily ineligible if: they were tuberculosis or hepatitis suspects (defined below); had a rash consistent with hypersensitivity, to ensure that those starting IPT were not unnecessarily stopped due to a pre-existing rash; or were women of child bearing potential that were required to have effective contraception prior to starting IPT. Participants who were temporarily ineligible were reassessed at a review visit and then reclassified as permanently ineligible or eligible to start IPT, depending on the results of tuberculosis or hepatitis investigations or whether they had started contraceptive use.

All screening was performed by trained study nurses and chest radiographs were read by experienced radiographers.

Definitions

The Thibela TB intervention was designed in 2004, predating the 2011 WHO guidelines on screening for tuberculosis prior to IPT [2], and so the development of the screening algorithm was based on our previous tuberculosis screening work in a gold mining population [5]. Hence, participants were defined as tuberculosis suspects if they had one or more of: cough for two weeks or longer, drenching night sweats, unintentional weight loss, another symptom that the study nurse thought could be due to tuberculosis or a chest radiographic abnormality suggestive of active tuberculosis. If the chest radiographic abnormality was suggestive of old tuberculosis, the study chest radiograph was compared with a previous one taken within the past two years (as part of the routine annual medical examination for fitness for work) and the participant was asked to return in one week. If the chest radiographic lesions were new or changing, or a previous chest radiograph could not be found, the participant was investigated as a tuberculosis suspect.

Tuberculosis suspects were investigated by collecting one spot sputum for fluorochrome microscopy and Mycobacterial Growth Indicator Tube (MGIT) culture. Positive cultures were confirmed for the presence of mycobacteria by examination of Ziehl-Neelsen stained slides for acid fast bacilli and for the presence of Mycobacterium tuberculosis using the anti MPB64 monoclonal antibody lateral flow assay (TAUNS, Numazu, Japan). Those who were smear or culture positive and those with unresolved symptoms at the follow up visit were referred to the routine mine health services for further investigations and were permanently ineligible for IPT in the study.

A hepatitis suspect was defined as a participant with any of the following: nausea or vomiting in the past week, at Division of AIDS grade 2 (moderate) or above [8]; right upper quadrant pain in the past week; urine darker than normal in past 48 hours; or jaundice (self-reported or on examination). Hepatitis suspects were then referred to the health service for liver function tests and reviewed four weeks later with the results. Participants were ineligible for IPT if at this review they reported any of: nausea or vomiting in the past 24 hours; right upper quadrant pain in the past week; urine darker than normal over past 48 hours; eyes had gone yellow recently (and the study nurse agreed this was the case); a medical doctor had told the participant they had a liver problem in the last four weeks; or elevated liver function tests (defined as any of: total bilirubin >5 times upper limit of normal [ULN]; alkaline phosphatase >10 x ULN; AST >2.5 times ULN; ALT >2.5 times ULN).

HIV testing was not part of the study. A proxy variable of “HIV care” combined those reporting being currently on antiretroviral therapy with those reporting previous IPT use (because targeted IPT was delivered by mine health services to HIV clinic attendees, with variable coverage, and rarely used otherwise). This variable will inevitably have underestimated those who genuinely had HIV; conversely, pilot work showed that the great majority of people who reported taking ART or IPT gave correct information. This variable thus had low sensitivity but high specificity for documented HIV infection. Current IPT use was an exclusion criterion for the Thibela TB study and so was not part of this variable.

Data collection and analysis

Data were directly entered into a proprietary database (InForm, Oracle, California), with appropriate range limits, validation checks and skip patterns. Data management and analysis used STATA v.11 (Stata Corporation, College Station, Texas). Enrolment to the intervention took place in two phases: during the first phase all employees and contractors working in the cluster were eligible for recruitment and were encouraged to attend the study centre during this time period; this was followed by a nine month phase to allow all individuals who had started IPT to complete their nine month course, during which time only new recruits to the workforce were eligible for enrolment (second phase). All those who consented to take part in Thibela TB during this first phase of recruitment were included in this analysis. All confidence intervals quoted were exact.

Results

Between July 2006 and May 2009, 27,126 individuals consented to take part in the Thibela TB study in the eight intervention clusters. Reflecting the general gold mining workforce, they were 94.7% male, median age 41 years (inter-quartile range: 32-47 years), median years of employment 16 years (inter-quartile range: 5-25 years), 98.1% were black, 59.5% were South African and 55.4% lived in hostels (Table 2). 12.2% reported previous tuberculosis, 0.6% reported ever taking IPT and 2.5% reported currently being on antiretroviral therapy.

At the enrolment visit, 1,249 of the 27,126 (4.6%) who consented were classified as permanently ineligible, 3,111 (11.5%) as temporarily ineligible and 22,766 (83.9%) were immediately eligible to start IPT. The most common reasons for being classified as permanently ineligible were: excessive alcohol consumption (427, 1.6%); being on tuberculosis treatment (241, 0.9%); contraindicated medications (226, 0.8%); history of convulsions (136, 0.5%); pregnancy, planning on becoming pregnant or unwillingness to use contraceptives while taking IPT (107, 0.4%); all other reasons were given by fewer than fifty participants, including those already on IPT (47, 0.2%). Participants with missing data (48, 0.2%) were considered as ineligible.
Table 2. Proportion ineligible for isoniazid preventive therapy in sub-groups (n=26,912).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Column %</th>
<th>N</th>
<th>Row % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>8,370</td>
<td>31.1%</td>
<td>594</td>
<td>7.1% (6.6%, 7.7%)</td>
</tr>
<tr>
<td>35-44</td>
<td>9,091</td>
<td>33.8%</td>
<td>826</td>
<td>9.1% (8.5%, 9.7%)</td>
</tr>
<tr>
<td>45-54</td>
<td>8,062</td>
<td>30.0%</td>
<td>998</td>
<td>12.4% (11.7%, 13.1%)</td>
</tr>
<tr>
<td>55+</td>
<td>1,389</td>
<td>5.2%</td>
<td>207</td>
<td>14.9% (13.1%, 16.9%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25,493</td>
<td>94.7%</td>
<td>2,409</td>
<td>9.4% (9.1%, 9.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>1,419</td>
<td>5.3%</td>
<td>216</td>
<td>15.2% (13.4%, 17.2%)</td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA</td>
<td>16,063</td>
<td>59.7%</td>
<td>1,605</td>
<td>10.0% (9.5%, 10.5%)</td>
</tr>
<tr>
<td>Lesotho</td>
<td>6,716</td>
<td>25.0%</td>
<td>745</td>
<td>11.1% (10.4%, 11.9%)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>2,953</td>
<td>11.0%</td>
<td>162</td>
<td>5.5% (4.7%, 6.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>1,180</td>
<td>4.4%</td>
<td>113</td>
<td>9.6% (8.0%, 11.4%)</td>
</tr>
<tr>
<td>Years in workforce</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>9,277</td>
<td>34.5%</td>
<td>710</td>
<td>7.7% (7.1%, 8.2%)</td>
</tr>
<tr>
<td>10-19</td>
<td>6,611</td>
<td>24.6%</td>
<td>551</td>
<td>8.3% (7.7%, 9.0%)</td>
</tr>
<tr>
<td>20-29</td>
<td>7,340</td>
<td>27.3%</td>
<td>812</td>
<td>11.1% (10.4%, 11.8%)</td>
</tr>
<tr>
<td>30+</td>
<td>3,684</td>
<td>13.7%</td>
<td>552</td>
<td>15.0% (13.8%, 16.2%)</td>
</tr>
<tr>
<td>Ethnic group</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>26,393</td>
<td>98.1%</td>
<td>2,565</td>
<td>9.7% (9.4%, 10.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>519</td>
<td>1.9%</td>
<td>60</td>
<td>11.6% (8.9%, 14.6%)</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hostel/family unit</td>
<td>14,841</td>
<td>55.1%</td>
<td>1,438</td>
<td>9.7% (9.2%, 10.2%)</td>
</tr>
<tr>
<td>Informal housing</td>
<td>1,930</td>
<td>7.2%</td>
<td>203</td>
<td>10.5% (9.2%, 12.0%)</td>
</tr>
<tr>
<td>Single quarters/other</td>
<td>652</td>
<td>2.4%</td>
<td>55</td>
<td>8.4% (6.4%, 10.8%)</td>
</tr>
<tr>
<td>House</td>
<td>9,489</td>
<td>35.3%</td>
<td>929</td>
<td>9.8% (9.2%, 10.4%)</td>
</tr>
<tr>
<td>Hx of tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>23,625</td>
<td>87.8%</td>
<td>1,914</td>
<td>8.1% (7.8%, 8.5%)</td>
</tr>
<tr>
<td>Yes</td>
<td>3,287</td>
<td>12.2%</td>
<td>711</td>
<td>21.6% (20.2%, 23.1%)</td>
</tr>
<tr>
<td>HIV care *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26,122</td>
<td>97.1%</td>
<td>2,458</td>
<td>9.4% (9.1%, 9.8%)</td>
</tr>
<tr>
<td>Yes</td>
<td>790</td>
<td>2.9%</td>
<td>167</td>
<td>21.1% (18.3%, 24.2%)</td>
</tr>
<tr>
<td>Weight (kg) **</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td>4,964</td>
<td>18.4%</td>
<td>713</td>
<td>14.4% (13.4%, 15.4%)</td>
</tr>
<tr>
<td>61-80</td>
<td>16,201</td>
<td>60.2%</td>
<td>1,489</td>
<td>9.2% (8.8%, 9.6%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>5,747</td>
<td>21.4%</td>
<td>423</td>
<td>7.4% (6.7%, 8.1%)</td>
</tr>
<tr>
<td>Alcohol use (units/week) ***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15,427</td>
<td>57.3%</td>
<td>1,295</td>
<td>8.4% (8.0%, 8.8%)</td>
</tr>
<tr>
<td>1-28</td>
<td>11,061</td>
<td>41.1%</td>
<td>906</td>
<td>8.2% (7.7%, 8.7%)</td>
</tr>
<tr>
<td>29+</td>
<td>424</td>
<td>1.6%</td>
<td>424</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

CI = confidence interval

* "HIV care" is a proxy for having ever taken IPT or currently being on ART

** Weight less than or equal to 40kg was an exclusion criteria, but none of the participants in this table were excluded on this basis.

***, for women grouping is 0, 1-21, 22+. Excessive alcohol use, defined as 29+ units/week for men and 22+ units/week for women, was an exclusion criterion; hence, no confidence interval was given for the proportion.

Note: 214 participants had missing data on at least one of these variables and so were excluded from this analysis; they were more likely to be ineligible than those with no missing data (33.2% versus 9.8% respectively, p<0.001).

doi: 10.1371/journal.pone.0081378.t002
used a two-stage screening process [15]. The first stage
studied-specific and 144 (13.2%) for non-study specific criteria
months isoniazid and ethambutol screened 1,095 HIV-infected
Another randomised trial comparing six months IPT to 36
excluded a further 776 (26%), most commonly due to chest
radiographs compatible with tuberculosis (296 of 776 [36%]).
randomised trial comparing six months versus 36 months of
screening for IPT among HIV-infected adults [14-17]. A
randomised trial comparing six months versus 36 months of
applied the exclusion criteria from the Botswana National IPT
programme to 4,018 consenting participants; this excluded
27% of those screened, predominantly due to illness, recent
history of tuberculosis and prior IPT (66%, 9% and 8%
respectively). The second stage applied study specific
exclusion criteria to the remaining 2,934 participants; this
excluded a further 776 (26%), most commonly due to chest
radiographs compatible with tuberculosis (296 of 776 [36%]).
Another randomised trial comparing six months IPT to 36
months isoniazid and ethambutol screened 1,095 HIV-infected
persons in India, of whom 268 (24.5%) were excluded for
study-specific and 144 (13.2%) for non-study specific criteria
(29 culture positive, 115 other unspecified criteria) [16]. A
randomised trial of four preventive regimens screened 1,528
tuberculin-positive, HIV-infected adults in South Africa, of
whom 324 were ineligible (21.2%), including 141 (9.2% of
1528) who would be ineligible under current guidelines (90
active tuberculosis, 39 chest radiograph compatible with
tuberculosis, 4 on tuberculosis treatment and 8 other) [17]. A
retrospective evaluation of intensified tuberculosis case finding
and IPT among newly diagnosed HIV infected adults in a
Voluntary Counselling and Testing clinic in Uganda found 5%
had active tuberculosis and a further 37% were excluded from
IPT, predominantly because of distance from the clinic, stage 4
HIV disease and previous history of tuberculosis (45%, 30%
and 27% respectively) [14]. Under the wider eligibility criteria
of “Thibela TB”, many of those excluded in these other studies
would have been eligible for IPT, either immediately or
following further tuberculosis investigations. In addition,
populations with relatively high proportions of people with later
stage HIV disease, where it is more difficult to exclude active
tuberculosis, are likely to have a higher proportion ineligible. As
HIV testing is scaled up and individuals are enrolled into care
at earlier stages of HIV disease, the proportion eligible for IPT
may increase as the prevalence of symptoms and undiagnosed
tuberculosis will be lower.

The generalisability of these results to other settings were
IPT is being rolled out at scale may be thought to be limited, as
the study investigated community-wide rather than the more
common approach of targeted IPT, and was conducted in the
mining industry with a predominance of men and possibly a
“healthy worker effect”. However, although this strategy of
community-wide IPT, which was conducted irrespective of HIV
status, is more likely to find healthy, asymptomatic people than
targeting HIV infected persons, the scale up of HIV testing is
likely to result in increasing proportions of healthy,
asymptomatic people entering HIV care. A “healthy worker
effect” may result in a population with less severe HIV disease
among those who are HIV infected than among those HIV
infected in the general population, but this is likely to be true of
other settings where community-wide IPT could be
implemented, for example, similar workforces and the military.
Although women were not well represented in this study, the
results presented here show that the vast majority of women
were eligible for IPT, which is generalisable. In addition, the
main reasons for increased ineligibility among women in this
study were the study-specific exclusion criteria of pregnancy or
risk of pregnancy. However the 2011 WHO guidelines have
made it make clear that these should not be reasons for
excluding IPT in a routine setting (Table 1 [2]) and so, eligibility
may be higher among women than reported here. Most studies
conducted in health care settings have a predominance of
women, so one advantage of this study is the large amount of
data provided for men.

Conclusions

This community-wide, nurse-delivered intervention found that
the vast majority of individuals assessed were eligible for IPT.
As HIV testing is scaled up, particularly community-based
testing, and more people with early HIV disease are identified,
a high proportion will be eligible for IPT, supporting immediate
scale up of HIV testing and IPT.

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Author Contributions

Conceived and designed the experiments: J JL KLF ADG GJC.
Performed the experiments: J JL KLF ADG VNC FP ML DM LC
GJC. Analyzed the data: J JL. Wrote the manuscript: J JL KLF
ADG VNC FP ML DM LC GJC.
References