Tuberculosis control in a South African community with high HIV prevalence: the role of intensified case-finding and antiretroviral therapy

by

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Declaration

I, Katharina Kranzer, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I acknowledge the following assistance in specific parts of the thesis. Dr. Richard White modelled average CD4 count improvements in individuals receiving ART for the time-updated CD4 count analysis. In the work analysing the association between ART coverage and TB risk, Dr. Leigh Johnson modelled ART coverage in the community using data from the ART cohort and CD4 prevalence survey.

Abstract

This thesis investigates active TB case finding and antiretroviral therapy for tuberculosis control in a setting with high HIV prevalence in Cape Town, South Africa. Many countries in sub-Saharan Africa have seen a worsening tuberculosis epidemic since the 1990s. Rising tuberculosis incidence rates have largely been attributed to high HIV prevalence in this region. Conventional tuberculosis control efforts focus on passive case finding and high cure rates in smear-positive patients, achieved through short course chemotherapy. These control strategies are insufficient in controlling the tuberculosis epidemic where HIV prevalence is high. Additional control strategies have been proposed, including active tuberculosis case finding, isoniazid preventive therapy for HIV infected individuals, infection control and antiretroviral therapy.

The feasibility, uptake, yield, treatment outcomes and costs of population-based active tuberculosis case finding are investigated in the first part of the thesis. The second part determines losses along the HIV care pathway, community antiretroviral coverage and the association between coverage and tuberculosis risk.

The main finding is that population-based active tuberculosis case finding linked to a mobile HIV testing service had a high uptake and yield. Treatment outcomes in patients diagnosed through active case finding were as good as outcomes in patients diagnosed through passive case finding in primary care clinics in Cape Town. Costs were USD 1,177 per TB case diagnosed and USD 2,458 per

successfully treated TB case, in an incremental costing analysis adopting a health service provider perspective.

Analysis of the HIV care pathway in a peri-urban impoverished settlement in the greater area of Cape Town highlighted substantial losses along the pathway between HIV diagnosis and antiretroviral therapy. These results illustrate the operational challenges in achieving high treatment coverage. Antiretroviral coverage in this community increased from 18% in 2004 to 84% in 2009. Increasing antiretroviral coverage was associated with decreasing tuberculosis risk among patients receiving antiretroviral therapy, even controlled for time-updated CD4 count, suggesting an effect on transmission, not just on individual risk reduction.

The impact of active tuberculosis case finding and antiretroviral therapy on tuberculosis incidence on a population level was beyond the scope of this thesis. Large scale cluster randomized controlled trials are needed to investigate the effect of these strategies on tuberculosis control. In the meantime researchers conducting active tuberculosis case finding studies should be encouraged to collect data on treatment outcomes and costs. In addition further interventions are needed to increase retention and linkage to care in individuals prior to initiating antiretroviral therapy.

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List of acronyms

AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
AUC	Area under the curve
CD4	CD4+ lymphocyte
CI	Confidence interval
DOTS	Directly observed short course
HR	Hazard ratio
IQR	Inter-quartile range
NHLS	National Health Laboratory Services
NIH	National Institutes of Health
NNS	Number needed to screen
PITC	Provider-initiated HIV testing and counselling
PMTCT	Prevention of mother-to-child transmission
PY	Person-years
TB	Tuberculosis
TI	Treatment interruption
UNAIDS	United Nations Joint Programme on HIV/AIDS
WHO	World Health Organisation

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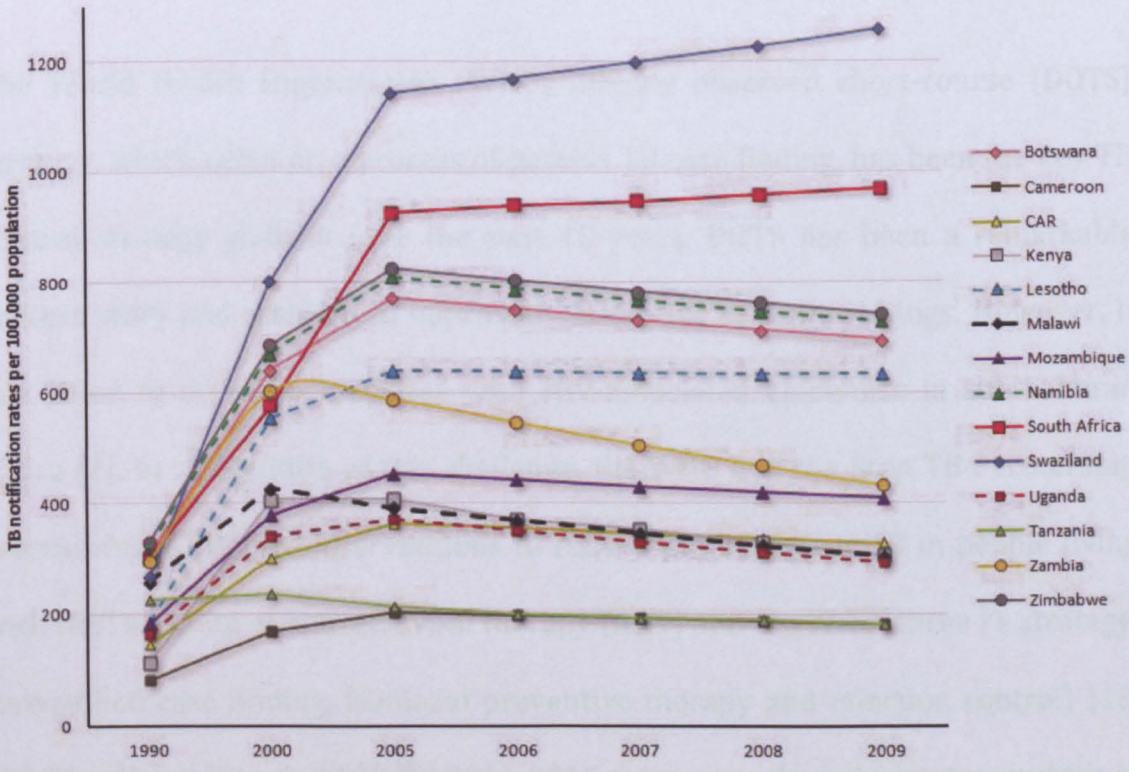
1 Introduction

1.2 Background

Estimated tuberculosis (TB) incidence in countries in sub-Saharan Africa increased from 171 per 100,000 population in 1990 to 345 per 100,000 population in 2009. Increases in TB incidence have been most pronounced in countries with high HIV prevalence where TB notification rates have increased 2- to 5-fold since 1990 (Figure 1.1) [1, 2]. HIV is thought to be the key driver of the TB epidemic in those countries. While TB notification rates are still increasing in some African countries with high HIV prevalence such as South Africa and Swaziland, they have started to decline in other countries like Malawi, Zambia and Uganda.

Figure 1.1: TB notification rates in sub-Saharan African countries with high HIV prevalence (>5%) from 1990-2009



Data source: Global Tuberculosis Control (2010) Geneva, Switzerland: World Health Organization.

South Africa ranks 4th among the 22 highest TB burden countries in the world and has the worst HIV and TB epidemics in the world with a national HIV prevalence of 18.1% and a TB incidence of 970 per 100,000 population in 2009 [1, 2]. TB notification rates have risen 3-fold over the last 30 years and yearly TB mortality rates have increased by 2.8 times from 1996 to 2006 [1, 2]. Historically the Western Cape Province always had the highest TB notification rates in South Africa and has only recently been overtaken by KwaZulu Natal Province [1, 3]. TB notification rates in Cape Town varied between 399 per 100,000 population in Mitchell's Plain and 1122 per 100,000 population in Khaylitsha in 2003 [4]. Sub-district variations are mainly due to variations in HIV prevalence and levels of deprivations [5-8]. TB notification rates as high as 2,000 per 100,000 population have been reported in one of Cape Town's peri-urban townships where adult HIV prevalence was 23% in 2010 [9-11].

The World Health Organization (WHO) directly observed short-course (DOTS) strategy, which relies on a process of passive TB case finding, has been the key TB control strategy globally over the past 15 years. DOTS has been a remarkable success story and resulted in improved TB control in many settings. However, it has failed to do so in countries with HIV-associated epidemics in sub-Saharan Africa [2]. In recognition of this challenge, the WHO and the Stop TB Partnership recommend additional interventions to reduce the burden of TB in people living with HIV: scale-up of antiretroviral therapy (ART) and the WHO 'three I's strategy' (intensified case finding, isoniazid preventive therapy and infection control) [12, 13]. The Global Plan to STOP TB 2011-2015 recognizes these four interventions in

addition to the DOTS strategy as key interventions to prevent HIV-associated TB [14].

The implementation of the three I's has seen limited success. The estimated percentage of HIV positive people who were screened for TB increased from 0.6% in 2005 to only 5.2% in 2009 [15]. A total of 60,509 HIV positive individuals in Africa received 6 months of isoniazid preventive therapy in 2009, which was less than 1% of the population living with HIV on the African continent at that time [15]. A meta-analysis of placebo-controlled trials showed that isoniazid preventive therapy in HIV-infected patients conferred an overall risk reduction of 33% [16]. However, benefit was only observed among patients who tested tuberculin skin test (TST) positive. A major programmatic obstacle to implementation has been the necessity to rule out active TB and to assess TST status before initiating isoniazid preventive therapy [17-19]. Thus even though policy recommendations for the use of isoniazid preventive therapy have been made years ago, national rollout has only been attempted in Botswana [18]. Isoniazid preventive therapy for HIV-infected individuals is not the standard of care in governmental health care clinics and therefore few HIV infected individuals benefit from this intervention. In contrast roll-out of ART has been much more successful, with almost 4 million people having initiated ART by the end of 2009 [15]. However, due to low HIV test uptake and losses along the pathway between HIV testing and ART treatment [20], ART coverage was estimated to be only 40% in sub-Saharan Africa in 2009 [15, 21, 22].

ART and isoniazid preventive therapy have been shown to reduce TB risk substantially in HIV infected individuals [16, 23, 24]. Studies from South Africa, Brazil and Botswana suggest a synergistic effect of the sequential or concurrent use of ART and isoniazid preventive therapy [24-27]. The benefit of intensified TB case finding and infection control seems intuitive, but so far no study has shown an effect on morbidity, mortality or transmission of *Mycobacterium tuberculosis* in HIV infected individuals.

Ideally one would hope that these additional control measures have an effect beyond the individual effect. While reduction of TB associated morbidity and mortality in HIV infected individuals is a worthwhile endeavour, TB control ultimately aims to reduce *Mycobacterium tuberculosis* transmission in the population. As such the three I's strategy targeting HIV infected individuals only, with ART accessible only to HIV infected individuals with advanced stage HIV disease might have limited impact even when implemented at scale [18, 28]. Therefore, community-based strategies including HIV negative individuals, higher ART coverage and ART initiation at earlier stage of HIV disease need to be explored to tackle the HIV/TB epidemic.

1.2 Active (intensified) tuberculosis case finding

Population-based surveys in sub-Saharan Africa have found a prevalence of 0.7-1.6% of previously undiagnosed culture-positive TB and 0.2-0.8% of previously undiagnosed smear-positive TB [22, 29-37]. Delays in TB diagnosis are multi-factorial and due to (i) patients not seeking health care, (ii) health care staff failing to identify the patient as a TB suspect and (iii) delays in receiving results of

diagnostic tests [38]. Community-based active TB case finding tries to address these delays by providing easily accessible services. A recent community-based TB case finding trial from Zimbabwe provided valuable evidence that active TB case finding can have a positive impact on TB control in a community with high HIV prevalence [39].

The first part of this thesis concentrates on active TB case finding in high HIV prevalence settings. This includes a literature review and the results of a study investigating the feasibility, acceptability, yield and cost of community-based active TB case finding linked to a mobile HIV testing service in communities with high HIV prevalence.

1.3 Antiretroviral therapy for tuberculosis control

Mathematical modelling suggests that ART, as currently implemented, may have limited impact on TB control on a population level [40]. However observational data from South Africa and Malawi showed decreasing TB notification rates following the scale-up of ART [9, 41]. These studies have several limitations. Uncontrolled before-and-after comparisons are vulnerable to coincidental time trends such as increased migration and changes in reporting systems. The South African study chose 2005 as the baseline comparison year - the year with the highest TB notification rates. ART was rolled-out in 2004 in the study community. If 2004 was used as the baseline comparison year, the study might not have found any effect of ART on TB notifications. None of the studies controlled for confounders. In addition precise population denominators are difficult to determine especially in settings with high migration rates.

More recently a strategy known as "test and treat" has been proposed to reduce HIV transmission. This strategy is characterized by very high coverage of HIV testing and immediate initiation of ART regardless of the stage of HIV progression [42]. Mathematical models predict a major reduction in TB if this strategy was to be successfully implemented [43]. Losses along the HIV care pathway are recognised as a substantial operational hurdle in achieving high ART coverage under the current guidelines [20] and are likely to remain a challenge if "test and treat" strategies are implemented.

The second part of this thesis investigates the losses along the different steps in the HIV care pathway, describes ART coverage in a community and investigates the association between ART coverage and TB risk in an ART cohort.

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Part I: Active TB case finding

2 Study question part I

This thesis aimed to examine strategies of active TB case finding as outlined in the WHO 3Is policy by conducting a systematic review. The key outcomes of the systematic review were yield of screening in specific target groups, screening strategies, treatment outcomes and cost-effectiveness.

The thesis further aimed to investigate population based mobile TB case finding in Cape Town South African. This was addressed in three studies. The first study was a pilote study of active TB case finding in lay health care workers using a mobile team. The second study compared sputum quality using a human powered nebuliser to an electronic nebuliser. The third study investigated the feasibility, uptake, yield, treatment outcomes and cost-effectiveness of a community-based active TB case finding program linked to a mobile HIV testing service in Cape Town, South Africa. All studies were conducted in under-serviced communities in the greater area of Cape Town (Figure 2.1).

Figure 2.1: Map of Cape Town indicating the main areas in which the mobile services operated.

1. **Athlone**: testing at a shopping mall/market, the roadside, a social housing project
2. **Cape Town city bowel**: testing at a college, service for homeless, service for commercial sex workers, two companies, two road sides
3. **Delft**: testing at two squatter camps, two clinics, two social housing projects, the road side
4. **Durbanville**: testing at two taxi ranks
5. **Grassy Park**: testing at the road side
6. **Guguletu**: testing at two shopping malls/markets, a clinic
7. **Hout Bay**: testing at a school, in a township, at the harbour
8. **Khayelitsha**: testing at a shopping centre/market, a school, in the township, at the station
9. **Macassar**: testing at the road side
10. **Kraaifontain**: testing at a clinic
11. **Langa**: testing at a shopping mall/market, the road side
12. **Masiphumelele**: testing in the township, at a shopping mall. *(See figure 7.1 for detailed view)*
13. **Milnerton**: testing at a company
14. **Mitchells Plain**: testing at the road side, a social housing project
15. **Belhar**: testing at a squatter camp
16. **Nyanga**: testing at a taxi rank, at a shopping centre
17. **Ocean View**: testing at a clinic, in the township
18. **Parkwood**: testing at two road sides
19. **Phillippi**: testing at two farms, three road sides
20. **Retreat**: testing at a clinic
21. **Wynberg**: testing at the road side
22. **Claremont**: testing at the road side
23. **Grabouw**: testing in the township, at the clinic, at the road side

3 Literature review: active TB case finding

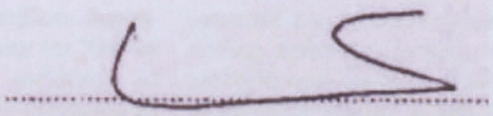
Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis

1. For a 'research paper' already published
   1.1. Where was the work published? ***The Lancet Infectious Diseases***
   1.2. When was the work published? ***2010***
   1.3. Was the work subject to academic peer review? ***Yes***
   1.4. Have you retained the copyright for the work? ***Yes***
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published?
   2.2. List the paper's authors in the intended authorship order
   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press

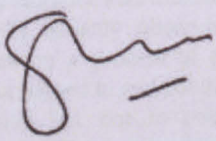
3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, developed the search strategy, conducted the search and screening of abstracts and titles, performed the data extraction and analysis and wrote the publication.



Candidate's signature

Super Supervisor or senior author's signature to confirm role as stated in (3)



Dr. Stephen D. Lawn
Supervisor and Co-Author

Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis

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Intensified case finding is the regular screening for evidence of tuberculosis in people infected with HIV, at high risk of HIV, or living in congregate settings. We systematically reviewed studies of intensified case finding published between January, 1994, and April, 2009. In 78 eligible studies, the number of people with tuberculosis detected during intensified case finding varied substantially between countries and target groups of patients. Median prevalence of newly diagnosed tuberculosis was 0·7% in population-based surveys, 2·2% in contact-tracing studies, 2·3% in mines, 2·3% in programmes preventing mother-to-child transmission of HIV, 2·5% in prisons, 8·2% in medical and antiretroviral treatment clinics, and 8·5% in voluntary counselling and testing services. Metaregression analysis of studies that included only people with HIV showed that for each increment in national prevalence of tuberculosis of 100 cases per 100 000 population, intensified case finding identified an additional one case per 100 screened individuals (p=0·03). Microbiological sputum examination of all individuals without prior selection by symptom screening yielded an additional four cases per 100 individuals screened (p=0·05). Data on the use of serial screening, treatment outcomes in actively identified cases of tuberculosis, and cost-effectiveness, however, were lacking. Concerted action is needed to develop intensified case finding as an important method for control of tuberculosis.

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Introduction

The sixth Millennium Development Goal target of halving the 1990 prevalence of tuberculosis and death rates by 2015 will not be achieved if present trends continue.[1] Any shortfall from this target worldwide will be associated with a failure to achieve these targets in sub-Saharan Africa where HIV has seriously undermined the control of tuberculosis. Worldwide there are more than 1·3 million cases of HIV-associated tuberculosis each year, resulting in almost half a million deaths; sub-Saharan Africa is estimated to account for 79% of this disease burden.[2] Although the incidence of HIV-associated tuberculosis worldwide is estimated to have peaked in 2006,[2] more progress is needed in reducing prevalence and mortality.

The WHO directly observed short-course strategy, which relies on a process of passive tuberculosis case finding, has helped to control tuberculosis in many parts of the world but not in countries with generalised epidemics of HIV (prevalence of HIV greater than 1% in the general population).[2,3] In recognition of this failure, WHO and the Stop TB Partnership developed an interim policy on collaborative tuberculosis and HIV activities[4] that included additional interventions to reduce the burden of tuberculosis in people living with HIV. Within this policy the four core prevention strategies for tuberculosis were intensified case finding, isoniazid preventive therapy, tuberculosis infection control, and scale-up of antiretroviral therapy.[5,6]

Despite clear policy guidelines, antiretroviral therapy is the only one of the four core strategies that has been used at a large scale.[6] Use of isoniazid preventive therapy is still limited and provided for only 0·1% of individuals infected with HIV.[2] Data on the use of tuberculosis infection control are scarce. Intensified case finding among patients attending HIV care services reached just 2·2% of the 33 million people estimated to be living with HIV in 2007.[2] To address the substantial gap in the scale-up of these interventions, WHO launched the 3Is policy initiative in 2008, which is a three-pronged strategy of intensified case finding, isoniazid preventive therapy, and tuberculosis infection control to be used with the scale-up of antiretroviral therapy.[7]

Several terms have been used for the screening of patients for active tuberculosis. The terms intensive case finding, active case finding, and enhanced case finding are often used interchangeably and all refer to strategies to identify and treat people with tuberculosis who have not sought diagnostic services on their own initiative. However, whereas intensified case finding and active case finding require face-to-face contact and on-site screening, enhanced case finding works primarily through making populations aware of the symptoms of tuberculosis and encouraging self-presentation to medical services.[8] In the 3Is policy, intensified case finding is defined as "the regular screening of all people with HIV or at high risk of HIV or in congregate settings (such as mines, prisons, military barracks) for symptoms and signs of TB followed promptly with diagnosis and treatment", and this is the definition we have used in this Review.[7] The policy also recommends screening of household contacts of people with tuberculosis.[7]

Intensified case finding is the central intervention of the 3Is strategy, because its aim is to identify patients as either having active tuberculosis (and in need of treatment) or free of the disease (and warranting preventive therapy), although in practice the status of some patients will be unclear and these patients need prospective evaluation. Intensified case finding is also the key means by which the prevalence of untreated

See Online for webappendix

disease can be reduced within clinical services, congregate settings, and in the community, thereby reducing the transmission of tuberculosis. In view of this new policy initiative, there is a great need for data that inform development of strategies of intensified case finding.

Whereas the specific investigations (eg, sputum microscopy, sputum culture, chest radiography) used in screening for tuberculosis might have an important affect on the yield of new cases of tuberculosis identified,[9] overall investigational strategy and target group are also very important. For example, establishing that a patient has the symptoms of tuberculosis has traditionally been central to screening strategies, and yet recent studies[9–13] have shown that a proportion of patients with HIV-associated tuberculosis have asymptomatic disease or very minor symptoms. As a result, the yield of intensified case finding in some groups might be higher if all individuals are investigated without preselection.

The identification of groups for which intensified case finding should be prioritised is a further issue. The yield of cases of tuberculosis is likely to be highly variable, depending on a range of factors that include the local prevalence of tuberculosis, the function of local tuberculosis control services, the prevalence of HIV in the target group, and the degree of associated immunodeficiency. In turn, the prevalence of tuberculosis detected established the number needed to screen (NNS) to identify one new case of undiagnosed active tuberculosis. Other important factors affecting decisions on implementing intensified case finding include the feasibility and cost of the screening, the laboratory capacity, and treatment outcomes in newly detected cases. Treatment outcomes are particularly important because adherence might be lower in patients identified in active screening without preselection than in those detected passively, potentially limiting the effect of intensified case finding on the control of tuberculosis.

The purpose of this systematic review is to examine strategies of intensified case finding as outlined in the WHO 3Is policy.[7] Key outcomes of interest in reviewed published work include the prevalence of tuberculosis in specifically targeted groups, the associated NNS, the screening strategy used, cost-effectiveness, and treatment outcomes of newly detected cases.

Methods

Search strategy and selection criteria

The searches and review process were done according to a prespecified protocol. We aimed to identify studies using intensified case finding in resource-limited settings. Both cross-sectional and cohort studies published in all languages were eligible for inclusion. We searched available systematic and narrative reviews for active case finding and household-contact investigations. Two systematic reviews were identified.[8,14] Additionally, we searched Medline, EmBase, and Global Health for reports published through April, 2009, and African Health Line up to March, 2009. Search strategies are presented in the webappendix. The search strategy for African Health Line included "tuberculosis", "active or intensified or enhanced case finding", "prisons or prisoners", "mines or miners", "homosexuals", "voluntary counselling", and "testing or VCT". Abstract books covering the years 1998–2008 of the World Conference on Lung Health published by the International Union Against Tuberculosis and Lung Disease were hand searched. Reference lists of primary studies, reviews, and editorials identified by the above methods were hand searched. Experts in the specialty were contacted for additional publications.

According to the WHO 3Is policy, regular screening for tuberculosis is recommended in groups at high risk of infection with HIV, individuals infected with HIV, groups living in congregate settings, and in contacts of people with tuberculosis. The strategy to be used in contact tracing is not explicitly described in the policy, and so for the purposes of this Review we focused on contact tracing studies in populations where the prevalence of HIV was at least 5% among notified cases of tuberculosis. We also defined groups at high risk for infection with HIV as prisoners, commercial sex workers, injecting drug users, men who have sex with men, and individuals attending voluntary counselling and testing centres and sexually transmitted disease clinics. Even though the 3Is policy does not recommend mass screening on a population level, it is arguable that general populations in sub-Saharan Africa constitute groups at high risk for HIV. Thus, surveys of the prevalence of tuberculosis in populations with a prevalence of HIV of greater than 5% were included in this Review.

Our Review was limited to studies published from 1993 (when WHO declared tuberculosis to be a worldwide emergency) to 2009.[15] We only included studies in low-income and middle-income countries, as defined by the World Bank in 2008,[16] and studies that screened a minimum of 100 people. We excluded editorials, case studies, case reports, studies screening only children younger than 15 years, and studies with unclear screening strategies or denominators. However, we included contact-tracing studies that screened both adults and children.

The initial database created from the electronic searches was compiled, duplicate citations were eliminated, and citations were screened by title and abstract to capture potentially relevant studies. The full text of these studies was obtained and reviewed according to inclusion and exclusion criteria. Screening of full text from citations found to be potentially relevant was done by two reviewers (KK and SDL). Queries on study design and study quality were discussed with another reviewer (JRG), and studies were only included if there was consensus.

Data extraction and analysis

Where data from a single study were present in multiple publications, these data were compiled. The data

extraction form was adapted from the STROBE statement checklist.[17] Variables recorded included title, objective, year of study, year of publication, study design, setting, eligibility criteria of participants, sources and methods of selection of participants, screening strategy, diagnostic criteria for tuberculosis, internal and external quality checks, efforts to reduce bias, numbers of individuals at each stage of the study, number of cases of tuberculosis, prevalence of tuberculosis, and funding source. One reviewer (KK) extracted data from all eligible studies. A second reviewer (SDL) independently extracted data from 20 of the included studies. The ratings given by the two reviewers were in complete agreement.

Primary outcome of interest was the yield of intensified case finding as defined by the prevalence of newly microbiologically confirmed or clinically or radiologically diagnosed cases of tuberculosis in the target population and the NNS to find one new case of tuberculosis. The NNS was calculated as the reciprocal of the prevalence of newly diagnosed tuberculosis. Secondary outcomes of interest were the screening strategy used, treatment outcomes, and cost per case found.

All analyses were done in Stata 10. We report medians and ranges; weighted medians were used to compare yield of screening for tuberculosis in individuals infected with HIV by use of different screening strategies. We used inverse-variance-weighted metaregression to investigate the association between yield of intensified case finding and country prevalence of tuberculosis, prevalence of HIV in the general population, screening strategies, availability of culture, and HIV status of the study population.[18,19] Country prevalence estimates for tuberculosis and HIV were obtained from the WHO Global Health Atlas.[20] We analysed residuals to check model assumptions.

Results

83 publications (69 published papers and 14 abstracts) published between January, 1994, and April, 2009, were eligible for inclusion (figure 1). After compiling multiple publications of the same study a total of 78 studies were included. Most studies (55) were published in the past 6 years, with the largest numbers of publications being in 2008 (12) and 2007 (13).

Of those studies included, 30 were from congregate settings, ten from voluntary counselling and testing settings, three from programmes preventing mother-to-child transmission (PMTCT), 16 from antiretroviral therapy and medical clinics, ten contact tracing studies, eight population-based surveys of the prevalence of tuberculosis, and one study among men who have sex with men and injecting drug users. Most studies were from sub-Saharan Africa (41); others were from the Americas (22) and Asia (19).

The proportion of eligible individuals who agreed to participate in these studies was variable, ranging from 40–100% in prisons, 44–100% in voluntary counselling and testing and PMTCT settings, 35–100% in clinic-based settings, 83–100% in contact tracing studies, and 66–100% in population-based surveys (webappendix). Clear external and internal quality-control procedures for microbiological and radiological investigations were only recorded in three studies in congregate settings, two studies in clinic-based settings, one study in household contacts, and four population-based surveys.

The prevalence of newly diagnosed tuberculosis varied greatly between different countries and specific target populations (table 1). The minimum was 0·01% in a contact-tracing study from Peru and the maximum was 24·7% in an antiretroviral therapy clinic in South Africa. Median NNS varied greatly, ranging from 148 in population-based prevalence surveys to just 12 in voluntary counselling and testing services and in antiretroviral therapy and medical clinics (table 1).

Results of studies of intensified case finding in prisons, psychiatric hospitals, mines, and refugee camps are presented in the webappendix. HIV status was established in three of 30 studies and screening strategies varied substantially, with most using an initial questionnaire on the symptoms of tuberculosis followed by diagnostic testing of people suspected to have tuberculosis. Three of six studies in miners combined the screening of symptoms with chest radiology to define those people suspected of having tuberculosis, whereas the other three studies used sputum microbiology irrespective of symptoms.

The median NNS in all prisons was 40 (range 14–833), but was lower in studies in prisons in sub-Saharan Africa

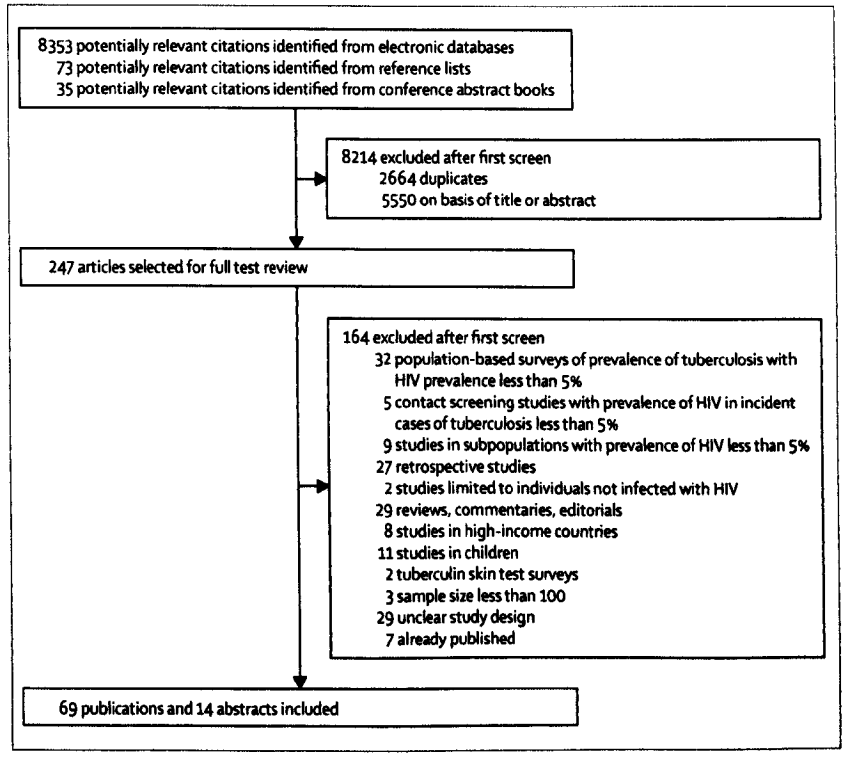

Figure 1: Study selection process

	Number of studies	Regions represented	Median prevalence of newly diagnosed tuberculosis (range)	Median number needed to screen (range)
Congregate settings (all)[21-50]	30	Africa, Asia, the Americas	2·2% (0·1-7·2)	45 (14-833)
Congregate settings (prisons)[21-41]	21	Africa, Asia, the Americas	2·5% (0·1-7·2)	40 (14-833)
Congregate settings (prisons)[27-33]	7	Sub-Saharan Africa	3·6% (1·8-7·2)	28 (14-55)
Congregate settings (mines)[43-48]	6	Africa, Asia	2·3% (1·2-5·0)	43 (20-86)
Voluntary counselling and testing services[51-61]	10	Africa, Asia, the Americas	8·5% (0·8-23·6)	12 (4-123)
Prevention of mother-to-child transmission services[62-64]	3	Africa, Asia	2·3% (2·1-3·5)	44 (29-47)
Antiretroviral therapy and medical clinics[9,10,65-81]	16	Africa, Asia, the Americas	8·2% (1·4-24·7)	12 (4-71)
Antiretroviral therapy and medical clinics[9,10,70-77]	8	Sub-Saharan Africa	8·6% (3·6-24·7)	12 (4-28)
Contact tracing[82-91]	10	Africa, Asia, the Americas	2·2% (0·01-14·5)	45 (7-10 000)
Population-based surveys[11,92-99]	8	Sub-Saharan Africa	0·7% (0·02-3·5)	148 (29-5000)

Table 1: **Tuberculosis prevalence and the number needed to screen to identify one new case in different target groups**

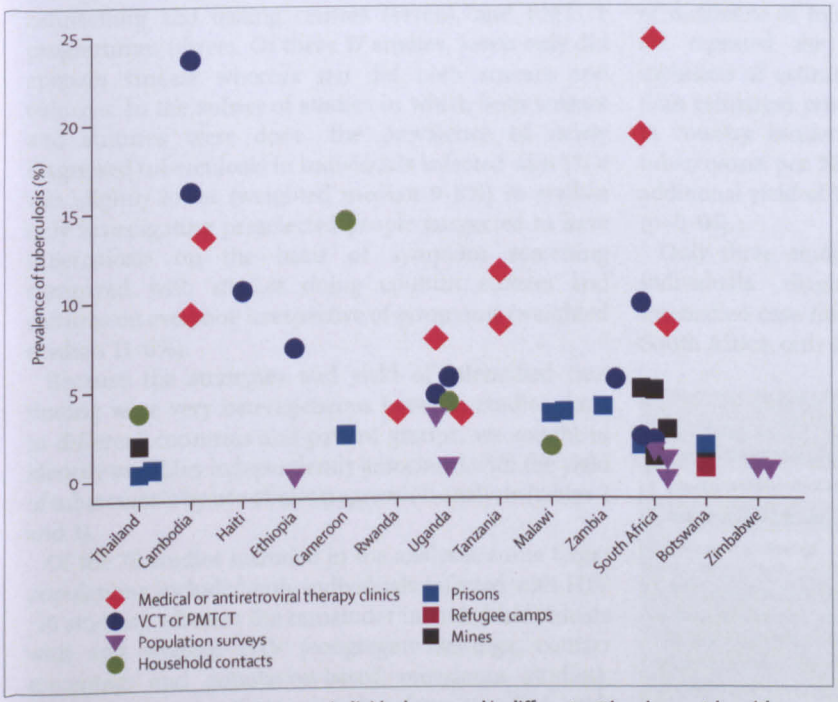

Figure 2: **Prevalence of tuberculosis among individuals screened in different settings in countries with generalised epidemics of HIV**
VCT=voluntary counselling and testing. PMTCT=prevention of mother-to-child transmission.

(median 28, range 14–55; table 1). The prevalence of HIV was established in only one study in a Brazilian prison (25%).[41]

Studies in miners and ex-miners found a median NNS of 43 (range 20–86; table 1). In one study enrolling only miners infected with HIV, the prevalence of newly diagnosed tuberculosis was 4·9%.[46] Of the remaining five studies only one study tested miners for HIV, and reported a prevalence of 27%.[47]

Most studies in voluntary counselling and testing clinics, PMTCT programmes, and in groups at high risk of infection with HIV (men who have sex with men and injecting drug users)[100] identified people suspected of having tuberculosis by screening their symptoms before using diagnostic tests (webappendix). Sputum microscopy was the only microbiological test available in half of the studies. The median NNS was 12 (range 4–123) in voluntary counselling and testing settings and 44 (range 29–47) in PMTCT settings (table 1).

Intensified case finding was done as part of isoniazid preventive therapy programmes or before antiretroviral therapy was started, in individuals infected with HIV accessing health care or enrolled in home-based care services. Half of the studies used questionnaires on the symptoms of tuberculosis as the first step before microbiological investigations for symptomatic individuals (webappendix). Median NNS was 12 (range 4–71; table 1).

Results from contact-tracing studies (webappendix) are not directly comparable with results from other settings since most studies included children. Microbiological examinations were only done in individuals that were symptomatic or in individuals with positive tuberculin skin tests. Median NNS was 48 (range 7–10 000; table 1).

Five of eight population-based surveys of the prevalence of tuberculosis in settings with high prevalence of HIV used a step-wise screening approach with screening for the symptom of tuberculosis preceding microbiological examination. The remaining three studies examined the sputum in all individuals irrespective of symptoms (webappendix). Median NNS was 148 (range 29–5000; table 1).

Figure 2 summarises data from 47 studies in countries with generalised epidemics of HIV. More than half the studies (27) reported a prevalence of newly diagnosed tuberculosis in the screened population of greater than 3% (NNS less than 33). Excluding population surveys, two-thirds (26 of 39) of the studies reported prevalence of newly diagnosed tuberculosis of greater than 3%.

The screening strategies varied widely across the studies. Symptom screening was used in all but one of the prison studies, screening of mine workers invariably included chest radiography, and all contact-screening studies used symptom screening and assessment of responses to the tuberculin skin test. Symptom questionnaires were diverse, ranging from any kind of

respiratory symptoms to various durations of productive cough plus or minus weight loss, night sweats, fatigue, fever, and haemoptysis. Similarly, the number and timing of sputum samples varied substantially.

In 12 studies that included only individuals infected with HIV, sputum examination was done irrespective of symptoms. Nine of these studies were done in antiretroviral therapy services, medical clinics, or home-based HIV care programmes and the remaining three were done in voluntary counselling and testing centres. All but one of these studies did both smears and cultures. 17 studies screened individuals infected with HIV with symptom-based questionnaires preceding sputum examination of people suspected to have tuberculosis. These studies were done in antiretroviral therapy and medical clinics (seven studies), voluntary counselling and testing centres (seven), and PMTCT programmes (three). Of these 17 studies, seven only did sputum smears whereas ten did both smears and cultures. In the subset of studies in which both smears and cultures were done, the prevalence of newly diagnosed tuberculosis in individuals infected with HIV was slightly lower (weighted median 9·8%) in studies only investigating preselected people suspected to have tuberculosis on the basis of symptom screening compared with studies doing sputum smears and cultures on everyone irrespective of symptoms (weighted median 11·6%).

Because the strategies and yield of intensified case finding were very heterogeneous between studies done in different countries and patient groups, we sought to identify variables independently associated with the yield of tuberculosis by use of metaregression analysis (tables 2 and 3).

Of the 78 studies included in the analysis, some target populations included only individuals infected with HIV (30 studies), whereas the remainder included individuals with and without HIV (congregate settings, contact screening, and population-based prevalence studies). Metaregression analysis was therefore stratified with regards to HIV status of the screened population.

In the univariate analysis of studies with patients with mixed or unknown HIV-status (48 studies), national prevalence of tuberculosis and HIV, screening strategy of microbiological investigations in all individuals, and availability of culture were not associated with yield of screening (table 2).

By contrast, univariate analysis of studies that only included individuals infected with HIV (30 studies) found that both the use of symptom prescreening and the country prevalence of tuberculosis were associated with the detected yield of tuberculosis (table 3). However, the availability of culture and the national prevalence of HIV were not associated with the detected yield of tuberculosis. Multivariate analysis showed that microbiological sputum examination (smear or culture) on all individuals without prior selection on the basis of screening for symptoms detected an additional four cases per 100 individuals screened (p=0·05). Furthermore, an increment in country prevalence of tuberculosis of 100 cases of tuberculosis per 100 000 population was associated with an additional yield of one case per 100 individuals screened (p=0·03).

Restricting the analysis to studies in individuals infected with HIV routinely doing both sputum smears and cultures as part of the microbiological investigations (22 studies) showed similar results with regards to effect estimate for symptom screening (slope 3·6, 95% CI −0·9 to 8·0).

Estimates of national prevalence of tuberculosis are infrequently on the basis of prevalence survey data, they are instead derived from estimates of the incidence of tuberculosis. In view of this and that national estimates of incidence of tuberculosis are more readily available, we repeated the metaregression analysis with the inclusion of estimated incidence of tuberculosis rather than estimated prevalence. In this model, an increment in country incidence of tuberculosis of 100 cases of tuberculosis per 100 000 people was associated with an additional yield of 0·7 case per 100 individuals screened (p=0·04).

Only three studies reported treatment outcomes of individuals diagnosed with tuberculosis during intensified case finding. In a population-based study in South Africa, only 13 (56%) of 23 people actively detected

	Slope (95% CI)	p value
Country prevalence of tuberculosis*	−0·2 (−0·5 to 0·1)	0·21
Country prevalence of HIV†	−4·8 (−12·8 to 3·3)	0·24
Availability of culture‡	−0·3 (−1·6 to 1·1)	0·65
Symptom screening§	−0·3 (−2·4 to 1·8)	0·77

*One unit increase=100 cases of tuberculosis per 100 000 people. †One unit increase=10% increase in prevalence. ‡Coded as 0 if no culture available or 1 if culture available. §Coded as 0 if symptom screening used to identify people suspected to have tuberculosis or 1 if all individuals screened with sputum smears or culture.

Table 2: **Univariate analysis of factors potentially affecting yield of intensified case screening in populations with mixed or unknown HIV status**

	Slope (95% CI) in univariate analysis	p value in univariate analysis	Slope (95% CI) in multivariate analysis	p value in multivariate analysis
Country prevalence of tuberculosis*	1·1 (0·2 to 2·0)	0·02	1 (0·1 to 1·9)	0·03
Country prevalence of HIV†	1·3 (−17·5 to 43·1)	0·4	..	..
Availability of culture‡	2·0 (−2·7 to 6·7)	0·39	..	..
Symptom screening§	4·3 (0·34 to 8·2)	0·03	3·7 (0·05 to 7·4)	0·05

*One unit increase=100 cases of tuberculosis per 100 000 people. †One unit increase=10% increase in prevalence. ‡Coded as 0 if no culture available or 1 if culture available. §Coded as 0 if symptom screening used to identify people suspected to have tuberculosis or 1 if all individuals screened with sputum smears or culture.

Table 3: **Factors potentially affecting yield of intensified case screening in populations with individuals infected with HIV**

with tuberculosis completed treatment.[97] Among 24 women infected with HIV in India diagnosed with tuberculosis after giving birth, 21 started treatment for tuberculosis and 17 (70%) were either cured or still receiving treatment at time of analysis.[62] In the Côte d'Ivoire, of 134 prisoners diagnosed with tuberculosis, 99 (74%) were cured, 32 (24%) died, and in three (2%) treatment failed.[28] None of these studies had data for treatment outcome available for those diagnosed passively.

None of the studies included in this systematic review did costing or cost-effectiveness analyses.

Discussion

Intensified case finding is a key component of the WHO 3Is policy that aims to strengthen the public health response to the epidemic of HIV-associated tuberculosis—a major stumbling block to attainment of the sixth Millennium Development Goal targets for worldwide control of tuberculosis. In this systematic review, we included 78 studies from 27 different countries, most from sub-Saharan Africa. The yield of screening for tuberculosis varied greatly between countries and target populations, with the highest yields in antiretroviral therapy and voluntary counselling and testing clinics, and the lowest yields in population-based surveys of the prevalence of tuberculosis. Our analysis showed that the yield of intensified case finding depends strongly on the prevalence of HIV of the target population, the national prevalence of tuberculosis, and the screening strategy. In studies only screening individuals infected with HIV, each increment in national prevalence of tuberculosis of 100 cases per 100 000 people resulted in an additional yield of one case per 100 individuals screened. Furthermore, substantially higher yields can be achieved if all individuals have sputum examination irrespective of symptoms. These data will help inform implementation of intensified case finding policies.

Using a process of passive case finding, the directly observed short-course strategy has failed to control rising incidence rates of HIV-associated tuberculosis in resource-limited settings,[101] and many patients dying with HIV/AIDS have tuberculosis that has not been diagnosed.[102] Intensified case finding aims to increase case-detection rates and shorten the time to diagnosis of tuberculosis, thereby reducing morbidity and mortality and shortening the period of infectiousness, and it should, in turn, reduce the risk of transmitting tuberculosis in community and health-care settings.[103–105] However, intensified case finding is more resource-intensive than passive case finding and a number of key issues must be considered. These issues include the populations to be targeted, the NNS to identify each new case, the screening strategy, laboratory capacity, operational feasibility, outcomes of newly identified cases of tuberculosis, and costs.

Prevalence of newly diagnosed tuberculosis and subsequently the NNS varied widely between different target populations with a median of 148 (range 29–5000) in population-based surveys, 45 (7–10 000) in contact tracing studies, 43 (20–86) in mines, 40 (14–833) in prisons, 12 (4–123) in voluntary counselling and testing, 44 (29–47) in PMTCT settings, and 12 (4–71) in antiretroviral therapy or medical clinics.

The upper limit for the NNS at which intensified case finding is deemed useful might differ between target populations. For example, the importance of identification of tuberculosis among prisoners is high because of the high probability of transmission to other prisoners, and among pregnant women it is high in view of the probability of transmission to unborn children.[107,108] Intensified case finding might also be prioritised in settings with known high prevalence of drug-resistant tuberculosis, such as prisons.

Guidelines originating from the era before HIV assume that state programmes for tuberculosis in resource-limited settings should screen an average of ten people suspected to be infected to identify one smear-positive case to prevent laboratory overload.[109] Laboratory equipment and consumables for tuberculosis are allocated on this basis. More recent experience has shown that in practice an average of seven people newly suspected of having tuberculosis are screened to identify one sputum smear-positive case of tuberculosis, although this number varies widely (3·3–20).[110] Irrespective of the specific target populations, we found that intensified case finding will need more resources. Scale-up will only be possible if laboratory capacity increases in parallel and quality assurance procedures are adequate.

The effectiveness of intensified case finding depends on the screening strategy used. In studies of groups of patients infected with HIV, intensified case finding with microbiological (sputum smear or culture) investigation in all patients irrespective of symptoms detected an additional four cases per 100 individuals screened. This finding is consistent with the observation that a substantial proportion of individuals infected with HIV have subclinical tuberculosis when screened actively.[10–13,96]

The WHO 3Is strategy recommends repeated intensified case finding in individuals infected with HIV. However, no empirical data exist on the use of this type of serial screening, especially in a population of people infected with HIV. Serial screening with mass radiography in Czechoslovakia in 1961–72 showed a decrease in prevalence of newly diagnosed tuberculosis from 36 cases per 100 000 people to 18 cases per 100 000 people.[111] Thus, a similar effect might happen with serial intensified case finding in individuals infected with HIV, although the yield in groups of patients infected with HIV is also likely to vary in parallel with changes to the degree of immunodeficiency. Studies establishing the yield obtained during serial screening, the optimum screening interval, and the implications for laboratory capacity are needed.

The diagnosis of tuberculosis by active screening is typically less advanced than the diagnosis of disease

during passive case finding.[105,112,113] Patients with less advanced disease might, in turn, have lower numbers of adherence to treatment, potentially resulting in poorer treatment outcomes among those whose disease is detected by intensified case finding. However, data on treatment outcomes are scarce. A study from South Africa found that the rates of treatment for tuberculosis were low (73%) among actively detected cases.[112] Similar results were reported from population-based prevalence surveys from India and Nepal showing higher treatment refusal and default rates in actively compared with passively detected cases of tuberculosis.[114,115] Therefore, intensified case finding must be accompanied with effective means of ensuring that newly identified cases of tuberculosis are effectively treated.

Our metaregression analysis found that each increment in national prevalence of tuberculosis of 100 cases per 100 000 people was associated with an additional yield of about one case per 100 screened individuals infected with HIV. These data provide some basis for estimating the potential benefits of intensified case finding in different countries. Although none of the studies presented in this Review investigated cost-effectiveness, modelling suggests that population-based intensified case finding symptom screening every 7 years would be highly cost-effective in sub-Saharan Africa, averting 29 million cases of tuberculosis and 13 million deaths by 2050.[116] One study from South Africa estimated a cost of US$12 for each person screened for tuberculosis in the community health centre and $7 per person in the primary health-care clinic. The cost per case of tuberculosis prevented was estimated to be $323–366, assuming that 25 cases of tuberculosis would be prevented for every 100 cases of tuberculosis detected by intensified case finding.[117] However, more country-specific and setting-specific data on costs are needed to inform policy makers.

Our systematic review has several strengths. Publication bias was limited by the use of a prespecified comprehensive search strategy and review process that included published and unpublished studies without language restrictions. Reproducibility of data extraction was verified for a subset of studies. Heterogeneity of study results was investigated using metaregression analysis. This Review, which is primarily descriptive, also has limitations. Assessment of ascertainment bias at study level was limited because of the lack of reporting of internal and external quality-control procedures. Furthermore, variable uptake in the proportions of eligible individuals who agreed to participate in these studies might have influenced reported prevalence of tuberculosis. Regression analyses could be subject to residual confounding.

Conclusion

In countries with high prevalence of tuberculosis, intensified case finding among individuals infected with HIV identifies a high yield of people with tuberculosis and the yield is significantly increased if all such individuals are screened microbiologically without preselection on the basis of the screening of symptoms. The data presented might help the prioritisation of specific groups for intensified case finding. Scaling-up of intensified case finding will need development of standardised screening algorithms, substantial increases in the capacities of quality-assured laboratories, and efficient systems to ensure that people newly diagnosed with tuberculosis receive adequate treatment. Concerted action in tandem with further research might help develop this policy as an important method to accelerate progress towards the tuberculosis targets within the sixth Millennium Development Goal.

Search strategy and selection criteria

These are described in detail in the Methods section

Contributors

KK did the searches of published work and data extraction with input from SDL and JRG. The meta-regression analysis was done by KK with input from RMGJH and JRG. KK and SDL wrote the paper with input from RMGJH, JRG, LGB, and RW.

Conflicts of interest

We declare that we have no conflicts of interest.

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4 Pilot study: active TB case finding in community health workers

Community health care workers in South Africa are at increased risk for tuberculosis

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Community health care workers in South Africa are at increased risk for tuberculosis

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To the Editor: High rates of tuberculosis (TB) and human immunodeficiency virus (HIV) in sub-Saharan Africa pose a serious threat to health care systems and health care workers (HCWs). Studies in South Africa[1] and Ethiopia[2] have indicated that HCWs have an increased risk of TB disease compared with the general population. The risk for TB disease is even higher among HCWs co-infected with HIV. Studies from South Africa found an HIV prevalence among HCWs of 15.7% in 4 provinces in 2002[3] and of 11.5% in 2 hospitals in Gauteng in 2005.[4]

Many sub-Saharan African countries face a severe shortage of qualified HCWs as a result of the dual HIV/TB epidemic, which has triggered task shifting to a range of lay community health care workers (CHWs) – for example, home-based care workers, lay counsellors and adherence supporters, for both TB and highly active antiretroviral therapy (HAART). CHWs may experience a considerable occupational TB risk; however, their risk of TB disease and HIV prevalence has never been documented.

The TB/HIV Care Association is a non-governmental organisation that employs CHWs to provide adherence support to both TB patients and patients taking HAART. The Desmond Tutu HIV Foundation partnered with the TB/HIV Care Association to provide HIV and TB testing to their CHWs, and subsequently determined the prevalence of diagnosed and undiagnosed TB and HIV among them.

Methods

Between October 2008 and February 2009, our mobile HIV testing unit (the TUTU tester) provided HIV testing, CD4 counts and TB screening to TB and antiretroviral adherence supporters employed by the TB/HIV Care Association in Cape Town on 8 days in 8 venues. All CHWs were asked about any previous HIV testing, history of TB treatment, hypertension, diabetes, and their most recent Pap smear. Verbal consent for HIV testing was obtained. HIV testing was performed according to the Western Cape guidelines. All CHWs were offered post-test counselling. Individuals who tested HIV-positive were offered a CD4 count test. Individuals who needed treatment or follow-up were referred to clinics.

Individuals who were HIV-positive and those with symptoms of TB were offered to undergo sputum induction. Smears and cultures were performed on 47 out of 62 sputum samples, and the remaining 15 sputum samples were only examined for acid-fast bacteria (AFBs) with light and fluorescence microscopy.

Results

A total of 215 female CHWs were offered HIV and TB testing; the most common age group was 40 - 49 years old (N=72, 33%); 58 (27%) had never had a previous HIV test, and only 57 (27%) had had an HIV test within the last 12 months (Table I). Older CHWs were significantly more likely to have never tested before (p<0.01).

A total of 42 CHWs (20%) were HIV-positive, 11 were newly diagnosed, and 31 already knew their status. Among the 31 known HIV-positive CHWs, 17 were on HAART, and 11 were not yet eligible for HAART. Of 26 CHWs who knew their most recent CD4 count, 6 had a CD4 count <350 cells/μl. Eight of those who were newly diagnosed as HIV-positive had had a CD4 count at the time of diagnosis, and 5 (63%) had a CD4 count <350 cells/μl. HIV prevalence (23%) and prevalence of newly diagnosed HIV (9%) was highest among the 30 - 39-year-old age group.

Sputum induction was offered to 80 CHWs; 38 were HIV-positive, and 42 reported TB symptoms. A total of 62 sputum samples were obtained – 29 from HIV-positive individuals and 33 from HIV-negative symptomatic individuals. Twelve CHWs were unable to produce sputum, and 6 refused sputum induction.

The overall TB prevalence was 5% (10/215); 6 (3%) were on TB treatment at the time of the study; 4 (2%) were newly diagnosed with TB, one was smear- and culture-positive, and 3 were smear-negative and culture-positive. Two of the newly diagnosed TB cases were HIV-negative and symptomatic, 1 was known HIV-positive and not yet on HAART, and 1 was on HAART.

Discussion

This is the first report of HIV and TB prevalence among CHWs in South Africa. The observed HIV prevalence of 20% is higher

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Table I. HIV testing experience, HIV prevalence and TB prevalence in lay community health care workers stratified by age

	Age in years				
	<30 *N* (%)	30 - 39 *N* (%)	40 - 49 *N* (%)	≥50 *N* (%)	Total *N* (%)
Previous HIV testing experience					
Never tested	6 (18)	5 (9)	16 (23)	31 (58)	58 (27)
Last test <3 months ago	5 (15)	5 (9)	4 (6)	4 (8)	18 (9)
Last test 3 - 6 months ago	2 (6)	1 (2)	3 (4)	0 (0)	6 (3)
Last test 6 - 12 months ago	6 (18)	12 (22)	12 (17)	3 (6)	33 (16)
Last test >12 months ago	6 (18)	19 (35)	28 (40)	12 (23)	65 (31)
Previously tested positive	8 (24)	13 (24)	7 (10)	3 (6)	31 (15)
HIV result					
Negative	23 (68)	36 (65)	61 (85)	48 (89)	168 (78)
Newly diagnosed positive	2 (6)	5 (9)	2 (3)	2 (4)	11(5)
Known positive	8 (24)	13 (24)	7 (10)	3 (6)	31 (14)
Refused	1 (3)	1 (2)	2 (3)	1 (2)	5 (2)
On TB treatment					
Yes	1 (3)	4 (7)	1 (1)	0 (0)	6 (3)
No	33 (97)	51 (93)	71 (99)	54 (100)	209 (97)
TB diagnosed on screening					
Yes	0 (0)	2 (4)	1 (1)	1 (2)	4 (2)
No	33 (100)	49 (96)	70 (99)	53 (98)	205 (98)

than the HIV prevalence of 17.9% among antenatal women in the Western Cape Metropolitan area in 2008.[5]

Only 27% of CHWs had an HIV test within the last 12 months; more importantly, 27% had never had an HIV test. A total of 11 new HIV diagnoses were established. At least half of the newly diagnosed HIV-infected CHWs would be eligible for HAART according to the WHO ART guidelines and the proposed new South African guidelines for implementation in the near future.

Only 5 CHWs did not consent to HIV testing, suggesting that HIV testing uptake is improved when access is facilitated. An obstacle to access may be concerns with confidentiality, and CHWs may not feel comfortable about testing in the health care facilities where they work.

TB prevalence among CHWs was 5%, with 4 out of 10 TB cases (40%) only identified through active case finding. A recent population-based prevalence survey in a township near Cape Town found a TB prevalence of 3% with a similar proportion of undiagnosed TB (48%).[6] However, the population-based survey included men and women, with men having a higher risk of TB disease, whereas the CHWs screened in this study were all women; this finding suggests that CHWs are at higher risk of TB disease than the communities they live in.

Limitations of this report include relatively small sample size and that the sample was not representative of all CHWs working in Cape Town. TB screening included only one induced sputum sample per person, and some of the sputum samples were not cultured.

We conclude that CHWs are at high risk for HIV and TB. HIV testing should be actively facilitated, CHWs should be screened regularly for TB, and more emphasis should be placed on effective infection control measures.

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5 Feasibility study: Sputum induction using a human powered nebuliser

Quality of induced sputum using a human-powered nebuliser in a mobile human immunodeficiency virus testing service in South Africa

1. For a 'research paper' already published
   1.1. Where was the work published? ***International Union Against Tuberculosis and Lung Disease***
   1.2. When was the work published? ***2011***
   1.3. Was the work subject to academic peer review? ***Yes***
   1.4. Have you retained the copyright for the work? ***Yes***
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   2.1. Where is the work intended to be published?
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   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate wrote the protocol, obtained the ethical approval, collected data, did the analysis and wrote the publication.

Candidate's signature .....

Super Supervisor or senior author's signature to confirm role as stated in (3)

Dr. Linda-Gail Bekker
Co-supervisor and Co-Author

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Quality of induced sputum using a human-powered nebuliser in a mobile human immunodeficiency virus testing service in South Africa

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SUMMARY

OBJECTIVES: To investigate the quality of induced sputum samples using a human-powered (HPN) and an electric-powered nebuliser (EPN).

METHODS: For each participant two sputum samples were induced using the HPN and the EPN. The sequence of the two nebulisers was allocated at random. The proportion of good quality sputum according to different assessment criteria was compared using an exact McNemar test. The difference in time to expectoration was compared using the Wilcoxon matched-pairs signed-rank test.

RESULTS: A total of 123 individuals were eligible for the study. Nine individuals refused to participate and five were unable to produce a sputum sample. The proportion of good quality sputum was higher among sputum samples induced by the HPN compared to those obtained using the EPN. The median time to produce a sputum sample was 2.2 min (IQR 1.13–4.1) for the HPN and 2.5 min (IQR 1.4–4.1) for the EPN.

CONCLUSION: The HPN induced good quality sputum within 3 min. The device operates without electricity and is suitable not only for remote clinics with unreliable electricity, but also for mobile services and community-based intensified tuberculosis (TB) case finding. Further research needs to investigate the yield of TB in sputum samples induced by the HPN.

KEY WORDS: tuberculosis; induced sputum; diagnosis; South Africa; resource-limited

POOR DIAGNOSIS remains a major obstacle to global tuberculosis (TB) control. An estimated 9.4 million new cases of TB were reported in 2008, and 1.8 million estimated deaths occur every year.[1] TB diagnosis is often based on microscopy of stained sputum smears.[2] Current World Health Organization (WHO) guidelines recommend a two-specimen case-finding strategy and same-day diagnosis by microscopy.[3,4] However, a substantial number of these cases occur among human immunodeficiency virus (HIV) positive individuals, including children, in resource-limited settings. Confirming TB infection in this population is particularly challenging due to paucibacillary presentations and difficulties in obtaining appropriate specimens.[5–7] HIV-infected individuals often present with few symptoms[7–9] and have difficulty expectorating spontaneously. Spontaneous sputum expectoration is difficult to achieve in children, and culture confirmation thus relies on sequential gastric lavages.[5]

For adults and children who are unable to expectorate sputum spontaneously, sputum induction is one way to obtain good quality sputum, and it has been shown to be as sensitive as bronchoalveolar lavage and gastric washing for detection of pulmonary TB in both adults and children.[10–13] A hypertonic saline solution is administered via a mouthpiece or mask using an ultrasonic nebuliser. The procedure is non-invasive and requires little staff training.[14]

However, sputum induction remains largely underutilised as a means of obtaining sputum samples for TB diagnosis, especially in highly under-resourced settings where access to consistent supplies of electrical power can be a challenge. Battery operated nebulisers exist, but recharging batteries typically requires electric power, and the costs of obtaining new batteries are considerable. Human-powered or solar-powered devices might be more suitable for under-resourced settings.

This study aimed to compare the quality of induced sputum samples using a human-powered (HPN) and an electric-powered nebuliser (EPN).

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METHODS

Study setting

This study was conducted as part of an evaluation of an intensified TB case-finding strategy linked to a mobile voluntary counselling and testing (VCT) service. The mobile VCT service is nurse-run, counsellor supported and operates in underserviced peri-urban areas in greater Cape Town.[15] All adults testing HIV-positive or with symptoms suggestive of TB were referred for sputum induction.

Study design

All clients referred for sputum induction as part of the intensified TB case-finding study between June and July 2010 were asked for their consent to participate in the study. Two induced sputum samples using the HPN and EPN were performed. The sequence of the two nebulisers was allocated using Stata version 11 (StataCorp, College Station, TX, USA) to randomly sample one of the two nebulisers as the first device to be used. The procedure was repeated 130 times, and patients started with either the HPN or the EPN per their allocation. Sputum induction was performed in an open-roofed tent using 15–20 ml sterile 3% hypertonic saline solution. The patient breathed through the nebuliser mouthpiece until a satisfactory sample was produced or he/she wished to abandon the procedure. The procedure was performed without nose clips.

Human-powered nebuliser

The HPN is a pneumatic piston pump system connected to a modified stationary bicycle frame (Figure 1). The output of the piston (Bimba, University Park, IL, USA) goes through one-way valves (US Plastics, Lima, OH, USA) and a flow regulator (Gates LLC, Houston, TX, USA) to achieve the necessary air flow rate of 8 l/min to make a jet nebuliser and mouthpiece (Hudson Micro Mist, Hudson RCI, Research Triangle Park, NC, USA; mass mean aerodynamic diameter 3.6 μm, nebulisation rate 0.25–0.3 ml/min) work properly. The one-way valves and flow regulator ensure that the HPN operates at 8 l/min or not at all. The HPN takes about 60 pedal cycles/min to operate; the effort of pedalling the HPN is equivalent to riding a bicycle at approximately 13 km/h. In bench top experiments, the output of the HPN was compared to the Pulmo-aide compressor (DeVilbiss, Somerset, PA, USA), which has a flow rate of ≥8 l/min using the same nebuliser. The time of nebulisation of 5 ml liquid was not different between the two (P = 0.41). In this study, assistants to the nurse in charge of TB testing pedalled the HPN. Tubing was long enough so that the assistants could either be in a separate tent or in the open away from the tent where the subject was seated.

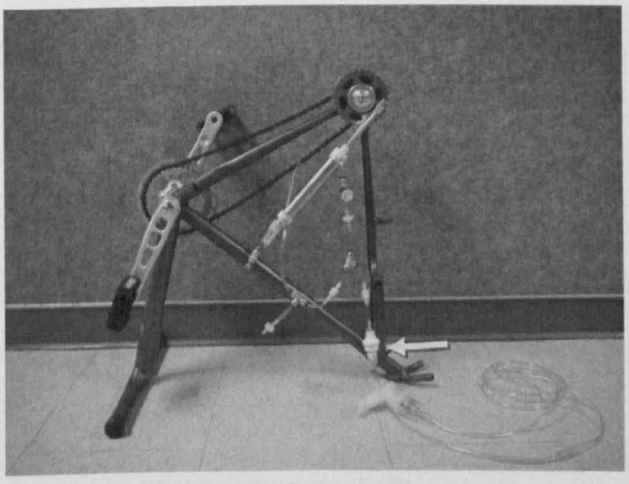

Figure 1 The HPN. One end of the piston is affixed to the frame and the other is connected to a rotating disk affixed to the rear gear system. There are two outputs of the piston and the tubing is set up with one-way valves so that air flows out of the HPN on both the upstroke and downstroke of the piston. The flow regulator is marked by an arrow. HPN = human powered nebuliser.

Electric powered nebuliser

An ultrasonic Flo-Eolo nebuliser (CA-MI, Pilastro, Italy) was used for electric sputum induction as a comparison.

Microscopy and culture of mycobacteria

Sputum samples were analysed within accredited laboratories using standardised protocols and quality control procedures. Following decontamination with *N*-acetyl-*L*-cysteine sodium hydroxide, centrifuged sputum deposits were examined for acid-fast bacilli (AFB) using auramine O fluorescent stain and cultured using mycobacterial growth indicator tubes (MGIT, BD, Sparks, MD, USA). Cultures positive for AFB were identified as *Mycobacterium tuberculosis* complex by inhibition of growth by *p*-nitrobenzoic acid or by the polymerase chain reaction.

Microscopic sputum quality assessment

Gram stains were performed on each sputum specimen and examined by laboratory technicians. The slides were evaluated for quality under low power (310). Salivary contamination was detected by noting the presence of squamous epithelial cells (SEC), and purulence was determined by noting the presence of polymorphonuclear cells (PMN). Sputum samples were considered of good quality according to the following assessment criteria: >0 PMN per low-power field (LPF; criteria from McCarter and Robinson[16]), >25 PMN/LPF (Van Scoy[17]), <25 SEC/LPF (Geckler et al.[18]), <10 SEC/LPF (Murray and Washington[19]) or PMN > SECs (Barlett[20]).

Statistical methods

All analyses were conducted using Stata version 11 (StataCorp, College Station, TX, USA). The proportion

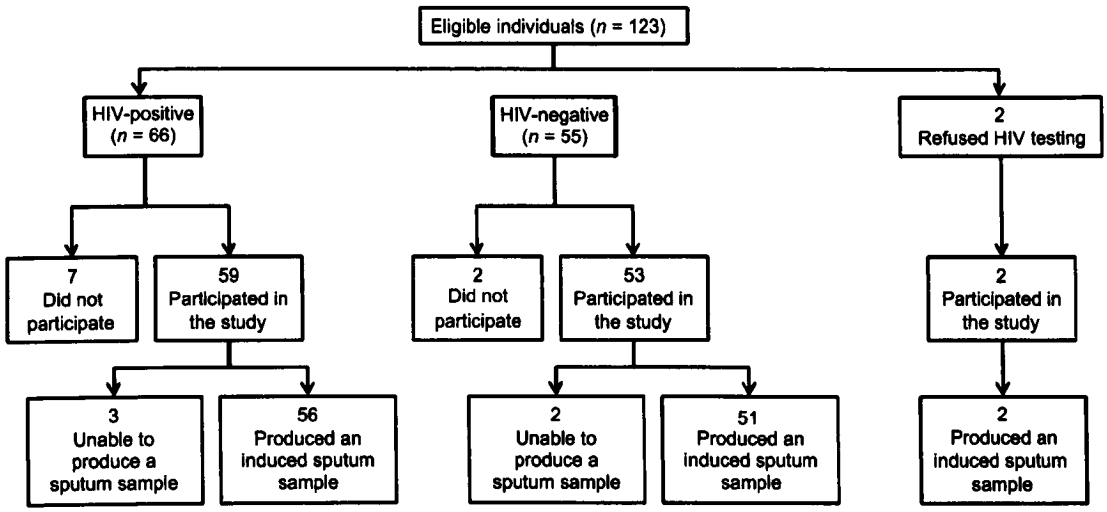

Figure 2 Flow diagram of eligible participants who were able to produce sputum samples. HIV = human immunodeficiency virus.

of good quality sputum according to the different assessment criteria between the two nebulisers was assessed using an exact McNemar test; the difference in time to expectoration was compared using the Wilcoxon matched-pairs signed-rank test.

Ethical approval

The study was approved by the University of Cape Town Ethics Committee and the Institutional Review Board of Marquette University. Written informed consent was obtained from all patients at enrolment.

RESULTS

Study population

A total of 123 individuals were eligible for the study, of whom 66 (53.7%) were HIV-positive, 55 (44.7%) were HIV-negative and two (1.6%) refused HIV testing. Median age was 39.0 years (interquartile range [IQR] 29.1–49.0) and 63 (51.2%) were women. Nine (7.3%) individuals refused to participate in the study: seven HIV-infected individuals and two HIV-negative TB suspects. Five individuals (4.4%) were unable to produce a sputum sample (Figure 2).

Sputum quality and time to induction

Sputum quality was assessed in 109 paired sputum samples. Overall, the proportions of good quality sputum according to the different assessment criteria were higher among sputum samples induced by the HPN compared to those induced using the EPN (Table 1). According to McCarter and Robinson's criteria,[16] 83.5% of HPN and 74.3% of EPN-induced sputum samples were of good quality, whereas only 26.6% of HPN and 22.9% of EPN-induced sputum samples were assessed as good quality using Van Scoy's criteria.[17] The proportion of good quality sputum samples according to Barlett's criteria[20] was significantly higher in sputum samples induced by HPN compared to EPN.

The median time to produce a sputum sample was 2.2 min (IQR 1.13–4.1) for HPN and 2.5 min (IQR 1.4–4.1) for EPN (P = 0.29). The median time was 3.1 min (IQR 1.3–7.1) for HPN and 3.1 min (IQR 1.8–4.8) for EPN when only the first induction was taken into account.

Smear and culture results

Three individuals were diagnosed with smear-positive TB. Two had smear-positive HPN and EPN samples, while the other individual had a smear-positive EPN sample but a smear-negative HPN sample. All six samples from these three individuals were culture-positive for TB (Table 2).

Four individuals were diagnosed with smear-negative, culture-positive TB, of whom two grew *M. tuberculosis* in both samples (HPN- and EPN-induced). However, the HPN samples of the remaining two individuals were reported as culture-negative.

The quality of the smear and/or culture-positive

Table 1 Number and percentage of good quality sputum induced by the human-powered and electric-powered nebulisers according to different assessment criteria

	McCarter and Robinson[16]		Van Scoy[17]		Geckler et al.[18]		Murray and Washington[19]		Barlett[20]	
Nebuliser	*n* (%)	*P* value	*n* (%)	*P* value	*n* (%)	*P* value	*n* (%)	*P* value	*n* (%)	*P* value
Human powered	91 (83.5)	0.08	29 (26.6)	0.63	94 (86.2)	0.11	67 (61.5)	0.88	30 (27.5)	0.05
Electric powered	81 (74.3)		25 (22.9)		85 (78.0)		65 (59.6)		19 (17.4)	

Table 2 Smear- and/or culture-positive cases: sputum quality according to different assessment criteria

Smear		Culture		McCarter and Robinson[16]		Van Scoy[17]		Geckler et al.[18]		Murray and Washington[19]		Barlett[20]	
HPN	EPN	HPN	EPN	HPN	EPN	HPN	EPN	HPN	EPN	HPN	EPN	HPN	EPN
+	+	+	+	Good	Good	Poor	Poor	Good	Good	Good	Good	Good	Good
+	+	+	+	Good	Poor	Good	Poor	Good	Good	Good	Good	Good	Poor
–	+	+	+	Good	Good	Poor	Poor	Good	Good	Good	Poor	Poor	Poor
–	–	–	+	Good	Good	Poor	Poor	Good	Good	Good	Good	Poor	Poor
–	–	–	+	Good	Good	Good	Poor	Poor	Good	Poor	Good	Poor	Poor
–	–	+	+	Good	Poor	Good	Poor	Poor	Good	Poor	Good	Poor	Poor
–	–	+	+	Good	Good	Good	Poor	Poor	Good	Poor	Poor	Poor	Poor

HPN = human-powered nebuliser; EPN = electric-powered nebuliser.

sputum samples varied greatly. The majority of the samples were assessed as good quality according to the criteria of McCarter and Robinson and Geckler et al., but were assessed as poor quality according to Van Scoy and Barlett.

DISCUSSION

To our knowledge, this is the first study to assess the efficacy of a nebuliser that does not require battery or electric power for sputum induction for TB diagnosis. We found that the HPN was comparable to the ultrasonic electric nebuliser in terms of sputum quality when used to induce sputum in HIV-negative TB suspects and HIV-positive individuals.

Sputum induction was successful in the majority of individuals (95.6%), and there was no difference in the time to sputum induction. This is important in under-resourced settings where human resources for health are scarce and staff would not be easily motivated to perform procedures that require additional time and may not be successful. The majority of the participants were able to produce induced sputum samples within 5 min, and none abandoned the procedure due to discomfort or bronchospasm. This emphasises yet again that sputum induction is safe, quick and easy to perform, as shown in several other studies.[10,12]

The prototype of the HPN was built with a specific focus on resource-limited settings. The material used for the construction of the HPN is cheap and readily available, and the device is easy to construct and repair by non-engineers. These characteristics make the HPN an ideal device for resource-limited settings where highly specialised biomedical engineers are not available.

The major limitation of this study is the lack of power to investigate the diagnostic yield for TB comparing HPN- and EPN-induced sputum. The majority of TB-positive specimens were classified as poor quality by criteria that used SEC counts to assess specimen quality, which is consistent with findings from other studies.[16,21] The fact that some TB cases were missed by the HPN is most likely due to chance, but will certainly need further investigation.

Another limitation of this study is the different make of the two nebulisers. The HPN was a jet nebuliser whereas the EPN was an ultrasonic nebuliser. The study therefore could not strictly compare the electric vs. the human powered compressor system. As this was a substudy of an ongoing intensified case-finding study that had been using an ultrasonic nebuliser previously,[22] it was felt that a change in nebuliser could possibly compromise the results of the main study. It was therefore decided that the jet HPN should be compared with the standard of care in this mobile HIV testing service.

The HPN weighs less than 5 kg and measures 50 × 55 × 38 cm. It does not require any electricity and it can be operated by lay community health workers. This device is suitable not only for remote clinics with unreliable electricity, but also for mobile services and community-based intensified TB case finding. Several recent community and workplace-based TB prevalence surveys in sub-Saharan Africa have shown the high burden of undiagnosed TB in communities,[23–27] raising the question of whether a clinic-based approach alone will be sufficient for TB control. Interventions to facilitate community-based TB and HIV diagnosis have been shown to be acceptable and feasible.[28–31] More importantly, a recent trial of community-based active TB case finding in Zimbabwe provided evidence that active case finding can have a positive impact on TB control.[32] However, community-based TB diagnosis often relies on spontaneously expectorated spot sputum samples, impeding TB diagnosis in individuals unable to produce sputum. Thus, the role of the HPN in community-based TB case finding merits further investigation.

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RÉSUMÉ

OBJECTIFS : Investiguer la qualité des échantillons d'expectoration provoquée lorsqu'on utilise respectivement un nébuliseur propulsé par l'homme (HPN) et un nébuliseur propulsé par le courant électrique (EPN).

MÉTHODES : Chez chaque participant, on a prélevé deux échantillons d'expectorations provoquées, utilisant respectivement l'HPN et l'EPN. La séquence des deux nébuliseurs a été attribuée au hasard. La proportion d'expectoration de bonne qualité, en fonction de différents critères d'évaluation, a été comparée par un test exact McNemar. La différence dans la durée avant expectoration a été comparée par le test « matched-pairs signed rank » de Wilcoxon.

RÉSULTATS : Au total, 123 individus ont été éligibles pour cette étude. Il y a eu refus de participation chez neuf d'entre eux et incapacité de produire un échantillon de crachats chez cinq. La proportion d'expectorations de bonne qualité a été plus élevée dans les échantillons de crachats induits par HPN par comparaison avec les échantillons de crachats obtenus après l'EPN. La durée médiane avant production d'un échantillon de crachats a été de 2,2 min (IQR 1,13–4,1) pour l'HPN et de 2,5 min (IQR 1,4–4,1) pour l'EPN.

CONCLUSION : L'HPN produit une expectoration de bonne qualité et ce dans les 3 min. Cet appareil n'exige pas l'utilisation d'électricité et est adapté non seulement aux dispensaires éloignés, où l'accès au courant électrique est irrégulier, mais aussi pour les services mobiles et pour les dépistages intensifiés des cas de tuberculose (TB) au sein de la collectivité. Des recherches complémentaires doivent investiguer le rendement en matière de TB dans les échantillons de crachats induits par l'HPN.

RESUMEN

OBJETIVOS: Investigar la calidad de las muestras de esputo inducido que se obtienen mediante la utilización de un nebulizador accionado en forma mecánica (HPN) y un nebulizador eléctrico (EPN).

MÉTODOS: Se obtuvieron de cada participante dos muestras de esputo inducido; una muestra se obtuvo mediante el uso de un HPN y la otra con un EPN. La secuencia de los nebulizadores se asignó de manera aleatoria. La proporción de muestras de buena calidad, según diferentes criterios de evaluación, se comparó mediante la prueba exacta de McNemar. Se comparó además el lapso hasta la obtención de la expectoración con la prueba de Wilcoxon para datos emparejados.

RESULTADOS: Ciento veintitrés personas cumplieron con los requisitos del estudio. Nueve personas rehusaron participar y cinco no pudieron producir muestras de esputo. La proporción de muestras de esputo de buena calidad fue más alta en las muestras inducidas con el nebulizador mecánico que con el nebulizador eléctrico. La mediana del lapso hasta obtener la muestra de esputo fue 2,2 min (IQR 1,13–4,1) con el HPN y 2,5 min (IQR 1,4–4,1) con el EPN.

CONCLUSIÓN: El HPN induce una muestra de esputo de buena calidad en un tiempo de 3 min. El dispositivo funciona sin electricidad y es adecuado, no solo en los consultorios alejados que no cuentan con un aprovisionamiento fiable de energía eléctrica, sino también en los servicios móviles y en las campañas comunitarias de búsqueda intensificada de casos de tuberculosis. Se precisan nuevas investigaciones que evalúen el rendimiento diagnóstico de las muestras de esputo inducidas por el HPN.

6 Feasibility, yield and cost of an active TB case finding program linked to a mobile HIV testing service in Cape Town, South Africa

6.1 Introduction

Active TB case finding in HIV infected individuals has been recommended by the WHO as part of the 'Three I's' policy initiative [1,2]. Screening of household contacts of infectious TB cases has also been recommended for a long time [3,4,5], but population-wide mass-screening has been widely discouraged due to high cost, low cost-effectiveness and poor sustainability [6,7]. However, more recently a study from Zimbabwe has shown a decline of TB prevalence from 6.5 to 3.7 per 1000 adults following community-level active TB case finding [6], which led to reactivated interest in population-wide interventions.

Active TB case finding aims at reducing barriers for early TB case detection such as delays in the person presenting to a health facility and the health worker identifying the person as a TB suspect and initiating appropriate investigations. The ultimate goal of active TB case finding is to reduce TB transmission in the community through improved case detection and reduction in diagnostic delays.

The yield of active TB case finding determines the number needed to screen and is context specific, depending on local TB prevalence, the function of local TB control services, HIV prevalence and the specificity and sensitivity of the screening tool [8]. Other important parameters framing decisions on implementing active TB case finding include the feasibility and cost of screening, the laboratory capacity, diagnostic tests available and treatment outcomes in newly detected cases.

The WHO is currently developing guidelines on screening for TB disease with the aim to inform national TB screening strategies based on the local epidemiological, demographic and health system situation [7]. However, the development of guidelines is complicated by significant gaps in knowledge regarding mass screening strategies in high TB and HIV prevalence settings. In particular, screening strategy, the type of diagnostic test, cost-effectiveness of active TB case finding and the treatment outcomes of actively detected cases remain unclear.

We report the results of a study investigating the feasibility, uptake, treatment outcomes and cost of an active TB case finding program linked to a mobile HIV testing service in Cape Town, South Africa.

6.2 Methods

6.2.1 Setting

This study was conducted at a mobile HIV testing service over 19 months from May 2009 to February 2011. The service operated in underserviced peri-urban areas in greater Cape Town, South Africa, and has been described in detail elsewhere [9]. In brief, this nurse-run and counsellor-supported unit provided free HIV counselling and testing in combination with free screening for other chronic conditions (hypertension, diabetes and obesity) and TB. Rapid HIV testing was performed according to the guidelines of the Provincial Government of the Western Cape [10]. The mobile unit was parked at township shopping centres, taxi ranks, stations, and the road side. The service was not formally advertised and hence attracted ambulatory clients who spontaneously accessed HIV testing or other services.

6.2.2 Mobile clinic procedures

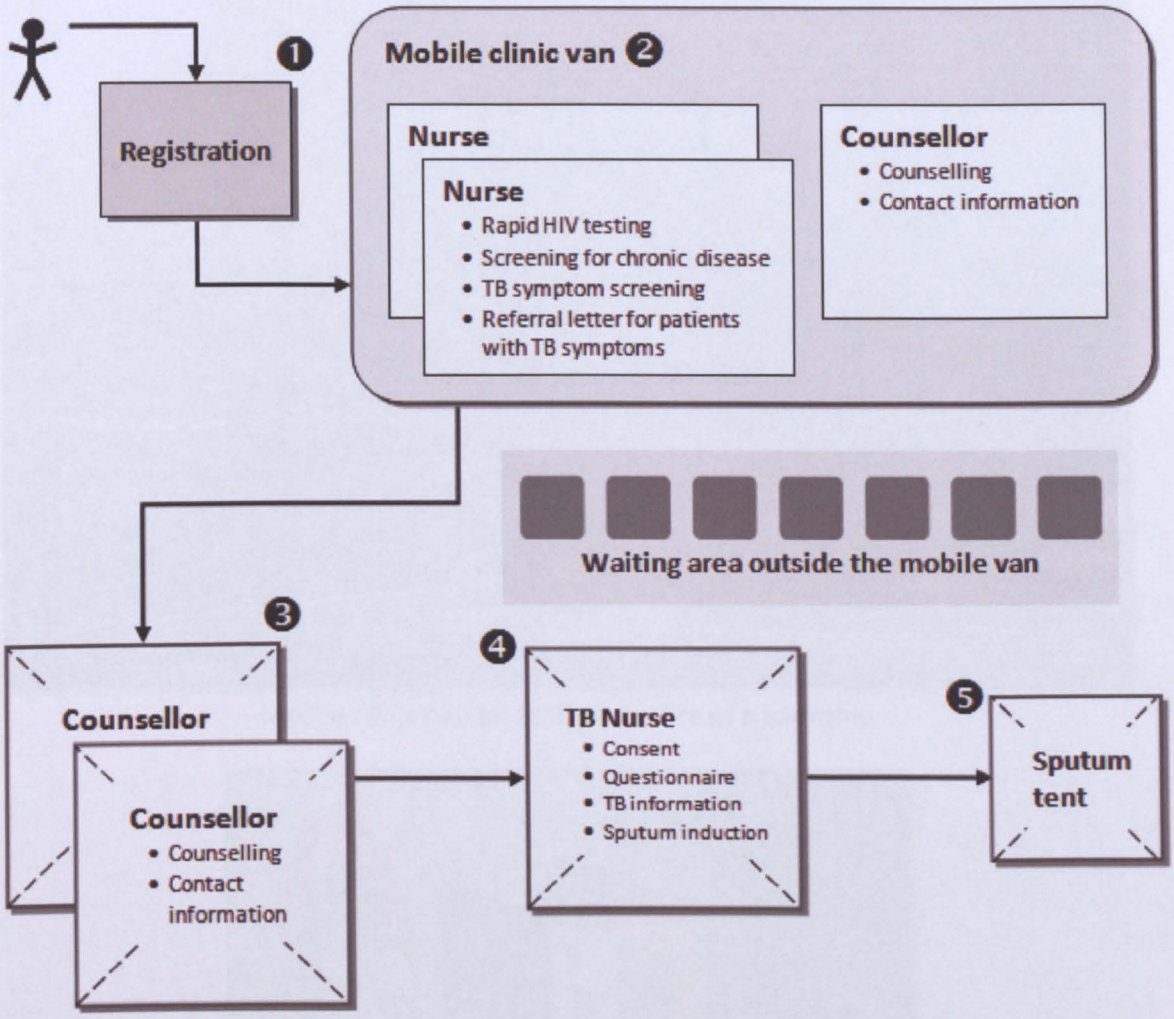
All individuals accessing the mobile clinic were registered using a biometric fingerprint system, with no names or other personal identifiers in the registration process (Figure 6.1). They were then seen by a nurse for rapid HIV testing and chronic disease screening including TB symptom screening, followed by a one-to-one counselling session. All individuals with symptoms suggestive of TB (TB suspects) received a referral letter to their nearest clinic for further evaluation as indicated. Figures 6.1 and 6.2 demonstrates the different steps a patient had to undergo when accessing the mobile clinic and active TB case finding programme.

6.2.3 Study procedures

6.2.4 Screening

All HIV negative adults with symptoms suggestive of TB and all HIV positive or diabetic adults regardless of symptoms were eligible for the study. All eligible individuals were identified as such by the nurse. The lay counsellor collected detailed contact information from eligible individuals and referred them to the study nurse for participation in the study (Figure 6.1). Individuals who consented to participate in the study were asked about symptoms, health seeking behaviour, previous TB episodes, educational status, employment and history of imprisonment. They were asked to provide one sputum sample and were encouraged to do so by sputum induction, but could choose to provide a spot sample. Sputum samples were sent to the laboratory within 24 hours. The samples underwent fluorescent microscopy and liquid culture.

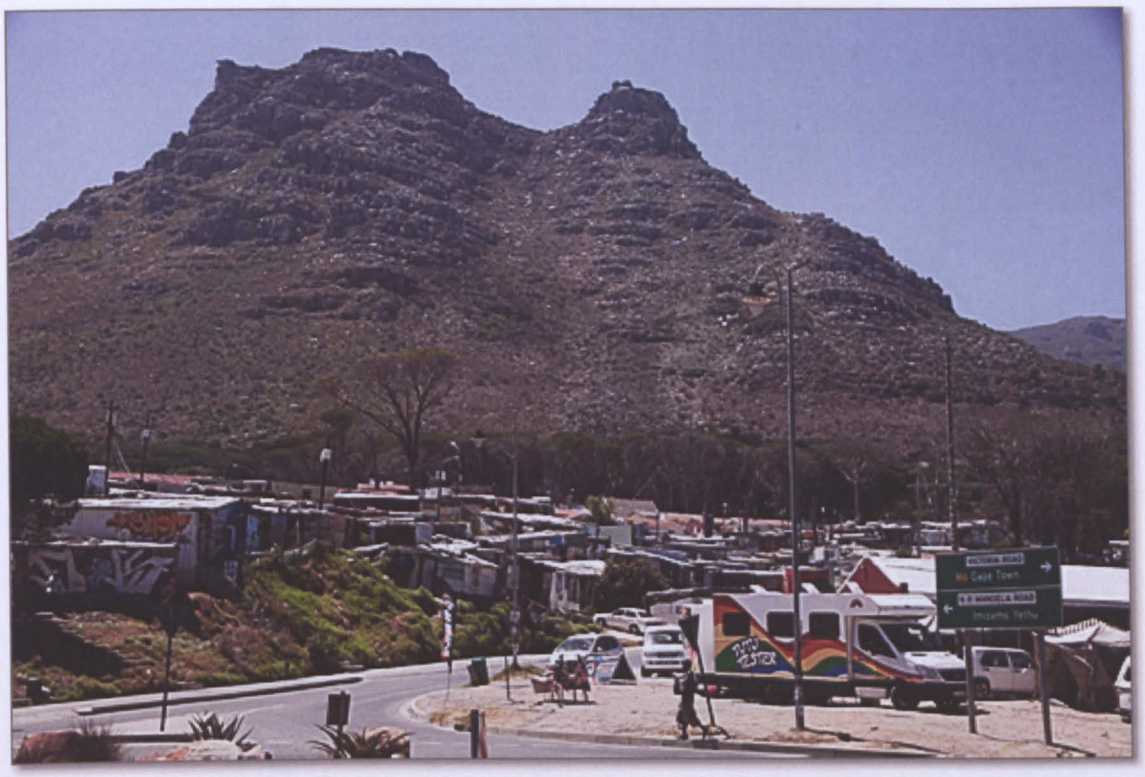
Figure 6.1: Procedures and patient flow in the mobile clinic



The numbers in black circles refer to the pictures in Figure 6.2.

Figure 6.2: Pictures showing the different procedures in the mobile service

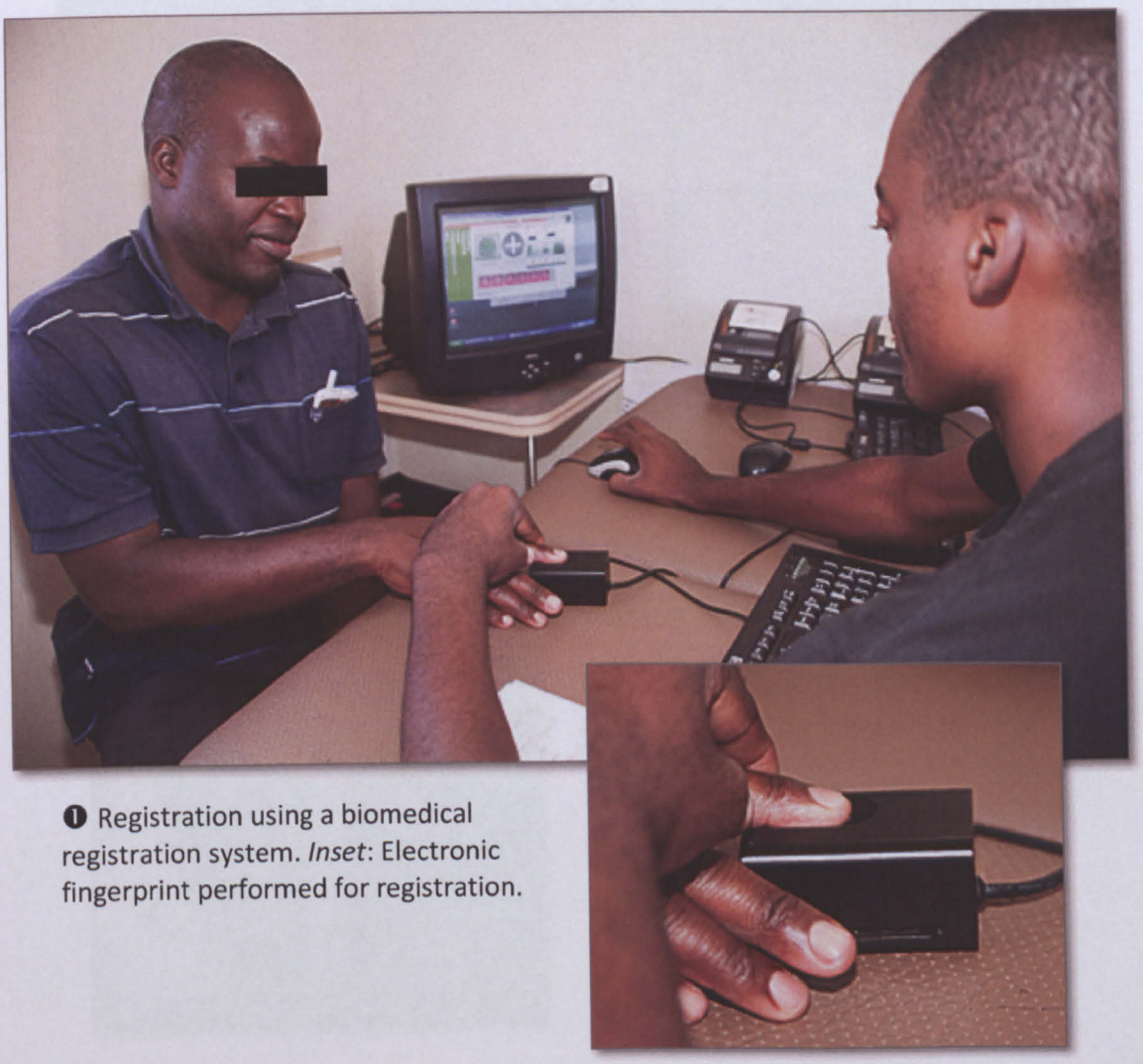
Typical township in Cape Town, where the mobile clinic operated.



Mobile Clinic parked at the entrance of a township.

❶ Patients waiting to be registered.

❶ Weight and height is measured as part of the registration process.

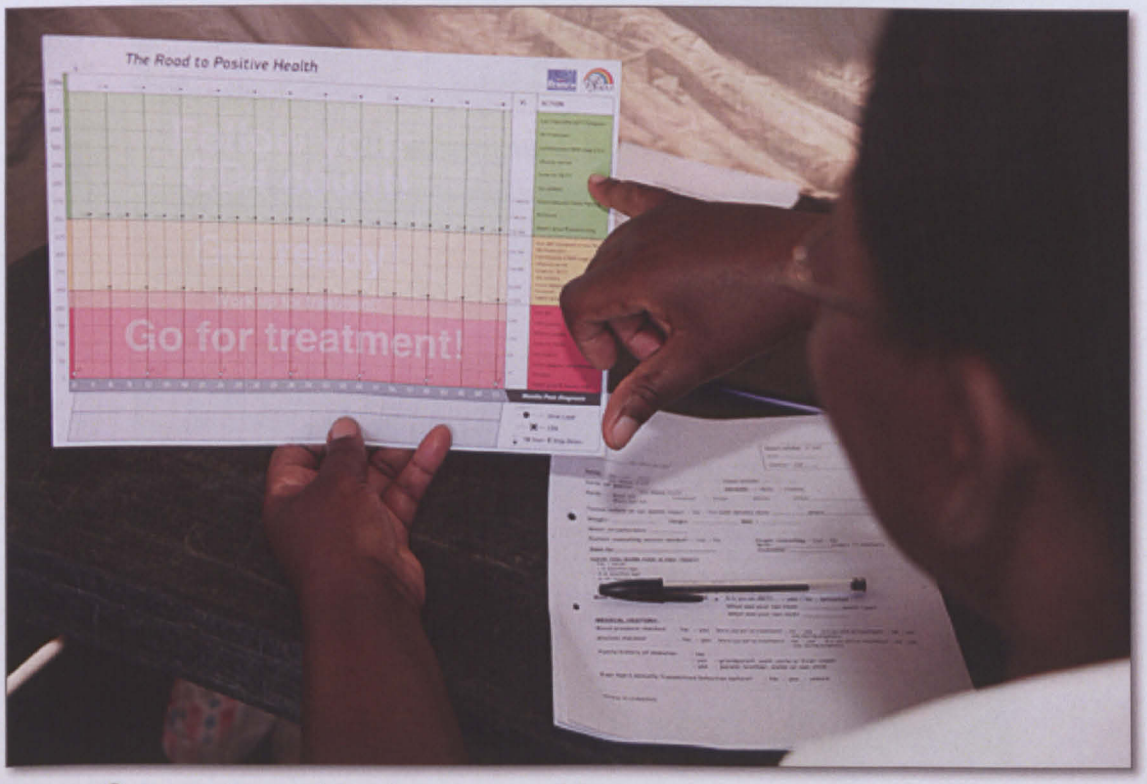


❶ Registration using a biomedical registration system. *Inset*: Electronic fingerprint performed for registration.

❷ HIV testing using a rapid HIV test.

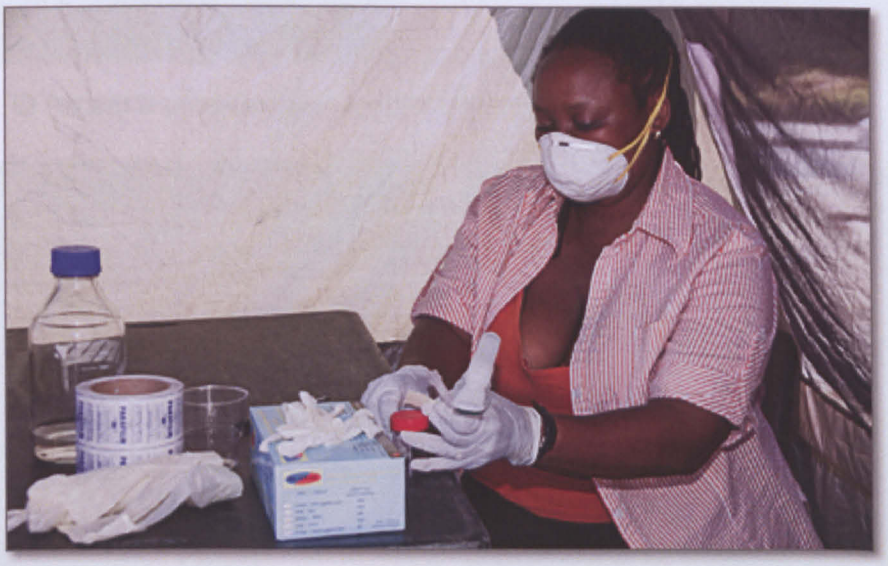
❷ CD 4 count testing using a point of care CD4 count machine (PIMA). *Inset*: PIMA machine.

❸ Counselling

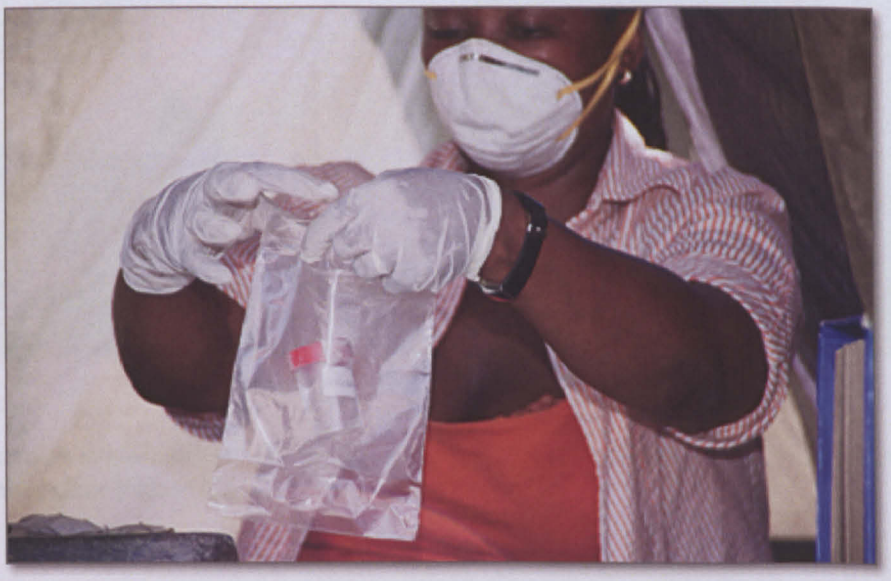


❸ Counsellor explains the meaning of CD4 counts using a road to health card.

❹ Research nurse prepares for sputum induction.

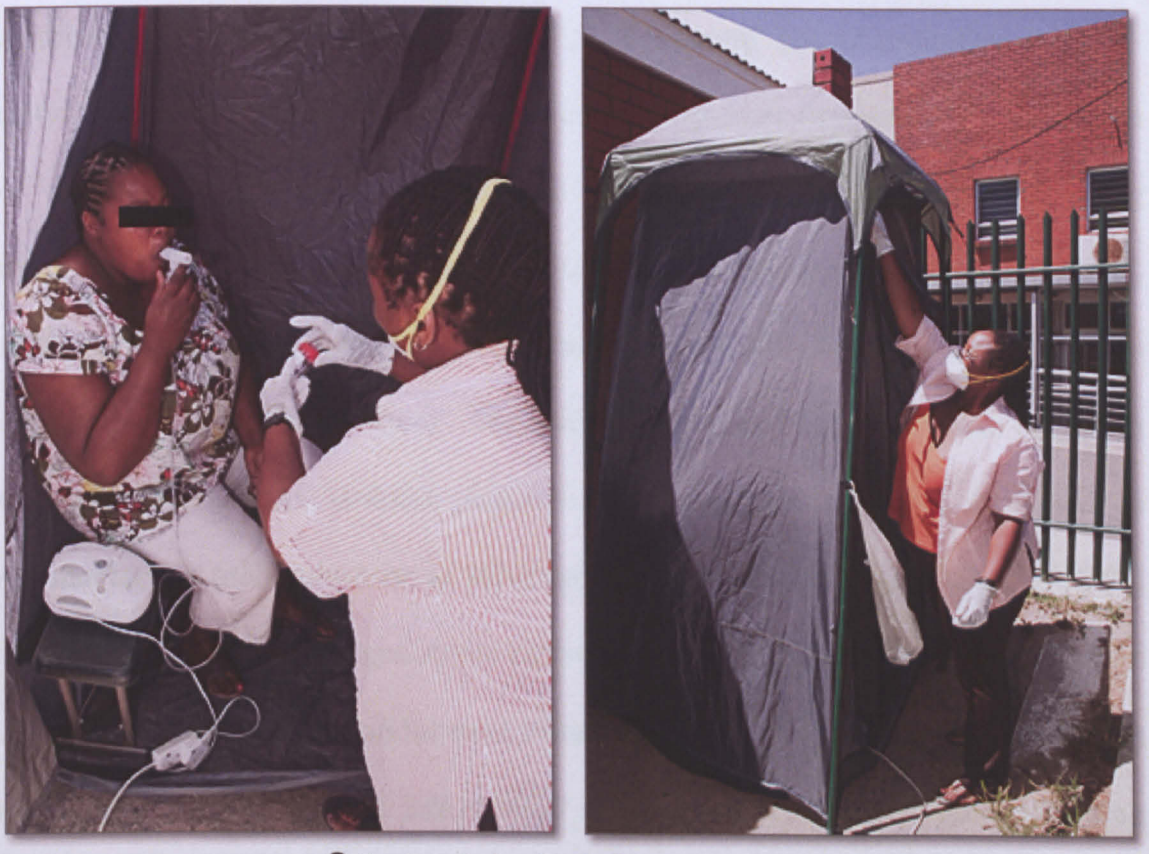


❹ Research nurse labels containers.



❹ Research nurse packs containers for transport.

❺ Patient is in the sputum tent. Research nurse explains the procedure.



❺ Sputum induction inthe sputum tent.

The numbers in black circles refer to the positions in the procedures and patient flow in the mobile clinic (Figure 6.1).

6.2.4.1 Sputum induction:

Individuals were asked to rinse their mouth with water before the procedure. Sputum induction was performed in an open-roofed tent using 15-20 ml sterile 3% hypertonic saline solution and an ultrasonic Flo-Eolo nebuliser (CA-Mi, Pliastro, Italy) powered by a generator. Individuals breathed through the nebuliser mouthpiece until a satisfactory sample was produced or he/she wished to abandon the procedure. The procedure was performed without a nose clip.

6.2.4.2 Laboratory procedure

Sputum samples were analysed within accredited laboratories using standardized protocols and quality control procedures. Following decontamination with *N*-acetyl-*L*-cysteine sodium hydroxide, centrifuged sputum deposits were examined for acid-fast bacilli using auramine O fluorescent stain and cultured using mycobacterial growth indicator tubes (MGIT, Becton- Dickinson, Sparks, Maryland, USA). Bacillary density was graded as scanty, 1+, 2+, and 3+, and all such smears were defined as "smear-positive". The time to automated culture growth detection was recorded. Culture isolates positive for acid-fast bacilli were identified as *Mycobacterium tuberculosis* or as Mycobacterium other than tuberculosis (MOTT) complex and assessed for genotypic resistance using the MTBDRplus assay (Hain Lifescience). Isolates also underwent phenotypic resistance testing for rifampicin and isoniazid by automated liquid MGIT culture (using the modified proportion method and standard protocols).

6.2.4.3 Follow-up

TB results were received from the laboratory on a daily bases by post and email. The laboratory contacted the programme manager or research nurse by phone for smear-positive results, who then contacted individuals with smear- and/or culture-positive TB to inform them of their positive result and referred them to a clinic of their choice. In the referral letter clinic nurses were asked to repeat sputum smears and cultures and perform chest radiograms if indicated. Multiple attempts were made to contact individuals either by phone, home visit or letter. Home visits were particularly time consuming and challenging in squatter camps and informal settlements. Individuals who were contacted face to face were asked to provide a second sputum sample to confirm the positive TB result. Clinics were contacted to ascertain dates of TB treatment initiation, TB register number and treatment outcomes. The research nurse performed clinic visits to check the TB register if the TB clinic nurse was unable to provide the information by phone. Individuals who did not attend the clinic were contacted again to encourage linkage to care. The Cape Town municipality's HIV, TB and STI unit was informed to notify TB cases where contact with the individuals could not be established.

6.2.5 Definitions

Active case finding in this program was defined as TB symptom screening followed by submission of sputum samples. TB screening was defined as sputum induction (or spot sputum). The 'traditional WHO symptom screen' was defined as any of the following: cough>2 weeks, weight loss, fever, night sweats or haemoptysis. The

'new WHO symptom screen' was defined as having any of the following symptoms: current cough, fever, weight loss, night sweats or haemoptysis [2,11].

6.2.6 Cost analysis

An incremental cost analysis investigating the costs of adding TB screening through sputum induction to an existing mobile HIV testing service was performed adopting a health service provider perspective. Financial costs included the costs of human resources (clinical nurse practitioner, programme manager, counsellor), equipment (tents, nebuliser, generator), consumables (gloves, masks, tubes disinfectant), transport, laboratory tests and rent. Costs were divided into capital and recurrent costs [12], and capital costs were annualized and discounted at 6% per year [13]. Cost data from previous years were adjusted for inflation to 2011 constant costs [14] and converted to US dollars (USD 1.00 = ZAR 7.40) [15]. Owing to the incremental nature of the cost analysis, resources shared with other interventions such as screening for HIV and other diseases were excluded from the analysis. Some of the resources were joint resources and were allocated proportionally. In order to analyse what staff time had been spent exclusively on TB screening activities, time-motion studies of all staff involved were conducted over one week in August 2010 and two weeks in January 2011, with a total of 13 complete screening days being observed. The two time periods were chosen, as attendance rates and working conditions varied according to season. Additionally, the research nurse kept a log file to estimate staff time spent on follow-up of individuals with positive smears and/or cultures. Cost of first line TB treatment was obtained from the literature [16,17], for patients who died or defaulted

treatment costs were allocated proportionately based on their time spent on treatment.

6.2.7 Measure of effectiveness

Effectiveness was measured as the rates of smear- and/or culture-positive disease, and the proportion of individuals with TB disease with a positive treatment outcome (cured or treatment completed). Treatment initiation dates, treatment outcomes and date of outcomes were determined by contacting TB clinics. The research nurses verified the outcomes by checking clinic TB registers.

6.2.8 Screening strategy and sensitivity analysis

Different screening strategies were assessed regarding their yield, treatment outcomes and cost. Screening strategies only differed with regards to HIV positive individuals. All HIV negative individuals with symptoms suggestive of TB (TB suspects) were assumed to undergo sputum investigations. Strategy I (base scenario) screened all HIV infected individuals regardless of symptoms. Strategy II assessed what would have been seen if screening was of all individuals with symptoms suggestive of TB according to the new WHO symptom screen. Strategy III assessed the effect of screening all individuals with CD4 counts ≤200 cells/μl or unknown CD4 counts regardless of symptoms and all individuals with CD4 counts >200 cells/μl and symptoms suggestive of TB according to the new WHO symptom screen. Strategy IV assessed the effect of screening all individuals with symptom suggestive of TB according to the traditional WHO symptom screen. Sensitivity

analyses were conducted for different levels of staff salaries, assuming that the outcomes would remain the same.

6.2.9 Statistical analysis

All analyses were carried out using Stata version 11.0 (Stata Corp. LP, College Station, TX, United States of America). Proportions were calculated for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. Differences in proportions were assessed using χ^2 test and differences in medians were assessed using Wilcoxon rank sum test. The mean cost per examined sputum, TB case and TB case with positive treatment outcome was calculated by summing the cost of all resources and dividing them by the number of sputum samples, TB cases diagnosed and TB case with positive outcomes.

6.2.10 Ethics statement

Written informed consent was obtained from all individuals participating in the study. Data collection and analysis was approved by the University of Cape Town Ethics Committee and Partners Human Subjects Institutional Review Board and the London School of Hygiene and Tropical Medicine Ethics Committee.

6.3 Results

6.3.1 Operational data

TB screening was performed on 181 days over a period of 19 months at 58 different sites. The majority of sites were in deprived areas, near townships and squatter camps. A total of 6,309 adults accessed the services of the mobile clinic,

85 were not tested for HIV, 5551 tested HIV negative, 370 were newly diagnosed with HIV and 388 were known HIV positive. Overall HIV prevalence in individuals tested was 12.0%. The median number of adults tested for HIV per day was 34 (IQR 27-41). The median number of individuals screened for TB was 6 (IQR 3-8), with a maximum number of 23 individuals per screening day.

6.3.2 Uptake of TB screening

A total of 1,385 individuals were eligible for TB screening through sputum induction: 627 were HIV negative, 370 were newly diagnosed HIV positive and 388 were known HIV positive (Figure 6.1). 1130 (81.6%) of all eligible individuals underwent screening. Individuals who were not screened were younger, more likely to be HIV positive and had a higher body mass index compared to individuals who underwent TB screening (Table 6.1). Failure to undergo screening was more likely in the first year of the study compared to the second year.

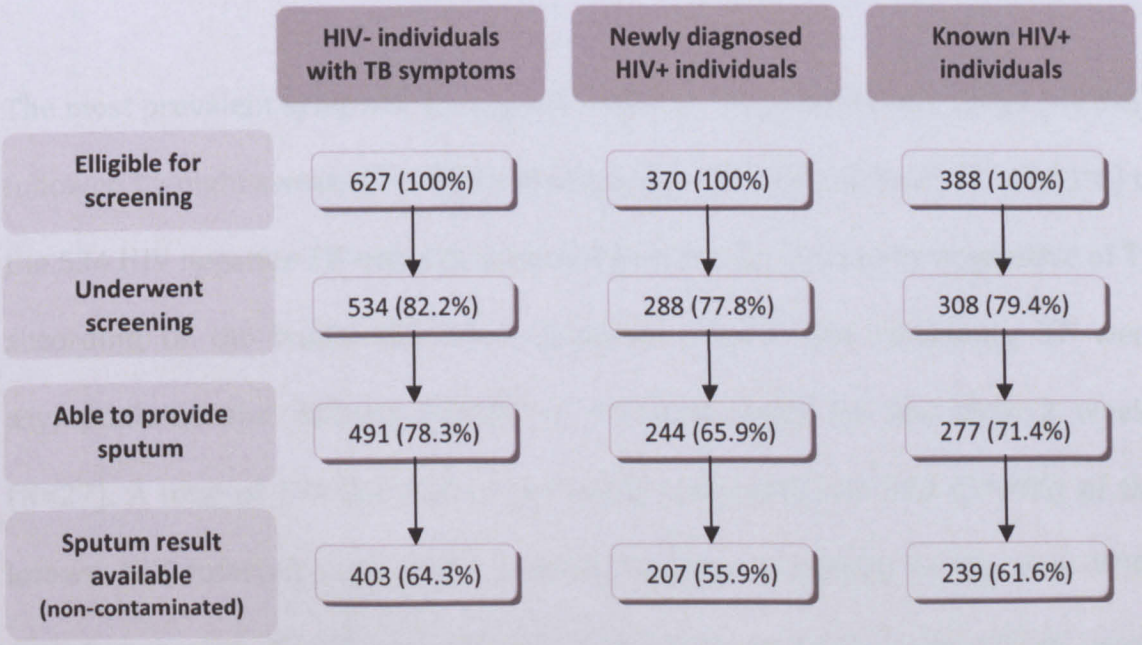
The majority of individuals (62.9%) who failed to complete TB screening said they did not have time to wait or they absconded without seeing the TB nurse. The remaining 164 individuals (37.2%) were missed because the nurses or counsellors did not refer them for screening. The proportion of individuals who absconded was highest in newly diagnosed HIV infected individuals (85.4%).

Among the individuals undergoing TB screening a considerable proportion was unable to produce a sputum sample or sputum results were inconclusive due to contamination (Figure 6.3). Overall 60.9% of all eligible individuals had an interpretable sputum result. Proportions with interpretable sputum results were 64.3%, 55.9% and 61.6% among HIV negative, newly diagnosed and known HIV infected individuals respectively.

Table 6.1: Baseline characteristics for clients eligible for the study stratified by screening

Variables		Total N=1395	Not screened N=265	Screened N=1130	P
Age	Median (IQR)	35.2 (27.6-44.7)	32.8 (26.6-42.1)	35.9 (27.9-45.7)	0.01
Men	N (%)	498 (35.7%)	92 (34.7%)	406 (35.9%)	0.71
HIV status					
Negative	N (%)	637 (45.7%)	103 (38.9%)	534 (47.3%)	0.05
Newly diagnosed positive	N (%)	370 (26.5%)	82 (30.9%)	288 (25.4%)	
Known positive	N (%)	388 (27.8%)	80 (30.2%)	308 (27.3%)	
CD4 cell count at screening (cell/µl) in HIV infected individuals	Median (IQR)	426 (302-606)	423 (300-603)	479 (308-631)	0.23
Body mass index	Median (IQR)	24.6 (21.4-29.7)	25.7 (21.8-30.5)	24.4 (21.4-29.4)	0.03
Diabetes	N (%)	58 (4.2%)	10 (4.0%)	48 (4.3%)	0.84
Study year					
Year 1	N (%)	827 (59.3%)	183 (69.1%)	644 (57.0%)	<0.01
Year 2	N (%)	568 (40.7%)	82 (30.9%)	468 (43.0%)	

Figure 6.3: Flowchart of individuals participating in the study



6.3.3 Baseline characteristics

A total of 1130 individuals participated in the study and underwent screening. The median age was 35.9 years and 35.9% were men (Table 6.2). Financial insecurity was high with 22.7% of individuals reporting no regular income. Among individuals with regular income, employment or regular work accounted for only 35.3%. The median income was ZAR 1000 (equivalent to USD 135) per month. The majority of individuals lived in informal settlements or squatter camps (63.1%) and had less than 12 years of school education (78.0%).

Median body mass index was 24.4 (IQR 21.4-29.4) A quarter of individuals had had TB before and 21.2% lived with somebody who had been treated for TB within the last year. The median CD4 count was 434 cells/μl (IQR 316-617) in newly diagnosed and 403 cells/μl (IQR 288-570) in known HIV infected individuals. 40% of the known HIV infected individuals were on ART at the time of screening with a median time on ART of 3.1 years (IQR 1.1-6.5).

The most prevalent symptom among HIV negative TB suspects was cough (84.3%), followed by night sweats (74.0%) and weight loss (53.2%). Overall 497 (93.1%) of the 534 HIV negative TB suspects screened positive for symptoms suggestive of TB according to the traditional WHO symptom screen. The remaining 37 were asymptomatic and diabetic (N=10) or reported cough for less than 2 weeks (N=27). A total of 174 (60.4%) of the newly diagnosed and 183 (59.4%) of the known HIV infected individuals screened positive according to the new WHO symptom screen. Cough was the most prevalent symptom among both newly diagnosed (43.1%) and known HIV infected individuals (43.2%).

Table 6.2: Socio-demographic and clinical characteristics and health seeking behaviour among those undergoing screening

Variables		Total N=1130	HIV- N=534	Newly diagnosed HIV+ N=288	Known HIV+ N=239
Socio-demographic (N=1130)					
Age (years)	Median (IQR)	35.9 (27.9-45.7)	40.2 (29.2-50.0)	33.4 (26.4-40.9)	33.5 (28.2-40.8)
Male gender	N (%)	406 (35.9%)	261 (48.9%)	96 (33.3%)	49 (15.9%)
Smoking[1]					
Never	N (%)	656 (58.2%)	224 (42.0%)	197 (68.6%)	235 (76.6%)
Stopped	N (%)	13 (1.2%)	8 (1.5%)	2 (0.7%)	3 (1.0%)
Currently	N (%)	458 (40.6%)	301 (56.5%)	88 (30.7%)	69 (22.5%)
Alcohol consumption[2]					
Never	N (%)	644 (57.2%)	280 (52.7%0	160 (55.6%)	204 (66.5%)
Once per week	N (%)	229 (20.3%)	98 (18.5%)	67 (23.3%)	64 (20.9%)
2-3 time per week	N (%)	190 (16.9%)	108 (20.3%)	52 (18.1%)	30 (9.8%)
Every day	N (%)	63 (5.6%)	45 (8.5%)	9 (3.1%)	9 (2.9%)
Current relationship[3]					
Single	N (%)	677 (60.0%)	296 (55.4%)	184 (63.9%)	197 (64.4%)
Partner	N (%)	377 (33.4%)	199 (37.3%)	85 (29.5%)	93 (30.4%)
Divorced	N (%)	22 (2.0%)	15 (2.8%)	4 (1.4%)	3 (1.0%)
Widowed	N (%)	52 (4.6%)	24 (4.5%)	15 (5.25)	13 (4.3%)
Regular income	N (%)	985 (87.3%)	472 (88.2%)	239 (83.0%)	275 (89.6%)
Source of income					
Government grants	N (%)	259 (26.5%)	121 (26.0%)	40 (16.7%)	98 (35.8%)
Casual work	N (%)	375 (38.3%)	184 (39.5%)	96 (40.2%)	95 (34.7%)
Regular work	N (%)	345 (35.3%)	161 (34.6%)	103 (43.1%)	81 (29.6%)
Income per month (ZAR)	Median (IQR)	1000 (400-1200)	1000 (400-1200)	870 (280-1200)	960 (400-1120)

Continued...

Continued: Table 6.2: Socio-demographic and clinical characteristics and health seeking behaviour among those undergoing screening

Variables		Total N=1130	HIV- N=534	Newly diagnosed HIV+ N=288	Known HIV+ N=239
Level of schooling					
None	N (%)	45 (4.00)	29 (5.4%)	6 (2.1%)	10 (3.3%)
Less than 8 years	N (%)	369 (32.7%)	218 (41.0%)	84 (29.2%)	67 (21.8%)
8-11 years	N (%)	465 (41.3%)	192 (36.1%)	122 (42.4%)	151 (49.2%)
Finished high school	N (%)	159 (14.1%)	49 (9.2%)	52 (18.1%)	58 (18.9%)
Tertiary education	N (%)	89 (7.9%)	44 (8.3%)	24 (8.3%)	21 (6.8%)
Participant ever having been imprisoned	N (%)	159 (14.1%)	92 (17.2%)	39 (13.5%)	28 (9.1%)
Participant living in informal settlement[6]	N (%)	712 (63.1%)	304 (57.0%)	207 (71.9%)	201 (65.3%)
Clinical (N=1130)					
Diabetes	N (%)	48 (4.3%)	36 (6.8%)	3 (1.1%)	9 (2.9%)
BMI	Median (IQR)	24.4 (21.4-29.4)	22.7 (20.2-27.4)	25.1 (22.2-30.1)	26.5 (23.3-30.9)
Current CD4 count (cells/µl)[7]	Median (IQR)	*NA*	*NA*	434 (316-617)	403 (288-570)
Currently on ART[8]	N (%)	*NA*	*NA*	*NA*	120 (39.0%)
Time on ART (years)	Median (IQR)	*NA*	*NA*	*NA*	3.1 (1.1-6.5)
Previous TB episode					
None	N (%)	845 (74.8%)	402 (75.3%)	247 (85.8%)	196 (63.6%)
One	N (%)	247 (21.9%)	115 (21.5%)	37 (12.9%)	95 (30.8%)
More than one	N (%)	38 (3.4%)	17 (3.2%)	4 (1.4%)	17 (5.5%)
TB within the last 2 years	N (%)	133 (11.8%)	60 (11.2%)	15 (5.2%)	58 (18.8%)
TB household contact	N (%)	240 (21.2%)	121 (22.7%)	63 (21.9%)	56 (18.2%)
Symptoms					
Cough	N (%)	707 (62.6%)	450 (84.3%)	124 (43.1%)	133 (43.2%)
Haemoptysis	N (%)	126 (11.2%)	94 (17.6%)	14 (4.9%)	18 (5.8%)
Fever	N (%)	119 (10.5%)	75 (14.0%)	21 (7.3%)	23 (7.47%)
Night sweats	N (%)	628 (55.6%)	395 (74.0%)	115 (39.9%)	118 (38.3%)
Weight loss	N (%)	458 (40.5%)	284 (53.2%)	78 (27.1%)	96 (31.2%)

Continued...

Continued: Table 6.2: Socio-demographic and clinical characteristics and health seeking behaviour among those undergoing screening

Variables		Total N=1130	HIV- N=534	Newly diagnosed HIV+ N=288	Known HIV+ N=239
Traditional WHO symptom screen positive	N (%)	838 (74.2%)	497 (93.1%)	160 (55.6%)	162 (52.6%)
New WHO HIV+ symptom screen positive	N (%)	866 (76.6%)	509 (95.3%)	174 (60.4%)	183 (59.4%)
Health seeking behaviour (N=821)					
Sought medical care	N (%)	170 (20.7%)	112 (23.0%)	19 (11.6%)	39 (23.1%)
Sputum sample sent by the clinic	N (%)	105 (61.8%)	69 (61.6%)	10 (52.6%)	26 (66.7%)
CXR performed by the clinic	N (%)	54 (31.8%)	35 (31.3%)	4 (21.1%)	15 (38.5%)

[1]3 missing values, [2]4 missing values, [3]2 missing values, [4]6 missing values, [5]3 values missing, [6]1 missing values,[7]30 missing values, [8]18 missing values

Only 20.7% (N=170) of all individuals reporting symptoms had previously sought health care for their current symptoms. Of those who had sought health care 61.8% had undergone sputum investigations and 31.8% had had a chest radiogram.

6.3.4 Yield of TB screening

Among all HIV negative individuals or individuals with unknown HIV status who accessed the mobile service and benefited from active case finding, including those who were unable to provide a sputum sample, prevalence was 0.2/100 (95% CI 0.1-0.4) for smear-positive TB and 0.5/100 (95%CI 0.3-0.7) for culture-positive TB. Among individuals newly diagnosed with HIV, TB prevalence was 2.2/100 (95%CI 0.9-4.2) for smear-positive and 4.9/100 (95%CI 2.9-7.6) for culture-positive disease. Prevalence was 0.3/100 (95%CI 0.0-1.4.) for smear positive and 3.0 (95%CI 1.6-5.) for culture-positive TB in individuals with known HIV infection.

The overall prevalence of smear positivity among individuals providing a sputum sample was 2.0/100 (95%CI 1.2-3.0) (Table 6.3). Prevalence of smear positive TB was 2.2/100 (95%CI 1.1-4.0), 3.3/100 (95%CI 1.4-6.4) and 0.4/100 (95%CI 0-2.0) in HIV negative TB suspects, newly diagnosed and known HIV infected individuals, respectively. Prevalence of culture-positive TB was 5.5/100 (95%CI 4.2-7.1) overall. In HIV negative TB suspects, newly diagnosed and known HIV infected individuals prevalence of culture-positive TB was 5.3/100 (95%CI 3.5-7.7), 7.4/100 (95%CI 4.5-11.5) and 4.3/100 (95%CI 2.3-7.4), respectively. Median time to culture positivity was 13.5 days (IQR 8-22). All isolates were sensitive to rifampicin and isoniazid.

Table 6.3 Tuberculosis prevalence in patients submitting a sputum sample

Variables		Total N=1011	HIV- N=491	Newly diagnosed HIV+ N=243	Known HIV+ N=277
Smear result					
Overall positive	N (%)	20 (2.0%)	11 (2.2%)	8 (3.3%)	1 (0.4%)
Scanty	N (%)	3 (0.3%)	1 (0.2%)	2 (0.8%)	0 (0.0%)
1+	N (%)	6 (0.6%)	3 (0.6%)	2 (0.8%)	1 (0.4%)
2+	N (%)	6 (0.6%)	4 (0.8%)	2 (0.8%)	0 (0.0%)
3+	N (%)	5 (0.5%)	3 (0.6%)	2 (0.8%)	0 (0.0%)
Culture result					
Negative	N (%)	746 (73.8%)	346 (70.5%)	180 (74.1%)	220 (79.4%)
Contaminated	N (%)	162 (16.0%)	88 (17.9%)	36 (14.8%)	38 (13.7%)
MOTT	N (%)	47 (4.7%)	31 (6.3%)	9 (3.7%)	7 (2.5%)
M. tuberculosis	N (%)	56 (5.5%)	26 (5.3%)	18 (7.4%)	12 (4.3%)
Days to culture positivity	Median (IQR)	13.5 (8-22)	12 (7-17)	13 (8-22)	19 (14.5-27)

6.3.5 CD4 counts and WHO symptom screens in HIV infected individuals

TB prevalence was highest in patients with CD4 counts ≤200 cells/µl (28.6%; 95%CI 9.7-30.9), followed by patients with missing CD4 counts (7.7%; 95%CI 9.5-25.1). TB prevalence was 5.3% (05%CI 2.0-11.1), 4.3% (95%CI 1.6-9.1), 2.8% (95% 0.9-6.3) in patients with CD4 counts of 201-350, 351-500, >500 cells/µl, respectively.

The new WHO symptom screen had a sensitivity of 87.7% (95%CI 69.3-96.2) and specificity of 39.4% (95%CI 35.0-43.9). Sensitivity was 100% (95%CI 71.5-100.0) and specificity 29.8% (95%CI 17.3-44.5) in patients with CD4 counts ≤200 cells/µl. The traditional WHO symptom screen had a sensitivity of 83.3% (95%CI 65.3-94.4) and specificity of 46.1% (95%CI 41.6-50.7) in HIV positives.

6.3.6 Contact rates, treatment initiation and treatment outcomes

Successful contact for follow-up after screening was made with 50 (89.3%, 95%CI 78.1-96.0) of the 56 individuals diagnosed with TB (Table 6.4). Contact success was higher in smear-positive individuals (95.0%, 95%CI 75.1-99.9) compared to smear-negative/culture-positive individuals (86.1%, 95% 70.5-95.3) The reasons for not being able to contact individuals were: imprisonment (N=1), relocation to an unknown area (N=3) and demolishment of the area where the individual had lived (N=2). The median time to successful contact from time of positive result was 4 days (IQR 1-10). Medium time to contact was shorter for individuals with smear-positive TB (1 day, IQR 0-2) compared to individuals with smear-negative/culture-positive TB (6 days, IQR 4-20).

Of the 50 individuals contacted, a total of 42 were confirmed to have started TB treatment by contacting the clinic and checking the clinic TB register. Treatment initiation rates were 89.5% (95%CI 66.9-98.7) in smear-positive and 80.7% (95%CI 62.5-92.5) in smear-negative/culture-positive cases. Two individuals had refused treatment and six individuals had not started treatment at their nearest clinic. Several attempts were made to contact these individuals, but all of them had moved to an unknown destination. Median time between screening and treatment initiation was 27 days (IQR 7-54) overall, 6.5 days (IQR 4.5-8) for smear-positive and 45 days (IQR 32-57) for smear-negative/culture-positive cases. Median time between successful contact and treatment initiation was 1 day (IQR 0-8).

Table 6.4: Contact rates and treatment success in patients diagnosed with tuberculosis

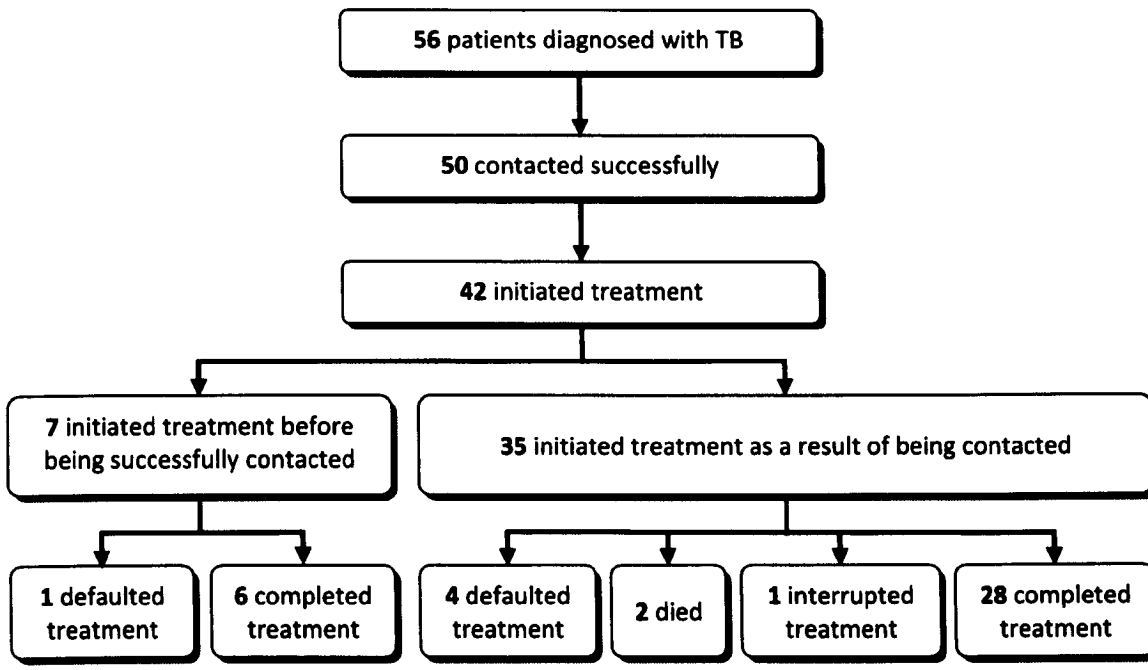
Variables		Total N=56	Smear + N=20	Smear -/culture + N=36
Successful contact	N (%)	50 (89.3%)	19 (95.0%)	31 (86.1%)
Time to successful contact from availability of positive result (days)	Median (IQR)	4 (1-10)	1 (0-2)	6 (4-20)
Treatment started				
No	N (%)	2 (4.0%)	1 (5.3%)	1 (3.2%)
Unknown	N (%)	6 (12.0%)	1 (5.3%)	5 (16.1%)
Confirmed	N (%)	42 (84.0%)	17 (89.5%)	25 (80.7%)
Time to treatment from screening date (days)	Median (IQR)	27 (7-54)	6.5 (4.5-8)	45 (32-57)
Time to treatment from availability of positive result (days)	Median (IQR)	24 (3-50)	1.5 (0-6.5)	43 (29-74)
Time to treatment from contact date (days)	Median (IQR)	1 (0-8)	0.5 (0-25)	2 (0-23)
Treatment outcome				
Treatment completed or cured	N (%)	34 (81.0%)	12 (70.6%)	22 (88.0%)
Died	N (%)	2 (4.8%)	1 (5.9%)	1 (4.0%)
Defaulted	N (%)	5 (11.9%)	3 (17.6%)	2 (8.0%)
Treatment interruption	N (%)	1 (2.4%)	1 (5.9)	0 (0.0%)

Overall treatment success rate was 81.0% (N=34/42) (95%CI 65.9-91.4). Treatment success was 70.6% (95%CI 44.0-89.7) for smear-positive and 88.0% (95%CI 68.8-97.5) for smear-negative/culture-positive cases. Two individuals died on treatment, two defaulted and one interrupted treatment, but restarted treatment 3 months after defaulting.

Of the 42 individuals who had initiated treatment, seven started before a successful contact could be made (Figure 6.4). In these cases, the initiation of treatment was not triggered by the positive sputum result. All patients with symptoms suggestive of TB received a referral letter from the mobile HIV clinic. These seven individuals had presented with their referral letter to a primary care

clinic and where started on TB treatment based on clinical presentation and investigations performed at the clinic.

Figure 6.4: Losses between tuberculosis diagnosis to treatment completion



6.3.7 Costs and cost effectiveness

The total cost of the screening program was USD 83,559. USD 22,367 (26.8%) were spent on laboratory tests, USD 37,427 (44.8%) on staff salaries, USD 17.652 (21.1%) on TB treatment, the remaining USD 6,108 (7.3%) were spent on transport, office rent and utilities, communication, generator and supplies. The costs were USD 1,117 per TB case detected and USD 2,458 per TB case with a positive treatment outcome (cured or treatment completed) (Table 6.5).

Outcomes and costs for different screening strategies are presented in Table 6.5 and compared to the base scenario (strategy I: sputum induction in all HIV infected individuals regardless of symptoms). Strategies differed only with regards to

sputum induction in HIV infected individuals. All HIV negative TB suspects were assumed to undergo sputum induction. Strategy II-IV did not significantly differ with regards to costs. Strategy IV (sputum induction in HIV infected individuals screening positive according to the traditional WHO symptom screen) was the most cost-effective strategy. However this strategy would have missed five TB cases resulting in one smear-positive case not being cured and one smear-negative/culture-positive case not completing treatment.

Table 6.5: Outcomes, costs and cost-effectiveness indicators for tuberculosis screening

Costs and outcomes	Strategy I (Base case)	Strategy II	Strategy III	Strategy IV
Number needing sputum induction	1130	891	920	856
Number of induced sputum	1012	814	841	780
Number of TB cases detected	56	52	52	51
Number of TB cases with positive outcome (cured or treatment completed)	34	33	33	32
Total cost of the program (2011 USD)	83,559	70,142	71,901	67,408
Cost per TB case detected (2011 USD)	1,177	1,019	1,053	996
Cost per TB case with positive outcome (cured or treatment completed) (2011 USD)	2,458	2,126	2,179	2,107

Screening strategy for HIV infected individuals (all HIV negative patients with symptoms suggestive of TB are screened in each of the strategies)

Strategy I (Base case) Sputum induction in all individuals regardless of symptoms

Strategy II Sputum induction in all individuals with symptoms suggestive of TB according to the new WHO symptom screen

Strategy III Sputum induction in all individuals with CD4 counts ≤ 200 cells/µl or unknown CD4 counts regardless of symptoms and all individuals with CD4 counts > 200 cells/µl and symptoms suggestive of TB according to the new WHO symptoms screen

Strategy IV Sputum induction in all individuals with symptoms suggestive of TB according to the traditional WHO symptom screen

6.3.8 Sensitivity analysis

Sensitivity analyses were performed for different levels of staff salaries assuming the same effectiveness. Substituting the clinical nurse practitioner by a staff nurse would have reduced the cost per TB case diagnosed by 9.1% to USD 1,015 and the cost per TB case with positive treatment outcome by 10.9% to USD 2,190. Further reduction in costs would have been achieved if TB screening had been performed by a lay counsellor and follow-up of TB cases, supervision and program management was performed by a clinical nurse practitioner. The costs per TB case diagnosed would have been reduced to USD 705 (36.9%) and the cost per TB case with a positive treatment outcome to USD 1,681 (31.6%).

6.4 Discussion

This study showed a high uptake and yield of community-based active TB case finding. It highlighted the substantial losses between TB diagnosis, contacting the client, treatment initiation and treatment completion or cure. This study is unique in that it followed patients beyond the diagnosis of TB and ascertained treatment outcomes. Once a patient had started TB treatment, treatment success was more than 80%, which was as high as reported from clinics in the Western Cape [18]. Costs were USD 1,177 per TB case diagnosed and USD 2,458 per successfully treated TB case.

Cost-effectiveness is influenced by various parameters, among them the yield of screening. The yield depends on the local TB control program, the target population, screening algorithms, prevalence of HIV infection and severe immune-

suppression, the number of specimens obtained (induced or not induced) and the diagnostic tests employed. The service described in this study was accessed by a severely socio-economically deprived population as evidenced by high unemployment, low income and low levels of education. In addition few individuals had sought medical attention for their symptoms prior to accessing the service. It is well documented that TB patients and suspects present late to stationary health facilities, which contributes to delays in diagnosis, morbidity and mortality [19]. Whether active TB case finding reduces these delays and/or results in diagnosis of otherwise undiagnosed TB is currently unknown.

HIV prevalence and prevalence of severe immuno-suppression in this mobile HIV testing service was low compared to stationary services [9]. In addition half of the HIV positive individuals knew their status already and 40% of the known positives were on ART at the time of screening. This and the fact that only one sputum sample was examined explains the lower yield of screening in HIV infected individuals in this study compared to studies screening individuals at stationary HIV testing sites [8,20] and at time of ART eligibility screening [21,22,23].

A recent study from South Africa reported results from active TB case finding in women accessing antenatal care [24]. Despite the women being symptomatic only half of them were able to produce a spot sputum sample. Few other active case finding studies report the percentage of sputum samples obtained [25,26]. In Uganda 78% of individuals with chronic cough were able to produce a spot sputum [25]. Rates were near to 100% in a population-based TB prevalence survey in Zambia, where sputum production was assisted by simple breathing techniques

[26]. In our study 88% of HIV positive individuals with and without symptoms and 92% of HIV negative TB suspects were able to produce a sputum sample. While these results provide some evidence for the benefit of sputum induction, the additional yield and costs were not assessed.

The choice and number of diagnostic tests used for screening depends on availability, feasibility, yield and cost. We chose to investigate all samples by microscopy and culture as smear-negative/culture-positive individuals contribute to transmission [27,28]. The yield of culture was more than double compared to microscopy with an additional cost of USD 12 per sample. A pilot study in lay health care workers showed that two inductions were not acceptable due to time constraints and discomfort [29]. We therefore decided to investigate one and not two induced sputum samples. A second sputum sample would have increased the yield, but also the costs. A population-based active TB case finding study from Zimbabwe investigated two sputum samples with fluorescent microscopy only. The additional yield of the second sample was 17% using microscopy, but the additional yield of culture was not assessed [6].

TB diagnosis in this study was made on the bases of one positive sputum result. False positive results due to cross-contamination occur at a frequency of 2-5% in low TB incidence settings [30,31,32]. An estimated 2.4% (95%CI 0.3–8.8) of all positive TB cultures were found to be false positive in the laboratory used for this study [33]. Assuming a cross-contamination rate of 8.8% a total of 5 false positive diagnoses would have been made in this study. However, we asked all individuals we contacted face to face for a second confirmatory sputum sample. A total of 29

interpretable sputum results (non contaminated) were available. Of those 24 (82.8%) were culture positive for *Mycobacterium tuberculosis.* The remaining five patients were symptomatic and three of them had a cough for more than 2 weeks.

The success of active TB case finding to decrease transmission relies on treatment success of actively found cases. Treatment success in actively detected cases initiated on treatment was comparable with outcomes from passively detected cases reported from clinics in Cape Town [18]. However we were unable to contact six individuals (10.7%), two (3.5%) refused treatment and treatment initiation was unknown for six. These results are similar to results from a population-based sero-prevalence survey in Cape Town reporting that seven (26%) of 27 individuals with culture-positive TB did not initiate treatment [34]. The same study showed that those who did start treatment had similar treatment success rates as passively detected TB cases (80%). Defaulters prior to treatment initiation are not reported as part of the routine TB outcome reporting, but rates of initial defaulting of 17-21% have been reported from stationary health care clinics in South Africa using passive case finding [35,36,37,38]. More recently a study from Cape Town reported initial defaulting rates of smear-negative/culture-positive TB cases as high as 39% [39]

Treatment outcomes might be even more important than the yield of screening. A new rapid diagnostic, the Xpert MTB/Rif with an overall sensitivity of 90% in TB suspects reduced the time to start treatment from 56 to 5 days and dropout rates from 39% to 15% in smear-negative, culture-positive cases in a primary health care clinic in Cape Town [39,40]. The reduction in diagnostic delay is particularly

important in mobile services, where contact success is higher the less time has passed since the person was seen. Contact success was higher in individuals with smear-positive disease, because results were available within 1-2 days, compared to individuals with smear-negative/culture-positive disease. Relatively more resources and time were spent to contact individuals with smear-negative/culture-positive disease, as patients' mobile phones stopped working or were lost, stolen or passed on and individuals had moved to different locations in the meantime.

To our knowledge this is the first study assessing cost of community-based active TB case finding using a mobile screening unit. Three studies investigated the costs of active TB case finding in HIV infected individuals only; either as part of isoniazid preventive treatment programs [41,42] or at the time of ART eligibility assessment [23]. All studies were performed at stationary HIV testing sites or clinics. The prevalence of undiagnosed TB in these studies was 19-26% [23,42] and thus the inflation-adjusted cost per TB case diagnosed was more than three times lower (USD 318-358) compared to our screening program. None of these studies assessed treatment outcomes.

This study has several strengths and limitations. The study was conducted as part of a routine service and provides an opportunity to understand the challenges faced by mobile services. Mobile services operate under time, space and weather constraints. As a result a considerable number of individuals were not referred or did not want to wait for TB screening. Furthermore the population accessing a mobile service is healthier, less health care seeking and more mobile than

individuals accessing stationary services, resulting in reduced yield, contact and treatment initiation rates.

Cost was assessed using an incremental approach. The results will inform policy makers when considering adding active TB case finding to existing mobile HIV testing services. Different screening strategies were assessed, showing that symptom screening in HIV positives prior to sputum induction was more cost-effective than screening all HIV positive individuals regardless of symptoms. HIV prevalence is lower in mobile services [9,43,44] compared to stationary services and therefore a more pragmatic approach to TB symptom screening might be indicated. For the sake of simplicity the use of a universal symptom screening algorithm for both HIV negative and positive individuals should be considered. The potential secondary benefit of the program with regards to numbers of TB cases prevented was not taken into account in this analysis. Active TB case finding is likely to have some effect on transmission. Thus taking transmission into account would have increased the cost-effectiveness of the programme.

This study was conducted at a single site and therefore the findings can only be generalised to similar settings with comparable levels of deprivation. TB diagnosis could not be established in 16% of individuals as a result of high contamination and single sputum investigation. The contamination rate was high probably due to population characteristics (poor mouth hygiene) or environmental factors (variable temperature, wind and dust). Previous studies conducted in the same laboratory reported considerable lower contamination rates [22,45,46].

A recent study from Kenya concluded that the highest impact would be achieved when population-based active TB case finding was combined with universal HIV testing and improved diagnosis of smear-negative TB [47]. Our active TB case finding program provided integrated TB and HIV services combined with improved TB diagnostics. The population-based TB case finding study from Zimbabwe provided valuable evidence that active TB case finding can have a positive impact on TB control [6]. Our study serves as an example of a TB screening program integrating HIV and TB services with high uptake, yield and treatment success and relatively low costs.

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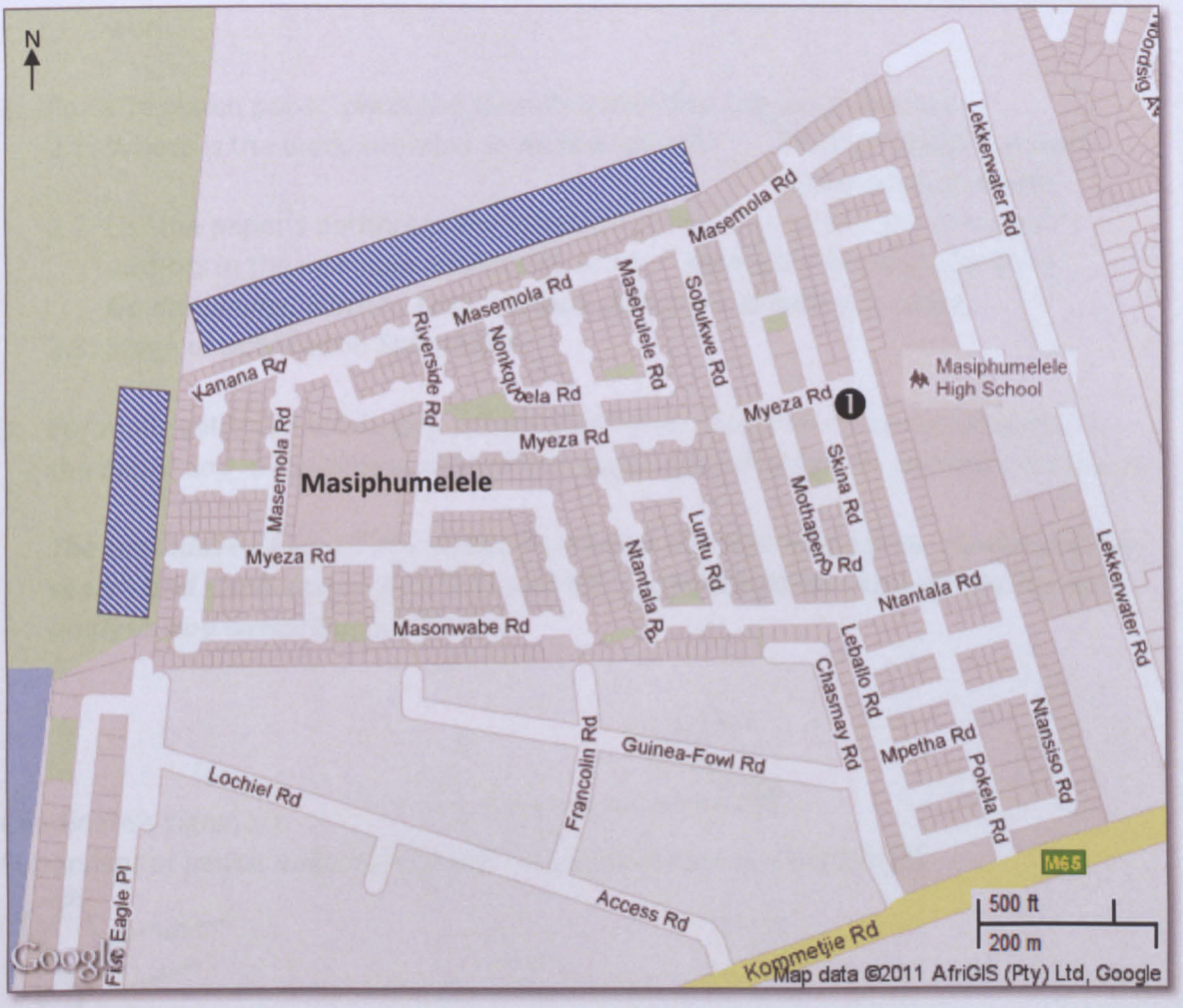
Part II: Antiretroviral therapy

7 Study question part II

This thesis aimed to investigate losses along the HIV care pathway first by conducting a literature review, second by describing losses along the HIV care pathway in a peri-urban settlement in the greater area of Cape Town (Figure 7.1), estimate ART coverage and investigate the association between ART coverage and TB risk in a cohort of HIV infected individuals receiving ART.

Figure 7.1: Map of the study community, Masiphumelele



❶ denotes the location of the clinic.
The shaded blue areas show the locations of the informal settlements/squatter camps outside the boundaries of Masiphumelele.

8 Literature review: losses along the HIV care pathway

Quantifying losses from the care pathway for people living with HIV infection in sub-Saharan Africa: a systematic review

1. For a 'research paper' already published
   1.1. Where was the work published?
   1.2. When was the work published?
      1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
   1.3. Was the work subject to academic peer review?
   1.4. Have you retained the copyright for the work?
      If yes, attach evidence of retention
      If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

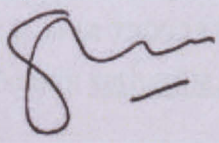
2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published? ***Tropical Medicine and International Health***
   2.2. List the paper's authors in the intended authorship order? List the paper's authors in the intended authorship order ***Katharina Kranzer, Darshini Govindasamy, Nathan Ford, Victoria Johnston, Stephen D. Lawn***
   2.3. Stage of publication ***Submitted***

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, developed the search strategy, conducted the search and screening of abstracts and titles, performed the data extraction and analysis and wrote the publication.

Candidate's signature 

Supervisor or senior author's signature to confirm role as stated in (3)



Dr. Stephen D. Lawn
Supervisor and Senior Author

Quantifying losses from the care pathway for people living with HIV infection in sub-Saharan Africa: a systematic review

Running head: Losses to HIV care in Africa

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World Count: Abstract = 195; Text = 3814; Tables = 7; Figures = 2; References = 139

8.1 Abstract

Scale-up of antiretroviral treatment (ART) has transformed the prognosis of people with HIV infection in sub-Saharan Africa. However, due to low HIV test uptake and losses at each step along the HIV care pathway, including assessment of ART eligibility, engagement in pre-ART care, initiation of ART and long-term retention on treatment, only a minority of the individuals in need ever receive the appropriate long-term care. This article describes this continuum of HIV care, quantifies losses along the pathway using systematic review and meta-analyses of published data and addresses possible interventions. Only 39% of HIV-infected individuals are estimated to know their sero-status. Of these, just 57% complete assessment of ART eligibility of whom approximately 50% require treatment at that time-point. Of those not yet eligible, only 45% remain in pre-ART care. Of those who are eligible, just 66% start ART and 65% remain on therapy after 3 years. These data highlight the huge losses occurring throughout the care pathway, especially prior to ART initiation. Data regarding interventions to address this issue are scarce, however. Research is urgently needed to identify effective solutions so that a far greater proportion of infected individuals can benefit from long-term ART.

Key words: HIV, Linkage to care, ART, sub-Saharan Africa, Retention in care, HIV testing, pre-ART

8.2 Introduction

The success of antiretroviral therapy (ART) roll-out in sub-Saharan Africa has been remarkable. Between 2004 and the end of 2009, almost 4 million people had initiated ART, leading to dramatic reductions in HIV-associated morbidity and mortality [1-5]. However, due to low HIV test uptake and losses along the pathway between HIV testing and ART treatment [6], only a minority of individuals in need of ART are estimated to ever start treatment [7]. This is further compounded by substantial additional losses that occur during long-term treatment [8, 9].

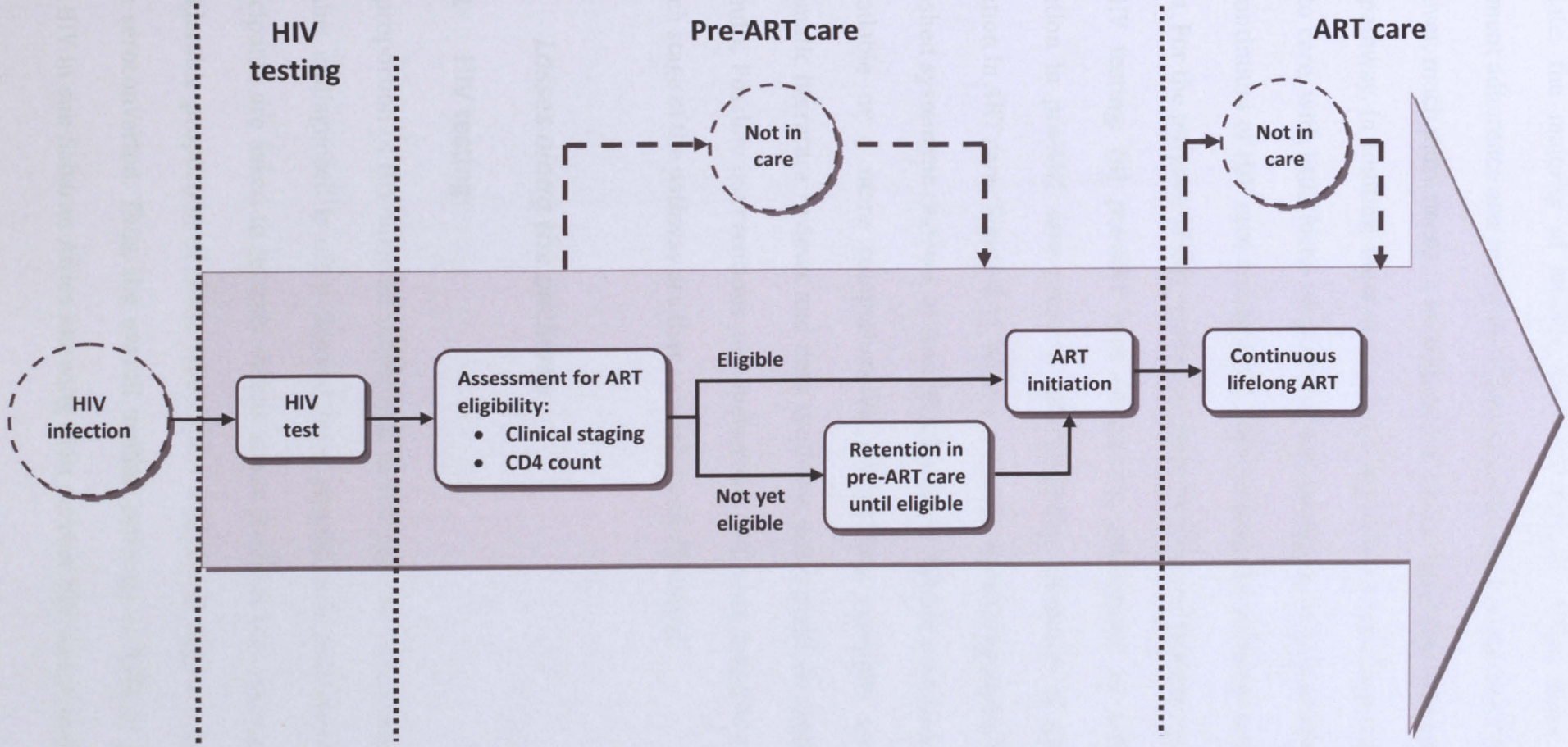
The essential steps in the HIV care pathway are HIV testing, assessment of eligibility for ART, pre-ART care, initiation of ART and long-term retention on ART. The importance of linkage and engagement in care has received considerable attention in high-income countries [10-12] where successes have resulted in improved health outcomes for the patient [13, 14] and reduced costs for the health care system [15]. Characterization of losses along the care pathway in high-income countries [15-17] have informed the development of potential interventions [11]. However, the scale of the challenge is so much greater in sub-Saharan Africa where millions of patients are in need of life-long treatment and health care systems are less well developed. It is unclear if interventions developed in high-income countries will be feasible in this resource-constrained setting.

In the majority of sub-Saharan African countries large scale ART roll-out commenced from 2004 as treatment became affordable and major donor funding mechanisms were established [18]. Rapid implementation of vertically driven

programmes was successful in providing life saving treatment for large numbers of patients in need. However, this success was achieved with insufficient attention being given to the establishment of the necessary linkages and integration of HIV care within the broader health system. These are essential for the establishment of an effective continuum of care both before and during ART.

Engagement in HIV care starts when an individual first tests positive for HIV (Figure 8.1). This should be followed by assessment for ART eligibility, which requires World Health Organization (WHO) clinical staging and/or CD4 count testing. CD4 count testing is a two-stage process, which requires that a patient's blood sample is obtained and sent for processing and then the patient has to return to receive this result (typically 1-2 weeks later). Patients who meet the national criteria for initiation of ART should commence ART without undue delay whereas patients not yet eligible should be retained in pre-ART care and undergo regular CD4 count monitoring until the eligibility threshold is reached. Once patients initiate ART, they should remain on uninterrupted treatment for life. Losses occur at different steps along this pathway, and may be temporary or permanent. The care pathway is not a simple linear process and the dynamic nature of linkage, retention, loss and re-engagement in care, especially in the pre-ART stage, makes this a challenging pathway to assess.

Figure 8.1: The HIV care pathway



Boxes within the grey arrow show the steps in the pathway of HIV care: HIV testing, assessment for ART eligibility, ART initiation, retention in pre-ART care until eligible, continuous lifelong ART. The dotted line and circle outside the grey arrow show the process of defaulting and re-engaging in care.

To date, the majority of studies from sub-Saharan Africa have focused on treatment adherence and retention of patients who have started ART [8, 9, 19-22]. However, much more needs to be understood about the earlier components of the care pathway. In addition, most studies have reported on rates and risk factors for loss to care, with little focus on potential interventions. In this article we review the continuum of HIV care and quantify losses along the pathway in sub-Saharan Africa. For the purpose of this review, we have divided the HIV care pathway into: (i) HIV testing; (ii) pre-ART care comprising assessment of ART eligibility, retention in pre-ART care prior to ART eligibility, initiation of ART; and (iii) retention in ART care (Figure 8.1). Where available, we used synthesized data from published systematic reviews, or from WHO reports. Where such data were either unavailable or a more comprehensive review was possible, we conducted systematic literature reviews and data synthesis using methods described in the appendix. Possible interventions and operational solutions aimed to reduce losses at each stage of the pathway are then reviewed and discussed.

8.3 Losses along the pathway

8.3.1 HIV testing

The proportion of HIV-infected individuals in sub-Saharan Africa whose infection remains undiagnosed is often derived from population-based surveys in which participants are asked to provide details about previous HIV testing. However, a considerable proportion of those who report a previous negative test may have since seroconverted. Thus, the overall median estimate of 39% of people living with HIV in sub-Saharan Africa knowing their correct HIV status may be an over-

estimate [7]. This is suggested by some country-level studies. For example, the Kenya AIDS Indicator Survey linked HIV test results to perceived HIV status [99]. This revealed that among HIV-positive individuals, 56% reported they did not know their status, 28% mistakenly thought they were HIV-negative and only 16% actually knew their HIV-positive status [23]. Similarly, in a peri-urban South African community with high HIV prevalence, the prevalence of previously undiagnosed HIV was 46% despite the coverage of HIV testing being extremely high (71%) [24].

This huge reservoir of undiagnosed HIV in sub-Saharan Africa drives high rates of HIV-associated morbidity, mortality and HIV transmission and has devastating consequences for individuals and communities. Many patients either die without a diagnosis being made or the diagnosis is only established once patients have presented to the health facility with advanced symptomatic disease. The proportion of undiagnosed HIV in a given population depends on the nature of the epidemic (generalized or concentrated), HIV incidence, HIV test uptake and frequency of testing (Table 8.1). In countries with concentrated epidemics, targeted testing of high risk groups may be the most efficient strategy. Conversely, in countries with generalized epidemics and high HIV incidence, universal and frequently repeated HIV testing is likely to be the only strategy to reduce the huge burden of undiagnosed HIV [25].

Table 8.1: Data from population-based surveys (source: World Health Organization, Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector Progress Report 2010)

Country	Year	Percentage of people who had an HIV test within the last 12 months		Percentage of people who ever had an HIV test		Percentage of people living with HIV who ever had an HIV test			Adult HIV prevalence
		Women	Men	Women	Men	Women	Men	Total	
Congo	2009	6.5	7.1	22.5	17.7	35.2	21.1	30.9	3.4 (3.1-3.8)
Democratic Republic of Congo	2007	4.1	3.8	8.6	9.2	8.7	-	10.7	1.3 (1.2-1.5)
Kenya	2009	29.3	22.8	56.5	40.4	73.5	58.6	68.9	6.3 (5.8-6.5)
Sierra Leone	2008	4.1	3.4	9.4	7.0	20.2	-	19.8	1.6 (1.4-2.1)
Swaziland	2007	21.9	8.9	35.8	17.1	44.0	28.8	38.7	25.8 (24.9-36.9)
United Republic of Tanzania	2008	19.1	18.9	37.2	26.5	43.7	30.8	39.0	5.8 (5.4-6.2)
Zambia	2007	18.5	11.7	35.3	19.8	45.4	28.3	38.4	13.7 (13.1-14.4)

8.4 Pre-ART care

8.4.1 Assessment of ART eligibility

For individuals who test positive for HIV infection, the next key step in the care pathway is assessment of ART eligibility – a process that might be regarded as indicative of initial linkage to care. We conducted a systematic literature review and meta-analysis of studies in which the losses occurring at this step in the pathway were quantified (methods described in Web Appendix 8.9). Of the 22 published studies we identified as eligible for inclusion (Table 8.2), the majority were conducted in South Africa (n=9) with the remainder from Ethiopia (n=2), Kenya (n=2), Malawi (n=2), Mozambique (n=1), Rwanda (n=1), Tanzania (n=1)

and Uganda (n=4). Eleven studies reported the proportions of patients enrolling into care post-diagnosis. Two studies were excluded because they were unrepresentative of the general population accessing clinics and hospitals; one was conducted in a mobile clinic [26] and another reported linkage to care in female sex workers in Rwanda [27].

The proportion of patients assessed for ART eligibility (reflecting linkage to care) ranged from 42% (95%CI 39-46%) to 70% (95%CI 68-72%), with an overall pooled estimate of 57% (95%CI 48-66%; τ^2 154.8). In 8 of the 11 studies, ART eligibility was assessed by CD4 cell count measurement and the proportions of patients in which this was successfully performed ranged from 55% (95%CI 51-60%) to 86% (95%CI 77-94%) with a pooled proportion of 66% (95%CI 54-78%; τ^2 309.9). However, only 5 of these studies reported the number of patients who returned for their test result, with proportions ranging from 30% (95%CI 26-34%) to 88% (95%CI 87-89%) and a pooled estimate of 51% (95%CI 25-78%; τ^2 924.8). This pooled estimate is similar to the finding of an earlier systematic review in which a median proportion of 59% completed ART eligibility assessment [6].

7.4.2 Proportion of individuals eligible for ART

We next assessed the proportions of individuals with newly diagnosed HIV infection who were assessed and found to be eligible for ART according to national ART guidelines currently in use at the time of the study. We identified 16 studies eligible for inclusion (Table 8.3) of which seven were from South Africa. Ten studies reported on the proportions of patients who were eligible for ART based

on a CD4 count threshold of ≤200 cells/μl, but two were excluded for reasons of non-generalizability [27, 28]. The proportion found to be eligible at this CD4 count threshold ranged from 21% (95%CI 20-22%) to 59% (95%CI 59-60%) with a pooled proportion of 40% (95%CI 27-55%; τ^2 392.6). Six studies also reported on the proportions eligible using a CD4 count threshold of ≤350 cells/μl, with proportions ranging from 45% (95%CI 44-47%) to 62% (95%CI 61-63%) and a pooled estimate of 57% (95%CI 50-63; τ^2 50.5). Six studies reported on the proportions of patients who were eligible for ART based on clinical criteria (WHO clinical stage 3 and 4). Proportions ranged from 49% (95%CI 48-51%) to 87% (95%CI 84-89%) with a pooled proportion of 64% (95%CI 53-74%; τ^2 166.4).

8.4.3 Pre-ART care prior to ART eligibility

We identified only 5 studies reporting on retention in care of individuals not yet eligible for ART; four of these were from South Africa (Table 8.4). The duration of pre-ART care assessed was highly variable between these studies [29-32]. No study reported the fundamentally more important variable which is the proportion retained in care on becoming eligible for ART. Retention in pre-ART care in South Africa ranged from 41% to 46% [29-32]. The remaining study from Malawi estimated retention in pre-ART care to be 59% [33]. The median proportion retained in pre-ART care was 45%. As few studies were identified, all with considerable heterogeneity regarding time-cut offs, a pooled estimate was not calculated. Two of the five studies did not specify any time-cut off [29, 33], while the other three studies assessed repeat CD4 count measurements or visits 6-12 months after the initial eligibility assessment [30-32].

Mathematical modeling suggests that retention in pre-ART care for individuals not yet eligible for ART increases the average life years saved [34]. This finding is supported by the South African study from the Free State showing that individuals who presented with an initial CD4 count >200 cell/uL and remained in pre-ART care had a two times reduced risk of mortality compared to individuals presenting with an initial CD4 count <200 cells/μl [31].

8.4.4 Initiation of ART

We identified 19 studies which reported the proportions of ART-eligible individuals who went on to start ART (Table 8.5). We term this step in the continuum of care as 'linkage to ART'. Ten studies in seven sites were conducted in South Africa with the remainder conducted in Kenya (n=1), Malawi (n=4), Mozambique (n=1), Swaziland (n=1) and Uganda (n=2). One study reported that amongst TB co-infected patients, linkage to ART was 14% (95%CI 12-17%) [35]. These patients have a very high mortality risk therefore this study was considered non-representative and was excluded from the meta-analysis. In the remaining 18 studies, the proportion linking to ART ranged from 31% (95%CI 29-33%) to 86% (95%CI 83-89%), with an overall pooled proportion of 66% (95%CI 58-73%; τ^2 264.2). An earlier review of 14 studies found the median proportion of individuals initiating ART was 68% [6]. Eight of the studies included in our meta-analysis did not specify the time period within which patients could link to ART care. However, in a subgroup analysis there was no difference in the proportion linking to ART care comparing studies that used a time cut-off for determining linkage with those that did not (p=0.24). Studies which reported on time between HIV testing or

staging, and initiation of ART showed that the majority of patients started treatment within 1 month; however, two studies reported median delays of between 2.4 and 6.6 months [36, 37].

Eight studies assessed the contribution of mortality as a potential cause for not starting ART and reported a median mortality of 5.5% (IQR 4.5-12%) among eligible patients waiting to start treatment [19, 31, 36, 38-41]. However, in these studies, it is difficult to ascertain whether death is the cause or the result of not starting ART. Using assessment of clinic records or databases some studies have traced individuals who were thought to have not started ART [39, 41]; between 3% and 19% of such patients were either retained in care in the same clinical service or had accessed treatment elsewhere.

Estimates of individuals successfully linking to ART should ultimately inform health care providers how to address gaps and leaks in the system. For that reason, neither death due to late presentation nor informal transfers to other clinics should be part of the defaulter estimates.

Table 8.2: Proportions of patients with newly diagnosed HIV infection who complete assessment of eligibility for antiretroviral therapy (ART)

Author	Country	Setting	Year of the study	N	Enrolled into HIV care as a prerequisite of accessing CD4 counts (time cut-off)	Blood sample for CD4 count provided (time cut-off)	Returned for CD4 results (time cut-off)	Enrolled in HIV care (time cut-off)
Assefa[105]	Ethiopia	Public sector sites	2008	1314				47% (immediately after testing)
Assefa[105]	Ethiopia	Mobile HIV testing service for high risk individuals	2008	2035				26% (2 months)
Mulissa[106]	Ethiopia	Urban, Hospital	2003-08	2191				70% (no time cut-off, but 49% enrolled the same day)
Amolloh[107]	Kenya	Asembo, Home based testing service	2008-09	737				42% (2-4 months)
Waxman[108]	Kenya	Eldoret, Emergency department, hospital	2006	61		87% (no time cut-off)		
Gareta[109]	Malawi	Lilongwe, hospital, pregnant women	2006-08	478				55% (no time cut-off)
Tayler Smith[110]	Malawi	Thylo, district hospital, patients with clinical stage I or II	2008-09	1428			45% (at least 1 months follow-up)	
Micek[37]	Mozambique	Urban, HIV testing services	2004-05	7005	57% (within 30 days)	77% (within 30 days)		
Braunstein [27]	Rwanda	Kigali, female sex workers	2007-08	141				85% (no time cut off)

Continued...

Continued: Table 8.2: Proportions of patients with newly diagnosed HIV infection who complete assessment of eligibility for antiretroviral therapy (ART)

Author	Country	Setting	Year of the study	N	Enrolled into HIV care as a prerequisite of accessing CD4 counts	Blood sample for CD4 count provided	Returned for CD4 results	Enrolled in HIV care
April[111]	SA	Cape Town, hospital, primary care clinic	2006	375		62% (within 6 months)		
Kranzer[29]	SA	Cape Town, hospital, primary care clinic	2004-09	988		63% (within 6 months)		
Larson[112]	SA	Johannesburg, hospital, clinic	2008-09	416		85% (within 12 weeks)	35% (within 12 weeks)	
Losina[113]	SA	Durban, semi-private hospital	2006-07	454		55% (within 8 weeks)	85% (within 8 weeks)	
Naidoo[114]	SA	Johannesburg, clinic		225			47% (within 1 week)	
Govindasamy [26]	SA	Cape Town, mobile HIV testing service	2008-09	192			73% (no time cut off)	42% (no time cut off) of those who received their CD4 result
Bassett[36]	SA	Durban, semi-private hospital	2006-08	1474		69% (within 90 days)		
Ingle[31]	SA	Free State, public sector clinics	2004-07	44844		74% (no time cut-off)		
Luseno[115]	SA	Community based trial		199				46% (no time cut off)
Nsigaye[77]	Tanzania	Clinic	2005-08	349				68% (no time cut-off)
Amuron[41]	Uganda	Jinja, clinic	2004-06	2483			88% (no time cut-off)	
Wanyenze [116]	Uganda	Kampala, hospital	2004-05	142				56% (within 6 months)
Nakigozi[117]	Uganda	Rakai community cohort study		1145				69% (6 months)
Wanyenze [118]	Uganda	Kampala, hospital	2004	211				48% (3 months), 57% (6 months)

Table 8.3: Proportions of individuals with new HIV diagnoses who are eligible for antiretroviral therapy (ART)

Author	Time	Country	Site	N	CD4 <200	CD4 <350	Stage 3	Stage 4	Eligible	Eligibility criteria
Mulissa[106]	2003-08	Ethiopia	Clinic	2191			49%	13.3%		
Mcgrath[38]	2005-6	Malawi	Hospital	730					87%	stage 3 or 4
Micek[37]	2004-05	Mozambique	Clinic	3046					49%	CD4<200/stage 4/CD4 200-350 and stage 3/pregnant
Nakanjako[119]	2004	Nigeria	Emergency department	111			49%	22.0%		
Braunstein[27]	2006-07	Rwanda	FSW	192	11%	43%				
Kranzer[29]	2004-09	SA	Primary care clinic, hospital	112	34%	60%				
van Schaik[28]	2008-09	SA	Mobile clinic	65	11%	25%				
Basset[36]	2006-08	SA	Semi-private hospital	1012	53%					
Ingle[31]	2004-07	SA	Public clinics, hospitals	33182	57% (04)[1] 54% (05/6) 67% (07)					
Lessels[30]	2007	SA	Clinic	7655	41%	62%				
Losina[113]	2006-07	SA	Semi-private hospital	248	53%					
April[111]	2006	SA	Primary care clinic, hospital	375	31%		31%			
Nunu[120]	2009	Swaziland	Hospital	637					57%	Not stated
Konde-Lule[121]		Uganda	Public clinics, hospitals	203	36%	57%				
Amuron[41]	2004-06	Uganda	Clinic	4321					58%	CD4<200 or WHO stage 4
Carter[122]	2003-08	Multisite	ANC, post pregnancy	6036	21%	45%	10%	1%		

[1]Proportions were calculated on the bases of calendar years

Table 8.4: Retention in care of individuals not yet eligible for antiretroviral therapy (ART)

Author	Country	Setting	Year of the study	N	Retention in pre-ART care (time cut off)	Assessment of pre-ART retention	Comment
Lessells[30]	SA	Rural Kwazulu Natal, public sector clinics	2007	4223	45% (13 months)	repeat CD4 count	
Ingle[31]	SA	Free State, public sector clinics	2004-07	11039	42% (6 months)	Visits	12% died, 46% loss to follow-up
Larson[32]	SA	Johannesburg, hospital, clinic	2007-08	356	CD4 200-350: 6% within 4 months, 41% within 1 year CD4 350+: 15% within 9 months, 26% within 1 year		
Kranzer[29]	SA	Cape Town, hospital, primary care clinic	2004-09	419	46% (no time cut-off)	repeat CD4 count	
McGuire[33]	Malawi	Rural Malawi, district hospital, clinics	2004-07	5685	59% (no time cut-off)		3% known dead, 6% transferred out, 31% loss to follow-up (a sample of the patients lost to follow-up were traced: 26% were alive, 35% were dead, 10% moved, 29% were not found)

Table 8.5: Proportions of HIV-infected individuals assessed as eligible for antiretroviral therapy (ART) who start treatment

Author	Country	Setting	Year of the study	N	Linkage to ART care for those eligible (time cut off)	Median (mean) time to ART initiation	Comment
Karcher[19]	Kenya	Nyanza, district hospital	2004-05	159	78% (no time cut-off)		3% died, 13% denied treatment
Tayler-Smith [123]	Kenya	Kibera slum, clinics	2005-08	2471	82% (1 month)		
Tayler-Smith [110]	Malawi	Thyolo, district hospital, patients with WHO stage 1/2 and CD4<250 cells/μl	2008-09	681	64% (6 months)	33 days (21-44)	
Gareta[109]	Malawi	Lilongwe, hospital, pregnant women	2006-08	222	69% (4 weeks)		
Zachariah [35]	Malawi	Thyolo, district hospital, TB patients	2003-04	742	14% (no time cut-off)		
Mcgrath [38]	Malawi	Karonga rural, district hospital	2005-06	659	86% (no time cut off)	22 days (13-27)	5% died, 0.5% had moved, 3% alive not taking ART, 5% untraceable
Micek[37]	Mozambique	Urban, HIV testing services	2004-05	1506	31% (90 days)	71 days	
Kranzer[29]	SA	Cape Town, hospital, primary care clinic	2004-09	219	67% (within 6 months)		
Ingle[31]	SA	Free State, public sector clinics, eligible at first CD4 measurement	2004-07	19089	59% (no time cut off)	95 days (53-170)	25% died, 3% in care, 13% not in care
Ingle[31]	SA	Free State, public sector clinics, eligible at subsequent CD4 measurement	2004-07	2994	58% (no time cut off)		13% died, 19% in care, 9% not in care

Continued...

Continued: Table 8.5: Proportions of HIV-infected individuals assessed as eligible for antiretroviral therapy (ART) who start treatment

Author	Country	Setting	Year of the study	N	Linkage to ART care for those eligible	Median (mean) time to ART initiation	Comment
April[111]	SA	Cape Town, hospital, primary care clinic	2006	72	68% (no time cut off)		
Bassett[39]	SA	Durban, semi-private hospital	2006	501	81% (3 months)		6% died, 3% accessed a different service, 0.6% moved away, 0.6% promised to return, 7% were untraceable
Bassett[36]	SA	Durban, semi-private hospital	2006-08	538	39% (12 months)	6.6 months	17% died
Kaplan[124]	SA	Cape Town, primary care clinic, women	2002-07	2131	81% (no time cut off)		4% died, 7% loss to follow-up
Lawn[40]	SA	Cape Town, primary care clinic	2002-05	1235	75% (no time cut off)	34 days (28-50)	5% died, 9% preparing for ART, 11% loss to follow-up
Feucht[125]	SA	Pretoria, hospital, children	2004	243	40% (no time cut off)		
Geng[126]	SA	Mbarara, clinic	2009-10	697	58% (3 months)		
Nunu[120]	Swaziland	Hospital	2009	363	58% (on the assigned date)		
Amuron [41]	Uganda	Jinja, clinic	2004-06	2182	85% (no time cut off)	33 days (15-406)	Survival status was investigated for all losses between testing and treatment (included losses of patients not returning for their CD4 result): 7% died, 8% on ART with a different provider, 6% were alive and not on ART, 4% untraceable
Parkes[127]	Uganda	NGOs and governmental health units	2004-06	458	61% (3 months)		

8.5 ART care

Patients receiving ART may leave clinical care for three reasons: death, transfer of care to another service (transfer-out) and loss to follow-up. Losses during ART are much better documented than those occurring earlier in the care pathway. Early mortality is typically very high in programmes in sub-Saharan Africa [42], accounting for between 8% and 26% of patients in the first year of treatment [43]. Systematic reviews have estimated that death accounted for around 40% of patient attrition during the first 2-3 years of treatment [8 44]. Key risk factors for this include a low baseline CD4 counts and advanced WHO stage of disease [43] and thus interventions upstream in the care pathway are needed to prevent late presentation. Long-term mortality risk decreases substantially, [43, 45-47], especially once a CD4 cell count threshold of 200 cells/μl has been exceeded [48].

Early in the scale-up of ART in sub-Saharan Africa, treatment sites were few, patients were typically severely immunocompromised at the time of ART initiation, and prognosis was uncertain. Thus, transfer of patient care between ART clinics was relatively uncommon. However, over time the number of decentralized treatment sites has expanded considerably and patients are generally less immunocompromised when commencing ART; patient confidence in ART has grown; and, patients on long-term ART are usually healthy, potentially economically active and therefore mobile. These factors may explain why in some settings, rates of transfer between services have risen steeply [45, 49]. In a South African cohort, the probability of patients transferring out during the first 6 years of the programme was approximately 20%, with the risk progressively increasing

with each sequential calendar year of enrolment [45]. However, data on true outcomes of patients transferred from one program to another are scarce [50, 51]. If transfer of care is successful, then the patient is effectively retained within the national ART programme. Although, it is possible that some patients might be unsuccessful in linking to another service and hence are lost to follow-up.

A huge challenge to rapidly expanding ART programmes in sub-Saharan Africa is the issue of retaining patients within care (i.e. preventing losses to follow-up). Patients are usually classified as 'lost to follow-up' if they fail to attend follow-up appointments over a specified duration without having been actively transferred to another ART clinic, and if they are not known to have died. A systematic review of 39 ART cohorts in sub-Saharan Africa conducted in 2010 reported an average retention of 65% at 3 year [8]. In recent years, many ART cohorts have rapidly increased in size with disproportionate increases in the numbers of patients compared to the number of health care workers. Losses to follow-up have reportedly grown substantially over successive calendar periods, indicating a growing problem with long-term retention in care [45, 46, 52]. A study from South Africa reported that patients starting ART in 2007-2008 had more than 4 times increased risk of being lost to follow-up than patients initiated in 2002-2004 [45].

Defining a patient as 'lost to follow-up' is often based on exclusion of other known reasons for failure of the patient to attend. However, this may conceal considerable unascertained mortality. A systematic review summarizing studies that traced individuals lost to follow-up showed that on average 46% of such individuals had actually died [53]. A study from South Africa reported that 78.0% of such deaths

occurred within the first 3 months after their last clinic visit [52], strongly suggesting these deaths were the reason and not the result of being lost to follow-up.

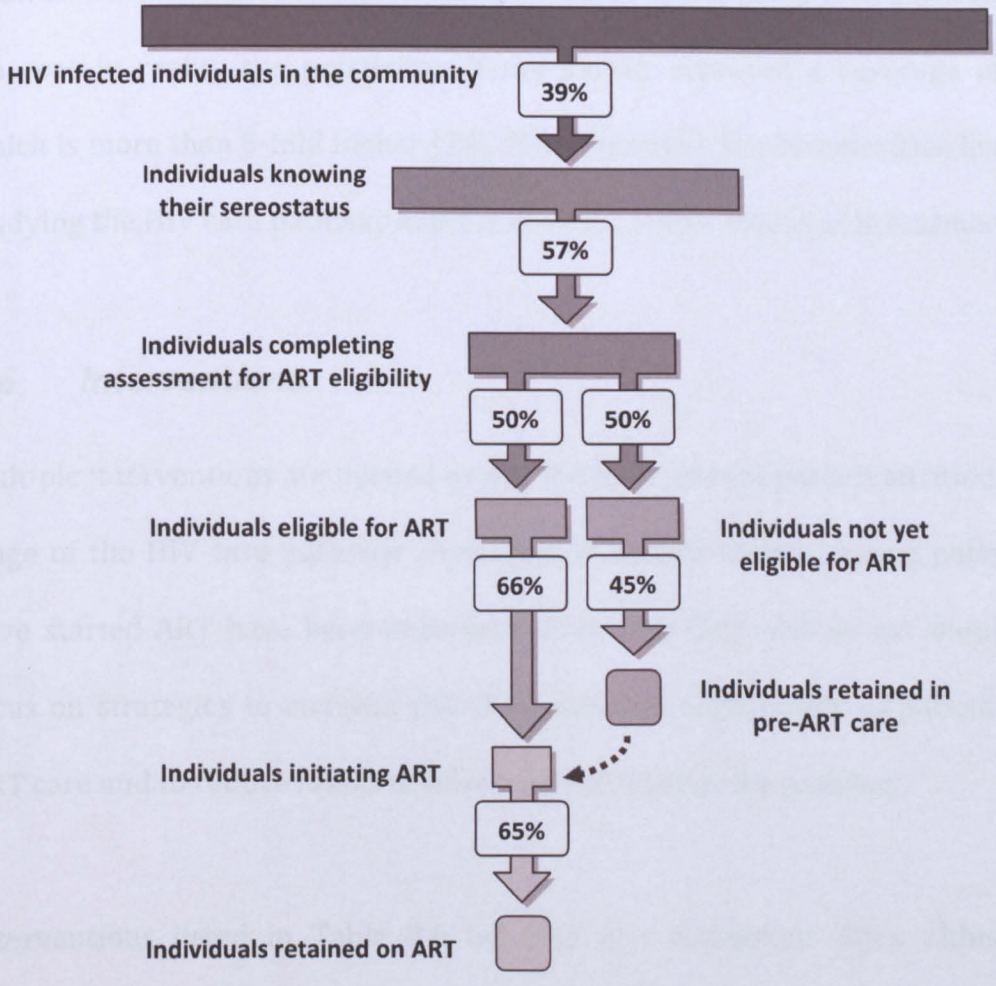
Another complexity in reporting rates of loss to follow-up is that patients may cycle in and out of care. Thus, patients who fulfil the widely used definition of loss to follow-up at one time point might re-engage with care at a later stage and thus cease to be lost to follow-up. A systematic review of this issue conducted in 2011 identified 9 studies from sub-Saharan Africa and found that an average of 12% of individuals on ART had previously interrupted but subsequently restarted treatment [54]. A study from a South African township reported 40% of defaulters resumed therapy within 3 years of defaulting [55].

8.5.1 Cumulative losses along the pathway

No study has yet measured the cumulative losses occurring along the entire care pathway. This would require long-term prospective demographic surveillance, although such a process in itself would likely alter the outcomes of interest. An alternative approach is to combine pooled estimates of losses from each of the steps in the care pathway that we have described. However, using data in this way from cross-sectional studies with typically short duration of follow-up is methodologically flawed [6]. A critical issue is that the care pathway is not a simple linear process and patients clearly cycle in and out of care; a patient who fails to complete one step in the pathway may re-engage with the treatment pathway at a later time-point and ultimately receive successful long-term ART. Thus, use of the individual estimates of the losses described thus far and summarized in Figure 8.2

might erroneously lead to the conclusion that of all HIV-infected individuals in the community, only 7% (0.39 x 0.57 x 0.50 x 0.66) would start ART and 5% (0.039 x 0.57 x 0.50 x 0.45) would be retained in pre-ART care for some duration.

Figure 8.2: Cumulative losses along the HIV care pathway as reported by cross-sectional studies addressing each step in the pathway.



The proportions (%) shown indicate the proportions of individuals who successfully complete each step in the pathway

The assertion that these are likely to be extreme underestimates of the true proportions receiving care is supported by detailed data from a well characterised high HIV prevalence community in South Africa. In a population-based HIV and CD4 count survey, 54% of all HIV-infected individuals knew their positive HIV

sero-status [24]. A study of this community from the same period also showed that 63% of HIV-infected individuals were assessed for ART eligibility by CD4 count measurement within 6 months of diagnosis, 26% were eligible for ART (CD4 count ≤200 cells/μl) and 66% started ART within 6 months of diagnosis [29]. Combining these estimates of losses along the HIV care pathway in this community would lead to an estimated ART coverage in the community of 6% (0.54 x 0.63 x 0.26 x 0.66), whereas in reality the population based survey reported a coverage of 33.5%, which is more than 5-fold higher [24]. This illustrates the complexities involved in studying the HIV care pathway and the need for better means of assessment.

8.6 Interventions

Multiple interventions are needed to address high rates of patient attrition at every stage of the HIV care pathway. Strategies to reduce deaths among patients who have started ART have been described elsewhere [56], and so we should rather focus on strategies to increase HIV diagnosis and engagement of patients in pre-ART care and to reduce losses to follow-up throughout the pathway.

Interventions listed in Table 8.6 fall into two categories. They either aim to increase the efficiency and capacity of services, or to improve the accessibility and acceptability of these services. Interventions to increase HIV testing include task-shifting (testing through lay health care workers) [57-59] and provider-initiated testing [60-62] as well as mobile, community, home-based and workplace services [63-68], which bring the service nearer to the patient and thus increases accessibility, which might in turn increase acceptability. Other interventions aimed

to increase acceptability of testing are self-testing [69] and incentivised testing [70, 71]. More recently, community-based strategies for HIV testing and ART delivery have been developed [64, 72, 73] as a way to further expand access to care. By virtue of being placed in the community, these strategies are decentralised and use task-shifting to engage lesser trained health staff, and thus might be more cost-effective [74].

Very few studies (n=4) have assessed interventions aimed at reducing losses in the pre-ART period. These have examined point of care CD4 count testing [75, 76], more efficient referral systems [77], transport vouchers [77] and regular visits to refill trimethoprim-sulphmethoxazole prophylaxis [78]. In contrast, many studies have reported on interventions to reduce loss to follow-up of patients on ART [79]. Some of these interventions are structural such as task shifting [80-84], decentralisation [57, 82, 84-87], integration [88, 89] and continuous drug supply [90, 91], whereas others are aimed at the individual such as adherence counselling [92, 93] and transport reimbursement [90, 94, 95].

Table 8.6: Interventions to increase HIV diagnosis and engagement of patients in pre-ART HIV care and to reduce losses to follow-up throughout the care pathway

Step	Targeting	Intervention/ operational solution	Evidence
HIV testing	*HIV testing capacity*	• Integration of HIV testing into other health care services • Testing by lay health care workers • Decentralisation of testing • Self-testing	• Observational studies [128, 129] • Observational studies [57-59] - • Feasibility study [69]
	Demand for HIV testing	• Targeted testing in high risk groups • Home-based and community-based testing, mobile services • Provider-initiated testing • Workplace testing • Incentivised testing • Self-testing	• Observational studies [130, 131] • RCT [63], observational studies [64-67, 73] • Observational studies[60-62] • RCT [68] • RCT [70, 71] • Feasibility study [69]
Pre-ART care	*Completion of staging and linkage to pre-ART and ART care*	• Point of Care CD4 count testing • Decentralisation • Integration into existing services/primary health care • Support tools (e.g. cell phone messages, patient held appointment cards) • Efficient referral service • Transport allowance	• Observational studies [75, 76] - - - • Observational study [77] • Observational study [77]
	Retention in pre-ART care prior to ART eligibility	• Adherence counselling • Regular visits (e.g. Cotrimoxazole prophylaxis) • Decentralisation • Integration into existing services/primary health care • Task shifting • Earlier initiation	- • Observational study [78] - - - - -

Continued...

Continued: Table 8.6: Interventions to increase HIV diagnosis and engagement of patients in pre-ART HIV care and to reduce losses to follow-up throughout the care pathway

Step	Targeting	Intervention/ operational solution	Evidence
ART care	*Increase retention*	• Home-delivered ART • Community ART • Targeted adherence counselling • Drugs with less toxicity, side effects and easier schedule • Task shifting • Decentralisation • Integration into existing services/primary health care • Support tools (cell phones, lay community adherence counsellors) • Continuous drug supply • Transport re-imbursement • Early initiation • Improved referral systems • Incentives such as nutritional support • Health information systems to allow patients to be tracked	• RCT [132] • Observational study [72, 133] • Observational studies [92, 93] • Some evidence from resource rich settings[234] • RCT[80], observational studies [81-84, 86, 93] • Observational study [57, 82, 84-87, 135, 136] • Feasibility study [88], RCT for PMTCT[89] • RCT [96], observational studies [137] • Observational studies [90, 91] • Qualitative studies [90, 94, 95] • Observational study[138] - - -
	Increase re-initiation for treatment interrupters	• Tracing of individuals loss to follow-up (home visits, cell phones) • Health information systems to allow patients to be tracked between services • Patient and community education	• Observational studies [97, 139] - - -

Few interventions have been assessed for their efficacy and cost-effectiveness in randomized controlled trials [63, 68, 71, 80, 96] and most observational studies have assessed feasibility rather than effectiveness [69, 88, 97]. Evidence for a positive effect of, for example, transport vouchers and secured drug supplies comes mainly from risk factor analysis and semi-qualitative studies [90, 91, 94, 95]. Some interventions have only been assessed for one specific step in the pathway, but not for others. An example is adherence counselling, which has been shown to have some effect on retention in ART care [92, 93], but the effect of counselling on retention in pre-ART care or on linkage to ART care has not been formally assessed. However, related interventions such as prevention of mother to child transmission (PMTCT) provide some rationale for this [98].

Integration of care has mainly concentrated on tuberculosis and PMTCT programs [89, 99] or the beneficial effects derived by other health services through the integration of HIV care [100]. The lack of a common conceptual framework on what integration means has impeded more rigorous evaluation of the impact of integration on retention and testing [101]. One study conducted in nine countries in sub-Saharan Africa, found that providing ART in an integrated approach resulted in substantially less defaulting from care compared to vertical ART delivery [102]. As HIV is chronic disease integration is important not only to improve retention, but also to provide comprehensive care (Table 8.7). This has been conceptualised in the WHO's Integrated Management of Adolescent and Adult Illness programme [103].

Table 8.7: Comprehensive HIV care

Prevention
Trimethoprim-sulphamethoxazole prophylaxis
Isoniazid preventive therapy
Intensified tuberculosis case finding
Cryptococcal antigen screening
Cervical cancer screening
Prevention of mother to child transmission
Prevention of transmission to sexual partners
Acute services
Tuberculosis
Mental health
Sexual transmitted diseases
Antenatal care
Family planning
Chronic services
Mental health
Chronic disease (e.g. diabetes, ophthalmological services etc)
Care of the elderly services
Social support

8.7 Conclusion

Substantial losses occur at every stage of the HIV care pathway for HIV-infected individuals in sub-Saharan Africa. Assessment of these losses is complex as engagement in care; loss to care furthermore, return to care is a dynamic, non-linear and time-dependent process. To date, no study has yet defined the cumulative losses throughout the pathway. Data regarding interventions to address these losses are scarce, especially with regard to the care pathway prior to ART initiation. Research is urgently needed to identify effective solutions so that a far greater proportion of HIV- infected individuals can gain the benefits of ART.

The "test and treat" approach to reducing HIV transmission proposes that very high coverage of HIV testing and immediate initiation of ART regardless of the stage of HIV progression would substantially reduce HIV transmission [104], and

has been met with considerable enthusiasm. The data in this review serve as a reminder of the huge operational challenges that will be faced in implementing such a strategy. Considerable investment and energy must be devoted to identifying effective interventions to strengthen the care pathway thereby permitting more effective implementation of current policy. As the care pathway is strengthened, then the 'test and treat' strategy will become a more viable strategy.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' Contributions

KK and SDL were responsible for the outline of the paper. KK and DG conducted the literature searches and data extraction. The meta-analysis was performed by NF and KK. KK and SDL wrote the paper with input from DG, NF, VJ. All authors contributed to, read and approved the final paper.

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8.9 Web Appendix: Methods

8.9.1 Search strategy and data abstracts

We aimed to identify studies reporting retention between HIV testing and initiation of ART and during long-term ART in sub-Saharan Africa. We searched three electronic databases for primary studies: Medline, Embase, and Global Health using the compound search strategy summarized in Supplement Table 8.8, and searched the bibliographies of retrieved articles for additional studies. Our search was limited to studies conducted in sub-Saharan African published from 2000 until the end of the search period (June 2011). We additionally searched for conference abstracts from all conferences of the International AIDS Society (2000–2010), and all Conference on Retroviruses and Opportunistic Infections (2000–2010). No language restriction was applied.

Studies were entered into an electronic database (EndNote X1) to screen potentially eligible studies by title and abstract. The full-length articles of all studies considered eligible upon initial screening were obtained and reviewed for eligibility; conference abstracts were screened first by title, then by full abstract. All reviews were done independently, in duplicate (GD and KK). Using a standard data extraction form, GD and KK extracted relevant data, including study site, sample size, dates of data collection, study design and outcomes and time cut-offs for outcomes. The results of the search are presented in Supplement Figure 8.3.

8.9.2 Data analysis

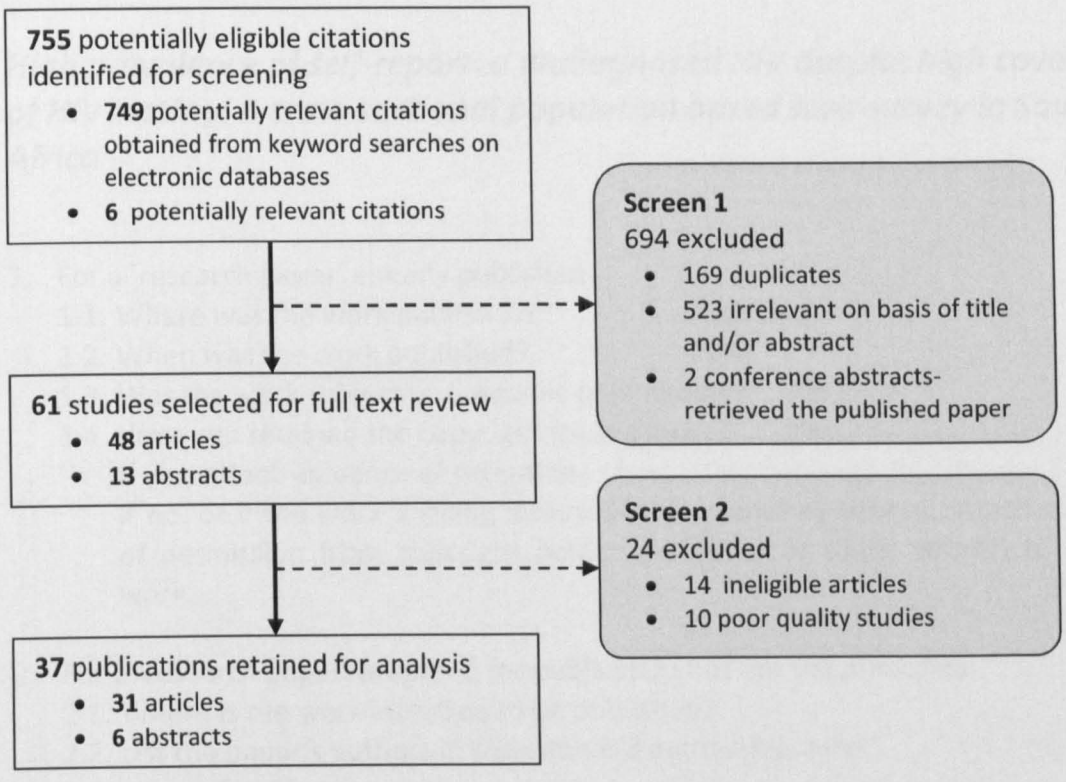
We calculated point estimates and 95% confidence intervals for the proportion of patients linking to care at various stages of the care pathway. The variance of the raw proportions was stabilised using a Freeman-Tukey type arcsine square-root transformation and estimates were pooled using a DerSimonian-Laird random effects model. We calculated the τ^2 statistic to assess between-study heterogeneity as this is less affected by the number of studies than the more commonly used I^2 statistic. For the overall proportion of patients linking to care, we ran a subgroup analysis to compare studies that used a time cut-off for determining linkage with those that did not. All P-values were two-sided, and a p-value of <0.05 was considered significant. Analyses were conducted using Stata (version 11, www.stata.com) and StatsDirect (version 2.5.2).

Supplement Table 8.8: Search strategy

SET	
	HIV
1	Hiv
2	Aids
3	HIV
4	HIV-1
5	ACQUIRED IMMUNODEFICIENCY SYNDROME
6	Set 1-5 were combined with "or"
	Retention
7	PATIENT DROPOUTS
8	LONG TERM CARE
9	CONTINUITY OF PATIENT CARE
10	patient dropouts
11	long term care
12	loss to follow-up
13	retention in care
14	attrition or defaulting
15	pre-art or (pre adj1 treatment) or (art adj1 initiation)
16	screening for art
17	art eligibility
18	eligible for art
19	eligibility for art
20	eligible for arv
21	art-eligible
22	Engaging
23	Engagement
24	continuum of care
25	Continuity
26	Set 7-25 were combined with "or "
27	Set 6 and 26 were combined with "and"
28	Set 27 was limited to years "2000-current"
	Country
29	DEVELOPING COUNTRY
30	AFRICA SOUTH OF THE SAHARA
31	AFRICA
32	sub-saharan
33	*all sub-Saharan countries included as Mesh and text term combined with or*
34	Set 29-33 were combined with "or "
35	Set 28 and 34 combined with "and"

Words written in capital letters were used as MeSH headings, the others were used as free text.

Supplement Figure 8.3: Flowchart of papers included in the review



9 HIV test uptake

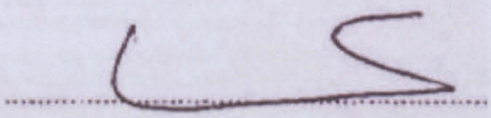
High prevalence of self-reported undiagnosed HIV despite high coverage of HIV testing: a cross-sectional population based sero-survey in South Africa

1. For a 'research paper' already published
   1.1. Where was the work published? ***PLos One***
   1.2. When was the work published? ***2011***
   1.3. Was the work subject to academic peer review? ***Yes***
   1.4. Have you retained the copyright for the work? ***Yes***
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published?
   2.2. List the paper's authors in the intended authorship order
   2.3. Stage of publication

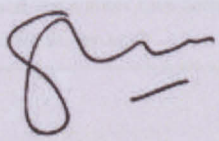
3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, wrote the ethics, collected the data, performed the data analysis and wrote the publication.



Candidate's signature

Supervisor or senior author's signature to confirm role as stated in (3)



Dr. Stephen D. Lawn
Supervisor and Co-Author

PLoS one

High Prevalence of Self-Reported Undiagnosed HIV despite High Coverage of HIV Testing: A Cross-Sectional Population Based Sero-Survey in South Africa

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Abstract

Objectives: To measure HIV prevalence and uptake of HIV counseling and testing (HCT) in a peri-urban South African community. To assess predictors for previous HIV testing and the association between the yield of previously undiagnosed HIV and time of last negative HIV test

Methods: A random sample of 10% of the adult population (≥15 years) were invited to attend a mobile HCT service. Study procedures included a questionnaire, HIV testing and CD4 counts. Predictors for previous testing were determined using a binominal model.

Results: 1,144 (88.0%) of 1,300 randomly selected individuals participated in the study. 71.0% (68.3–73.6) had previously had an HIV test and 37.5% (34.6–40.5) had tested in the past 12 months. Men, migrants and older (>35 years) and younger (<20 years) individuals were less likely to have had a previous HIV test. Overall HIV prevalence was 22.7 (20.3–25.3) with peak prevalence of 41.8% (35.8–47.8) in women aged 25.1–35 years and 37.5% (26.7–48.3) in men aged 25.1–45 years. Prevalence of previously undiagnosed HIV was 10.3% (8.5–12.1) overall and 4.5% (2.3–6.6), 8.0% (CI 3.9–12.0) and 20.0% (13.2–26.8) in individuals who had their most recent HIV test within 1, 1–2 and more than 2 years prior to the survey.

Conclusion: The high burden of undiagnosed HIV in individuals who had recently tested underscores the importance of frequent repeat testing at least annually. The high prevalence of previously undiagnosed HIV in individuals reporting a negative test in the 12 months preceding the survey indicates a very high incidence. Innovative prevention strategies are needed.

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Introduction

HIV counseling and testing (HCT) services are important entry points for prevention and care [1]. Studies from different countries have shown that individuals take precautions to protect their partners once they know they are HIV positive [2,3,4] and modeling studies have found HCT to offer substantial clinical benefits and to be cost-effective even in settings where linkage and access to care is limited [5].

The past decade has seen a rapid global scale-up of HCT [6]. Recent surveys from Tanzania, the Democratic Republic of the Congo, Kenya, Zambia, Swaziland and South Africa reported that between 8.6 and 56.6% of women and 9.2 and 43.0% of men ever had an HIV test [6,7]. HCT uptake is associated with a range of socio-demographic factors, and is generally lower among men, younger and older age groups, those with limited education and income [6,8,9]. Identifying characteristics of individuals who have never tested is important to develop services targeted at first time testers and thus to achieve universal access to HCT.

Sexually active individuals in high HIV prevalence settings are at continuous risk of infection and should therefore test at regular intervals. The World Health Organization (WHO) recommends annual testing in high HIV prevalence settings as do the 2010 South African guidelines [10,11]. A recent study from South Africa found annual screening to be very cost-effective even in the Western Cape, the province with the lowest rates of HIV infection in South Africa [5]. Despite the importance of annual testing, population surveys from six sub-Saharan African countries showed

a median of only 19% of women and 10% of men had an HIV test in the 12 months preceding the survey [6]. Even though South Africa is above average with 24.7% of the population reporting a test within the last 12 months in 2008, it is still sub-optimal [7].

This study was conducted in a well characterized peri-urban community in the Western Cape, South Africa [12,13]. The study community has been exposed to 9 years of community-based HIV prevention research and has seen provider-initiated HIV testing and antiretroviral therapy (ART) roll-out earlier than most other communities in South Africa. This community provides a unique opportunity to examine the effect of high HCT coverage and frequent testing. The aims of this study were to measure HIV prevalence and HCT uptake, to determine predictors for previous HIV testing and to assess the association between the yield of previously undiagnosed HIV and time of last negative test.

Methods

Ethics statement

Written informed consent was obtained from all individuals participating in the study. Data collection and analysis was approved by the University of Cape Town Ethics Committee and Partners Human Subjects Institutional Review Board and the London School of Hygiene and Tropical Medicine.

Setting

The study was based in a peri-urban township in the greater area of Cape Town, South Africa. Regular household censuses have shown that the community has undergone a rapid population growth from 5000 residents in 1996 to 17000 in the most recent census in August 2010 [12]. Adult HIV prevalence was 23% in 2005 and 25% in 2008 as measured in previous population based HIV prevalence surveys.

The community was served by a single public-sector primary care clinic, which provided outpatient care including HCT and ART free of charge. A nearby hospital (5 km away) provided all secondary care, including inpatient and antenatal services. The hospital also provided ART for some HIV-infected individuals from the community. ART provision at the primary health care clinic and hospital began in 2004. Since 2005, there has been a significant scale-up of the ART program in this community, with 13% of all individuals infected with HIV receiving ART in 2005 and 21% in 2008 [14].

Voluntary counseling and testing services have been available to all individuals accessing either the local clinic or the hospital since 2001 with provider-initiated testing routinely given to any patient accessing TB services whose HIV status was unknown; this was extended to all pregnant females accessing the hospital or clinic in 2002 and patients accessing STI services in 2007. HIV testing rates rose from 4% of the total population per year in 2001 to 20% in 2006 [15]. The total number of tests performed in the primary health care clinic or hospital among residents of this community was more than 10500 between January 2004 and March 2009 [16]. The community has also been served by a mobile HCT service 1–2 days per month since July 2008. The mobile HCT service has done more than 1000 tests in this community.

Community-based cross-sectional survey

A population-based HIV sero-prevalence survey was conducted between September and December 2010. A house-to-house enumeration of the community in August 2010 provided a database of 12520 residents 15 years or older of whom 1300 residents were randomly selected for inclusion in the study (10% of the community). Simple random sampling was performed using Stata 11.0 (Stata Corp. LP, College Station, TX, United States of America). Each adult resident in the community had an equal chance of being selected for the survey. The census 2010 data were used as a sampling frame. Field workers invited the selected individuals to attend the mobile HIV testing service. Field workers visited households of selected individuals up to 5 times to encourage participation. No study procedures were performed in people's homes. Consent, questionnaires and HIV testing were performed at the mobile HIV testing service when a potential participant attended the service.

Mobile HIV testing service

The mobile HIV testing service used in this study has been described elsewhere [17]. In brief, this nurse-run and counselor-supported unit provides free HCT services in combination with free screening for other chronic conditions (i.e. hypertension, diabetes and obesity) and TB. HIV testing is performed according to the Provincial Government of the Western Cape guidelines [18]. Whilst the South African guidelines for HIV testing recommend written informed consent, the mobile, community based nature of this service led to the agreement by local health authorities to allow verbal consent in clients voluntarily accessing this service since 2008. Individuals approaching the mobile services give verbal consent for HIV testing which is recorded on the consultation form.

The mobile testing service was parked in front of the primary school in the centre of the community. It operated on weekdays and weekends as well as after hours to ensure that individuals with regular work had an opportunity to participate.

Participants could choose one of three options to receive their result: i) to test and receive their HIV result together with screening for chronic diseases, ii) to provide blood and not receive their HIV result, but undergo screening for chronic diseases or iii) to only provide blood and not receive their HIV result. Individuals who consented to rapid HIV testing and tested positive were subsequently staged according to the WHO staging manual and underwent a point of care CD4 count test (Alere™Pima™ CD4 Analyser, Waltham, MA, USA) using venous blood samples. All participants were compensated for transport and time with ZAR 70 (approximately 9.6 US dollars) gift vouchers.

Data collection and management

Age, sex, nationality, migration history and previous HIV testing experience were recorded via a short questionnaire. Data were double entered and verified in EpiData version 3.1.

For HIV testing experience this included asking whether they had tested for HIV before and whether this was <3 months ago, 3–6 months ago, 6–12 months ago, 1–2 years ago or >2 years ago. Where individuals had tested on the mobile clinic before, this information was available from their previous records accessed using a biometric system. Recent migrants were defined as individuals who had moved into this community from either within South Africa or from neighboring countries within the 3 years preceding the survey.

Individuals who tested HIV positive and chose to receive their result were asked as part of the questionnaire if they were aware of their positive sero-status. Individuals who were unaware of their positive sero-status underwent the routine procedure of the mobile testing service for newly diagnosed HIV positive individuals. These procedures included clinical staging, CD4 count testing, pregnancy tests for women, screening for sexually transmitted disease, referrals to primary health care clinics and targeted counseling. All newly diagnosed HIV positive individuals were called by their counselor 7 days after diagnoses to ensure that they received

enough support to deal with the new diagnosis. All counselors were extremely experienced and as such able to confirm if an individual was unaware of their sero-status. Twelve individuals who initially said that they were unaware of their HIV positive sero-status admitted to the counselor that they had known their positive sero-status before. This information was used to amend the data. For patients who chose to test anonymously and tested positive (N = 16) no additional information could be collected by the counselors.

Statistical analysis

All analyses were carried out using Stata version 11.0 (Stata Corp. LP, College Station, TX, United States of America). Proportions and confidence intervals were calculated for categorical variables, and medians and interquartile ranges for continuous variables. The proportion of individuals who tested for HIV within the last year was calculated using individuals at risk for testing as a denominator. Thus, the denominator excluded individuals who had tested HIV positive more than one year ago. The prevalence of newly diagnosed HIV in individuals who had tested before excluded individuals known to be HIV positive from the denominator.

Differences in proportions between study participants who had tested previously and study participants who had never tested were calculated using cross-tabulation and $\chi 2$ test.. Risk ratios investigating association between age, gender, nationality, migration and previous HIV testing were calculated using a binominal model. Differences in median CD4 counts in individuals newly diagnosed with HIV, known to be HIV positive but not on ART and individuals on ART was assessed using the Kruskal-Wallis test.

Results

Characteristics of the study population

Of 1300 individuals randomly selected from the community, 1144 (88.0%) participated. Among the 156 individuals who did not participate in the study two had died before the study started, five refused to participate, and the remaining 149 did not attend the mobile HCT service despite multiple visits to their households. Individuals who did not participate in the study were older (median age 31; IQR [interquartile range] 27–38) and more likely to be men (76.2%) compared to individuals who participated in the study (median age 28; IQR 23–35, 48.6% men) (table 1).

The majority of study participants were South African and approximately one quarter had migrated to the study community within the last 3 years. Most migrants came from a neighboring province, the Eastern Cape, (52.6%) while 11.9% came from elsewhere in the Western Cape and 22.6% from neighboring countries. Non-South Africans (77.1%) were more likely to have recently migrated to the study community compared to South Africans (32.3%).

Prevalence and predictors of previous HIV testing

71.0% (95% CI 68.3–73.6) of study participants had previously had an HIV test and more than one third (37.5%) had tested in the 12 months preceding the survey (table 1). The proportions of women, South Africans and long term residents were higher among individuals who had previously tested for HIV than among individuals who had never tested (table 2). In multivariate analysis women and South African nationals were more likely to have a previous HIV test. Migrants and younger and older individuals were less likely to have been tested before.

Table 1. Characteristics, HCT coverage and HIV prevalence (N = 1144).

Variables	N	Percent	95% CI
Characteristics of participants			
Testing and receiving result	1078	94.2	92.9; 95.6
Women	588	51.4	48.5; 54.3
Age <20 years	134	11.7	9.9; 13.7
Age 20–34.9 years	714	62.4	59.5; 65.2
Age ≥35 years	296	25.9	23.4; 28.5
South African	1034	90.4	88.7; 92.1
Moved into the community during the past 3 years	309	27.2	24.6; 29.8
Previous HIV testing			
Previously tested for HIV	812	71.0	68.3; 73.6
Tested within the last year	386	37.5	34.6; 40.5
HIV prevalence			
Newly diagnosed HIV+	118	10.3	8.6; 12.1
Known HIV+	142	12.4	10.5; 14.3
HIV-	884	77.3	74.8; 79.7

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HIV prevalence

Overall the proportion of people tested who agreed to receive their result was high (94.2%, 95%CI 92.9–95.6). A total of 66 individuals chose to test anonymously among whom 16 (24.2%) tested positive.

Overall HIV prevalence was 22.7% (95%CI 20.3–25.3). Just over half (54.6%, 95%CI 48.3–60.8) of the HIV-infected individuals knew their serostatus (table 1). Among the 142 HIV infected individuals who knew their positive serostatus, 87 were on ART (61.3%, 95%CI 52.7–69.3). The median CD4 count was 389 cells/uL (IQR 269–611) in individuals newly diagnosed with HIV, 430 cells/uL (IQR 287–631) in individuals known to be HIV positive but not on ART and 440 cells/uL (IQR 295–627) in individuals on ART. CD4 counts were not significantly different across the three groups.

HIV prevalence and the proportion of undiagnosed HIV was associated with age and sex (figure 1). HIV prevalence was 12.1% (95%CI 7.4–16.8) in women 15–25 years of age compared to 41.8% (95%CI 35.8–47.8) in women aged 25.1–35. HIV prevalence in men was highest among the 35.1–45 year olds (37.5%, 95% 26.7–48.3). The proportion of positive tests that were new HIV diagnoses was significantly higher in men (62.1%, 95%CI 51.0–72.3) compared to women (37.0%; 95%CI 29.8–44.7).

Prevalence of previously undiagnosed HIV

Prevalence of previously undiagnosed HIV was 18.4% (95%CI 14.2–22.4) in individuals who had never tested for HIV and 8.5% (95%CI 6.4–10.6) in individuals who reported HIV testing prior to the survey ($p<0.001$). Prevalence of previously undiagnosed HIV was 4.5% (95%CI 2.3–6.6), 8.0% (95%CI 3.9–12.0) and 20.0% (95%CI 13.2–26.8) in individuals who had their most recent HIV test within 1 year, 1–2 years and more than 2 years prior to the survey. There was no difference in prevalence in individuals last tested <3 (4.1%), 3–6 (4.9%), 6–12 (4.9%) months prior to the survey. A sensitivity analysis excluding the 16 individuals who tested positive but did not want to receive their test results revealed

Table 2. Comparison of previously tested and untested individuals (N = 1144).

Variables	Previously tested for HIV (N = 812)			Never tested for HIV (N = 332)			p value (χ^2 test)	Predictors of previous HIV test		
	N	Percent	95% CI	N	Percent	95% CI		RR	95% CI	p value
Women	486	59.9	56.5; 63.2	102	30.7	25.7; 35.7	<0.01	1.33	1.33; .143	<0.01
Age <20 years	75	9.2	7.3; 11.4	59	17.8	13.8; 22.2	<0.01	0.79	0.68; 0.91	<0.01
Age 20–34.9 years	532	65.5	62.1; 68.8	182	54.8	49.3; 60.3		1.00		
Age ≥35 years	205	24.3	22.3; 28.4	91	27.4	22.7; 32.5		0.87	0.81; 0.95	<0.01
South African	758	93.3	91.6; 95.1	276	83.1	79.1; 87.2	<0.01	1.29	1.06; 1.57	0.01
Moved into the community during the past 3 years	187	23.1	20.2; 26,1	122	37.2	31.9; 42.5	<0.01	0.83	0.80; 0.95	0.02

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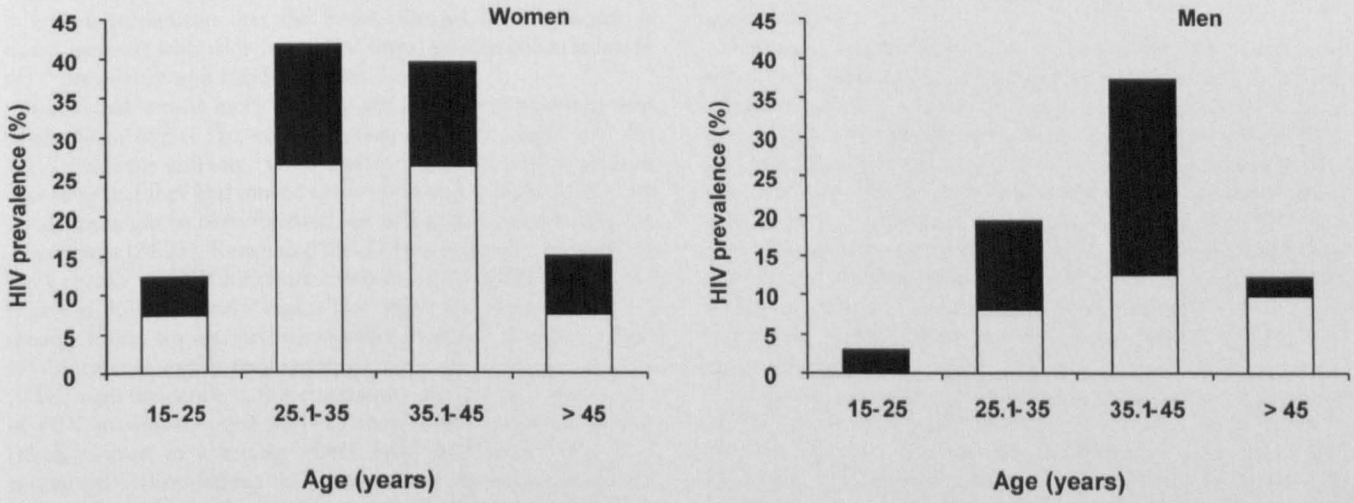
similar prevalence estimates except for the prevalence estimate in individuals last tested <3 months ago (1.2%).

In long-term residents, prevalence of previously undiagnosed HIV was 3.9% among those tested within 12 months and 6% among those tested within 1–2 years prior to the survey . Individuals who had recently moved into the community had a higher prevalence of previously undiagnosed HIV: 6.1% in individuals tested in the past 12 month and 14.3% in individuals tested 1–2 years ago.

Discussion

This cross-sectional population based sero-survey found a peak HIV prevalence in the age group 25.1–35 in women (41.8%) and 35.1–45 in men (37.5%) in this peri-urban community. Almost half (45.4%) of the individuals infected with HIV were unaware of their HIV positive sero-status despite 71.0% of the population reporting that they had previously had an HIV test. Younger and older individuals, immigrants, individuals who had recently moved to the community and men were less likely to have previously tested for HIV. The prevalence of undiagnosed HIV was strongly associated with a history of HIV testing. Even among individuals who reported their most recent negative HIV test in the 12 months prior to the survey, the prevalence was 4.5%. CD4 count distributions were similar in HIV positive individuals on ART and not ART probably due to high ART coverage in this community [19].

In this community 71.0% had previously tested for HIV and 37.5% had an HIV test within the last 12 months. This is substantially higher than the corresponding national estimates



Overall HIV prevalence and 95% confidence intervals

Gender	15-25 years	25.1-35 years	35.1-45 years	>45 years
Women	12.1 (7.4-16.8)	41.8 (35.8-47.8)	39.5 (28.2-50.7)	14.8 (5.0-24.6)
Men	3.0 (0.6-5.4)	19.5 (14.4-24.6)	37.5 (26.7-48.3)	12.2 (1.7-22.7)

Figure 1. HIV prevalence by age and sex.
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from 2008 of 50.8% and 24.7%, respectively [7]. HCT services were strengthened and provider-initiated as well as voluntary testing was implemented as early as 2002 through the ongoing research program in this community which might explain some of the differences. Furthermore HCT has been scaled up on a national and provincial level over the last years. [7]. In April 2010 a national HCT campaign was launched aiming to test 15 million people for HIV by June 2011. This might have led to increased testing rates in the months before this survey.

In a community with such high testing rates one would expect the majority of HIV infected individuals to be aware of their HIV positive sero-status. The high proportion (45.6%) of undiagnosed HIV in this community may be due to a very high incidence. This study was not designed to measure HIV incidence. However a 4.5% prevalence of undiagnosed HIV in individuals reporting a negative test within the last 12 months translates into an incidence of 12.4 per 100 person-years assuming that the infection occurred at the mid-point between the last negative test and the positive test. Even when excluding individuals who tested positive, but did not want to receive their results, as these individuals might have known their positive sero-status before, the HIV incidence remains at 8.5 per 100 person-years. The method used to calculate these incidence estimates has not been validated and thus the estimates should be viewed with caution. They are, however in keeping with the incidence of 7.2 per 100 person-years reported from a cohort in this community in 2004–2005 [20]. Similar incidence rates of 6.4 per 100 person-years have been reported in women in rural and urban in KwaZulu Natal, South Africa [21]. These incident rates are in stark contrast to a recent estimate of 1.3 per 100 person-years using data from three national surveys [22]. National incidence estimates provide an average of incidence estimates across South Africa therefore very high incidence in some communities [23] might be compensated for by low incidence in others. In addition, it is well recognized that the South African HIV epidemic is heterogeneous with wide inter- and intra- provincial variation in HIV prevalence and incidence rates.

Individuals tested more recently are a self-selected group who might be at higher risk of HIV infection, which might bias the HIV incidence estimate. With almost a third of the population reporting that they had moved to the community in the last 3 years incidence might be overestimated due to high risk of HIV infection in migrants [24,25]. Restricting the analysis to long-term residents only, reveals an HIV incidence estimate of 6.1/100 person-years, which is still extremely high. The HIV prevalence of 12.1% among young women provides further evidence for a very high HIV incidence in this community.

The high incidence in this community and the high prevalence of HIV in women aged 25.1–45 show that current prevention efforts – even in a setting where HIV prevention research is conducted – are failing. HIV prevalence estimates from this community with a peak prevalence of 41.8% in women and 37.5% in men are as high as reported from rural Kwazulu Natal, the South African province hardest hit by the HIV epidemic [26]. This community was exposed to more intensive prevention messages and better resourced HIV services than most other South African communities as evidenced by higher HCT coverage and the lower prevalence of newly diagnosed HIV in repeat testers in long-term residents as compared to recent migrants.

However prevention tools in 2011 are still very limited and these data would indicate that testing and awareness alone are insufficient to reduce HIV acquisition risk. Of note, a high HIV incidence has also been reported from the CAPRISA 004 microbicide trial in KwaZulu Natal, South Africa. Women participating in the CAPRISA 004 trial were all exposed to a package of prevention consisting of condoms, monthly testing and risk reduction counseling, but even so HIV incidence was reported at 9 per 100 person-years in the placebo assigned study group [27]. Clearly there is a need for additional and innovative prevention programs to reduce HIV incidence.

The high prevalence of undiagnosed HIV even in individuals who reported testing negative within the 3 months preceding the survey underscores the importance of counseling individuals on the window period as well as frequent repeated HIV testing especially for those at high risk of HIV infection. However, another reason for the high prevalence of undiagnosed HIV despite recent testing might be the low sensitivity of rapid HIV tests due to poor adherence with correct testing procedures in routine clinical practice and previous testing in the 'window period' during serocoversion [28].

Any annual screening program for a chronic and possibly fatal disease using a cheap point of care rapid test with a yield of 4.5% should be cost-effective [5]. With a yield of 4.5% in individuals who had tested negative in the 6 months preceding the survey even more frequent testing might be justified.

Previous testing experience and awareness of the HIV positive sero-status was assessed by self report which might be influenced by social desirability bias. In addition the exact time of testing might have been influenced by recall bias resulting in misclassification. Some of the individuals participating in the survey had tested at the mobile clinic before (N = 50). All but two reported the correct time of previous test. Bias and chance could explain the steady prevalence of 4–5% in individuals tested within 0–3 months, 3–6 months and 6–12 months prior to the survey. However an alternative explanation is that individuals testing at higher frequency might have a higher risk of HIV infection or that anonymous testers who tested positive in this survey knew their status already. Excluding those individuals did not change the overall results.

This study found that men, non-South Africans, younger and older individuals and individuals who had moved to the community within the last 3 years were less likely to have ever tested before, consistent with other studies from South Africa [7,25,29,30]. More importantly the yield of newly diagnosed HIV was twice as high in individuals who had never tested before compared to individuals who reported a prior HIV test, emphasizing the need for frequent testing and expanding services to segments of the population which are hard to reach. This study highlights again that men are particularly underserviced as almost two thirds of HIV infected men were unaware of their HIV positive sero-status.

Among the limitations of this study are: a non-attendance rate of 12%. Reasons for non-attendance were temporary absenteeism (prolonged visits to the neighboring province), work commitment and silent refusals. These data are similar to other population based HIV sero-prevalence surveys from sub-Saharan Africa reporting absenteeism rates of 0.8–35.2% and refusal rates of 2.7–35.9% [31,32,33]. HIV prevalence found in this survey is consistent with estimates from previous surveys from the same community [34], thus non-response bias due to differences in age and gender between attendees and non-attendees seems negligible.

Fear of stigma and lack of confidentiality have been shown to be a major barrier for HIV testing [35,36,37,38,39,40]. The high uptake of open (non-anonymous testing) is particularly encouraging and might be attributed to a well functioning and efficient ART program, reduced stigma due to a long period (9 years) of community-based HIV prevention research in this community

and the fact that none of the team members working on the mobile HCT service were part of the community.

In conclusion this study showed a high burden of undiagnosed HIV despite high HCT coverage. The yield of previously undiagnosed HIV was 4.5% in individuals with a negative HIV test within 12 months preceding the survey. This suggests a very high HIV incidence. The results emphasize the importance of repeat testing perhaps even more frequently than annually. It underscores the notion that innovative and effective prevention interventions in addition to post test counseling are urgently required.

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Author Contributions

Conceived and designed the experiments: KK NS KM SDL RW L-GB. Performed the experiments: KK UK ES. Analyzed the data: KK. Contributed reagents/materials/analysis tools: KK RW L-GB KM. Wrote the paper: KK NS UK ES SDL KM RW L-GB. Responsible for research infrastructure: L-GB RW.

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10 Linkage between testing and HIV/ART care

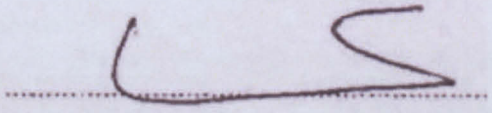
Linkage to HIV Care and Antiretroviral Therapy in Cape Town, South Africa

1. For a 'research paper' already published
   1.1. Where was the work published? ***PLos One***
   1.2. When was the work published? ***2010***
   1.3. Was the work subject to academic peer review? ***Yes***
   1.4. Have you retained the copyright for the work? ***Yes***
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published?
   2.2. List the paper's authors in the intended authorship order
   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press

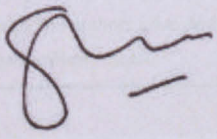
3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, wrote the ethics, cleaned the data, linked the data, performed the data analysis and wrote the publication.



Candidate's signature

Supervisor or senior author's signature to confirm role as stated in (3)



Dr. Stephen D. Lawn
Supervisor and Co-Author

Linkage to HIV Care and Antiretroviral Therapy in Cape Town, South Africa

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Abstract

Background: Antiretroviral therapy (ART) has been scaled-up rapidly in Africa. Programme reports typically focus on loss to follow-up and mortality among patients receiving ART. However, little is known about linkage and retention in care of individuals prior to starting ART.

Methodology: Data on adult residents from a periurban community in Cape Town were collected at a primary care clinic and hospital. HIV testing registers, CD4 count results provided by the National Health Laboratory System and ART registers were linked. A random sample (n = 885) was drawn from adults testing HIV positive through antenatal care, sexual transmitted disease and voluntary testing and counseling services between January 2004 and March 2009. All adults (n = 103) testing HIV positive through TB services during the same time period were also included in the study. Linkage to HIV care was defined as attending for a CD4 count measurement within 6 months of HIV diagnosis. Linkage to ART care was defined as initiating ART within 6 months of HIV diagnosis in individuals with a CD4 count ≤200 cells/μl taken within 6 months of HIV diagnosis.

Findings: Only 62.6% of individuals attended for a CD4 count measurement within 6 months of testing HIV positive. Individuals testing through sexually transmitted infection services had the best (84.1%) and individuals testing on their own initiative (53.5%) the worst linkage to HIV care. One third of individuals with timely CD4 counts were eligible for ART and 66.7% of those were successfully linked to ART care. Linkage to ART care was highest among antenatal care clients. Among individuals not yet eligible for ART only 46.3% had a repeat CD4 count. Linkage to HIV care improved in patients tested in more recent calendar period.

Conclusion: Linkage to HIV and ART care was low in this poor peri-urban community despite free services available within close proximity. More efforts are needed to link VCT scale-up to subsequent care.

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Introduction

South Africa is home to one-sixth of the world's population living with HIV and has the largest antiretroviral therapy (ART) programme in the world [1,2]. ART roll out began nationally in late 2003 and by the middle of 2008, 568,000 adults and children were receiving ART. This translated into around 40% of eligible adults receiving ART in 2008 [3], although the latest guidelines recommend earlier initiation for certain patients, thus increasing the numbers eligible for ART and widening the treatment gap [4].

In an effort to increase access to prevention and care, South Africa launched an ambitious national campaign in April 2010 aiming to test 15 million people for HIV and to reach 1.5 million people with ART by June 2011. Increased HIV testing may impact on risk behavior in the short-term [5]. However, there is also a need to ensure that those who need treatment are linked to the appropriate services while those not eligible for treatment are monitored and started on ART when appropriate. A study from Durban, South Africa, reported that almost two-thirds of newly diagnosed patients accessing care in a semi-private hospital were lost to care between HIV diagnosis and getting a CD4 count, and another one in five patients were lost between CD4 testing and ART initiation [6,7]. Another study from South Africa found that only 45% of eligible patients started ART in a public sector ART project in Free State. Mortality and TB incidence in patients failing to initiate ART was more than 2 times higher compared to patients initiating ART [8].

The impact of ART on mortality, morbidity, TB incidence [9,10] and HIV transmission [11] at a population level depends on ART coverage. ART coverage defined as the number of patients

receiving ART at a point in time, divided by the number needing treatment is determined by timely HIV diagnosis and effective linkage to ART. This study investigates linkage to HIV and ART care using a random sample of individuals testing HIV positive either provided-initiated (through antenatal care (ANC), tuberculosis (TB), sexually transmitted infection (STI) services) or client-initiated (through voluntary counseling and testing (VCT) services) in a peri-urban township in the Western Cape Province in South Africa. Linkage to care was defined first as attending for a CD4 count measurement within 6 months of a positive HIV test and second as the proportion of eligible individuals starting ART within 6 months of their HIV diagnosis.

Methods

Setting

The study was based in a peri-urban township in the greater area of Cape Town, with a population of approximately 15,000 people and a measured adult HIV prevalence of 23% in 2005 [12]. The community is served by a single public-sector primary care clinic, which provides outpatient care including ART free of charge. A nearby hospital (5 km away) provides all secondary care for the population, including inpatient and antenatal services. The hospital also provides ART for some HIV-infected individuals from the community.

HIV testing, CD4 count measurements and ART services

Client-initiated HIV testing services have been available to all individuals accessing either the local clinic or the hospital since 2001. Clients who tested on their own initiative are referred to as having tested through VCT services. Provider-initiated testing was routinely provided to any patient accessing TB services whose HIV status was unknown. This was extended to all pregnant females accessing the hospital or clinic in 2002 and patients accessing STI services in 2007. All testing required signed consent. All CD4 count tests were free for patients and performed by the centrally located National Health Laboratory Services (NHLS) in Cape Town.

ART provision at the primary health care clinic and hospital began in 2004.

Linkage to HIV and ART care

Linkage to HIV care was defined as attending for a CD4 count measurement within 6 months of HIV diagnosis. We did not ascertain if individuals actually received their CD4 counts. Linkage to ART care was defined as initiating ART within 6 months of HIV diagnosis in individuals with a CD4 count $\leq$200 cells/μl taken within 6 months of HIV diagnosis. Having a repeat CD4 count was defined as having had a repeated CD4 count in individuals not yet eligible for ART (CD4 count >200 cells/μl) and tested before 2009.

Data collection

We collected data from 3 sources. First, the primary care clinic and hospital HIV testing registers provided all data on HIV infected, adult community residents ($\geq$18 years) diagnosed between January 2004 and March 2009. Data at the primary health care clinic were missing for the period from February 2008 to August 2008. For each test encounter recorded in the registers, we retrieved data on client identification variables (first name, surname, date of birth, and medical record number); place of residence; sex; test acceptance; test result and service. For HIV infected individuals who tested more than once, the earliest positive HIV test was considered. Second, data on CD4 counts performed at either the primary care clinic or the hospital in the period from 2004 to October 2009 were obtained from NHLS. The date of CD4 count was the date the client provided blood. Third, data from residents who initiated ART care at the primary health care clinic or hospital were obtained from electronic ART registers at the clinic and hospital.

These three databases were merged on first name, surname, medical record number and date of birth. In cases where identifiers did not match completely two researchers (PG and KK) independently confirmed that records in different databases were from the same individual. Concordance between the two researchers was 97%. Cases where the two researchers disagreed were discussed until consensus was reached. For all subsequent analysis data was stripped of all personal identifiers.

Ethics

Written informed consent was obtained from all individuals initiated on ART and screened for ART. Individuals testing for HIV are routinely entered into the HIV testing register. Informed consent was not obtained from HIV positive individuals not linking to care, as this was a retrospective study and individuals were not actively follow-up. Data collection and analysis was approved by the University of Cape Town Ethics Committee and Partners Human Subjects Institutional Review Board and the London School of Hygiene and Tropical Medicine.

Statistical analysis

A random sample (n = 885) of adults testing HIV positive through ANC, STI and VCT services between January 2004 and March 2009 was selected for this analysis. All adults testing positive through TB services were included in this analysis to ensure an adequate sample size in this group.

All analyses were carried out using Stata version 11 (Stata Corp. LP, College Station, TX, United States of America). Proportions were calculated stratified by service. Total proportions were calculated taking the different sampling proportions into account. Risk ratios investigating associations between age, sex, calendar period and timely linkage to HIV care, CD4 count $\leq$200 cells/μl and repeated CD4 counts were estimated for each service. Risk ratios were calculated using a log binominal model [13].

Results

HIV testing and HIV prevalence

A total of 8515 records of HIV tests were available for adult members of the community. The majority of individuals tested through VCT (n = 5345, 62.8%) services (Table 1). The overall HIV prevalence among those tested was 23.5% with the highest prevalence among patients tested through TB (37.9%) and VCT services (24.9%) (χ^2 test, $p<0.01$). The median age of individuals tested was 26 (interquartile range (IQR), 22–32) and 67.9% were women. HIV prevalence was 21.6% in men and 24.4% in women.

A total of 2002 clients tested HIV positive. Their median age was 28 years (IQR, 24–33) and the majority were women (70.3%). The proportion of women testing HIV positive was 100% in ANC, 66.2% in STI, 38.8% in TB and 66.4% in VCT clients. 1330 (66.4%) individuals tested HIV positive through VCT, 332 (16.6%) through ANC, 237 (11.8%) through STI and 103 (5.1%) through TB services.

Linkage to HIV and ART care

Linkage to HIV and ART care was assessed in a random sample of 47% of individuals testing HIV positive through ANC, STI and VCT services and 100% of individuals testing through TB services: 150 tested through ANC, 113 through STI, 662 through VCT and 103 through TB services. Only 62.6% (95%CI

Table 1. Number (%) of individuals who tested for HIV and who were found to be positive stratified by type of clinical service.

	ANC service	STI service	TB service	VCT service	Total
Tested N (%)	1525 (17.9)	1370 (16.1)	275 (3.2)	5345 (62.8)	8515 (100)
Positives N (%)	332 (16.6)	237 (11.8)	103 (5.1)	1330 (66.4)	2002 (100)
HIV Prevalence	21.8%	17.3%	37.5%	24.9%	23.5%

All HIV testing records available for the period from January 2004 until March 2009 from adult patients were included in this analysis.
ANC = antenatal care, STI = sexual transmitted infections, TB = tuberculosis, VCT = voluntary counseling and testing.
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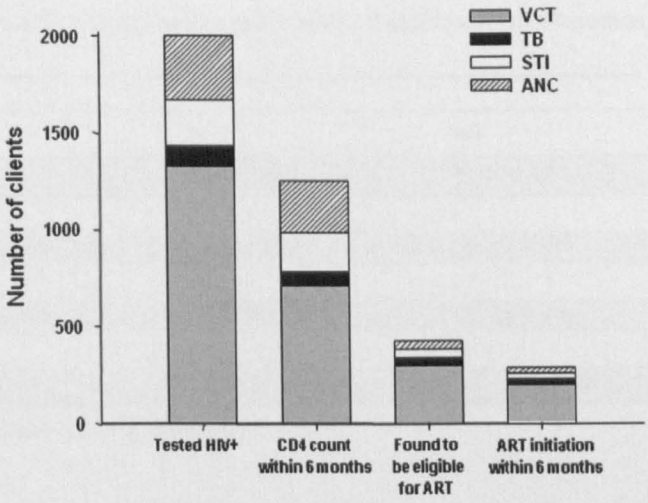

Figure 1. Number of clients testing HIV+, with timely CD4 counts, eligible for ART and initiating ART estimated using proportions from table 2. ART = antiretroviral therapy, ANC = antenatal care, STI = sexual transmitted infections, TB = tuberculosis, VCT = voluntary counseling and testing.
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59.6–65.5) of clients attended for a CD4 count measurement within 6 months of testing HIV positive (Table 2) and 26.3% (95%CI 23.5–29.0) did not have any recorded CD4 count test. The proportion of individuals attending for a CD4 count measurement within 6 months was highest among individuals tested through ANC (81.3%) and STI (84.1%) services and lowest among those who learnt of their status via VCT (53.5%) (Table 2).

Among individuals with a CD4 count measurement within 6 months, 34.1% (95%CI 30.4–37.7) were eligible for ART according the South African Department of Health criteria (CD4 count ≤200 cells/μl) at the time of the study (Table 2). Low CD4 counts were more prevalent among individuals tested through TB (54.9%) and VCT services (42.6%). In individuals attending for a CD4 count measurement within 6 months the median time between HIV test and CD4 count measurement was: 2 days (IQR 2–6) for ANC, 3 days (IQR 2–4) for STI, 3 days (IQR 2–5) for TB and 2 days (IQR 2–4) for VCT clients. Overall 4.3% of clients attended for a CD4 test at the same day as the HIV test. The majority of clients attended for CD4 count testing within 1 week (84.9%), 14.2% within 8 days and 3 months and only 0.9% within 3 and 6 months.

In individuals with a delayed first CD4 count measurements, the mean time between HIV diagnosis and first CD4 count was 490 days (IQR 345–769). Among patients with delayed first CD4 count measurements, 33.2% (95%CI 24.3–42.1) had a CD4 count ≤200 cells/μl and 26.2% (95%CI 17.8–34.8)−43.2) had a CD4 count of 201–350 cells/μl.

Only 66.7% (95% CI 60.2–73.1) of eligible individuals with a timely CD4 count accessed ART care within 6 months of HIV testing (Table 2). Linkage to ART care was highest among individuals tested through ANC services (72.2%). Among individuals not yet eligible for ART only 46.3% (95%CI 41.4–51.1) ever had a repeat CD4 count. Median time between the first and the second CD4 count was 236 days.

Figure 1 summarizes the number of people tested through different services and the numbers linking to HIV and ART care by service using the proportions estimated from the random sample.

Table 2. Percentage of individuals linking to HIV care (as defined by attending for a CD4 cell count measurement), distribution of CD4 count measurements, percentage of patients subsequently initiating ART and percentage of clients non-eligible for ART returning for a repeat CD4 count.

Variables		ANC (n = 150) % (N)	STI (n = 113) % (N)	TB (n = 103) % (N)	VCT (n = 622) % (N)	Total %
First CD4 count after HIV test	**≤6 months**	81.3 (122)	84.1 (95)	68.9 (71)	53.5 (333)	62.6 (59.6–65.5)
	>6 months	2.0 (3)	2.7 (3)	13.6 (14)	14.8 (92)	11.1 (9.2–13.1)
	None	16.7 (25)	13.3 (15)	17.5 (18)	31.7 (197)	26.3 (23.5–29.0)
First CD4 count within 6months of HIV test	**≤200 cells/μl**	14.8 (18)	22.1 (21)	54.9 (39)	42.3 (141)	34.1 (30.4–37.7)
	201–350 cells/μl	24.6 (30)	32.6 (31)	23.9 (17)	23.7 (79)	25.3 (21.8–28.8)
	>351 cells/μl	60.7 (74)	45.3 (43)	21.1 (15)	33.9 (113)	40.6 (36.8–44.4)
ART initiation within 6 months of HIV test in eligible individuals with timely first CD4 count	**Yes**	72.2 (13)	52.4 (11)	71.8 (28)	67.4 (95)	66.7 (60.2–73.1)
	No	27.8 (5)	47.6 (10)	28.2 (11)	32.6 (46)	33.3 (26.9–39.*)
Repeat CD4 count in individuals with a first CD4 count >200 cells/μl	**Yes**	48.5 (47)	57.6 (38)	34.5 (10)	42.3 (96)	46.3 (41.4–51.1)
	No	51.5 (50)	42.4 (28)	65.5 (19)	57.7 (131)	53.7 (48.9–58.6)

ANC = antenatal care, STI = sexual transmitted infections, TB = tuberculosis, VCT = voluntary counseling and testing.
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Table 3. Factors associated with linkage to HIV care (attending for a CD4 count measurement within 6 months of HIV diagnosis) stratified by service.

Variables	ANC	STI	TB	VCT
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Female	NA	1	1	1
Male	NA	0.93 (0.79–1.09)	1.01 (0.82–1.25)	1.10 (1.01–1.33)
Age<30 years	1	1	1	1
Age≥30 years	0.97 (0.90–1.04)	1.17 (1.01–1.35)	1.07 (0.84–1.35)	1.16 (0.96–1.26)
Tested in 2004–2006	1	NA	1	1
Tested in 2007–2009	**0.87 (0.74–0.99)**	NA	**1.67 (1.27–2.21)**	**1.60 (1.40–1.84)**

ANC = antenatal care, STI = sexual transmitted infections, TB = tuberculosis, VCT = voluntary counseling and testing.
NA = not applicaple.
doi:10.1371/journal.pone.0013801.t003

Predictors of low CD4 count, linkage to HIV, and repeated CD4 counts

Risk ratios investigating predictors for linkage to HIV care showed that linkage to care in TB (RR 1.67, 95%CI 1.27–2.21) and VCT (RR 1.60, 95%CI 1.40–1.84) clients was more likely in 2007–2009 compared to 2004–2006 (table 3). This was not the case for ANC (RR 0.97) clients who were slightly less likely to link to HIV care if tested more recently (table 3). Linkage to ART care could only be assessed in VCT clients due to the small sample size in the other groups. Neither age (RR 0.85, 95%CI 0.67–1.09) nor sex (RR 1.03, 95% CI 0.81–1.31) nor year of testing (RR 1.02, 95% CI 0.81–1.30) predicted linkage to HIV care in VCT clients.

The risk of having CD4 count measurement ≤200 cells/μl was higher in individuals aged more than 30 years regardless which service they tested through (table 4). Repeated CD4 counts were 1.3 times more likely in individuals more than 30 years of age, but this result only reached significance in the VCT clients (RR 1.25, 95% CI 1.00–1.55).

Discussion

This study evaluated the proportion of individuals linking to HIV care in a public sector service in Cape Town, South Africa. Only 63% of patients attended for a CD4 count measurement within 6 months of diagnosis. Although a substantial proportion of patients had CD4 counts ≤200 cells/μl (34%) and were therefore eligible for ART according to South African guidelines [14], only 67% of these started ART within 6 months. Among those who did have a timely CD4 count but were not yet eligible for ART, only 46% returned for a repeat CD4 count after a median time of 8 months. Individuals testing through ANC services had better linkage to HIV and ART care and higher CD4 counts at time of HIV diagnosis compared to individuals accessing the other services.

HIV is a chronic disease and comprehensive HIV care needs to be provided within a continuum of care [15]. ART is just one of the components of HIV care and care of individuals not yet requiring ART is equally important [16]. The continuum of HIV care starts when an individual is diagnosed with HIV. ART eligibility should be assessed when individuals are newly diagnosed and in regular (6 monthly) intervals thereafter. Individuals not yet eligible for ART should receive comprehensive HIV care including cotrimoxazole, isoniazid preventive therapy, screening for TB and cervical cancer, contraceptive advice, counseling and social support until they become eligible for ART. Following initiation of ART individuals needs to be supported within the same framework to ensure good adherence and retention in care.

We identified a number of important issues in our study. First, people who tested on their own initiative were least likely to have a timely CD4 count measurement done, underscoring the need to ensure that scale up of VCT programmes will be accompanied by clear plans to ensure that those who test positive go on to receive appropriate care. Second, almost a third (28%) of eligible patients with TB did not receive ART despite recommendations in favour of concomitant treatment since 2003 [17], and ART being associated with a 64–95% reduction in mortality in such patients [10,18,19,20]. This underscores the importance of integrating HIV and TB services [21].

Table 4. Factors associated with having a CD4 count ≤200 cells/μl within 6 months of HIV diagnosis.

Variables	ANC	STI	Tb	VCT
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Female	NA	1	1	1
Male	NA	0.82 (0.36–1.86)	0.97 (0.62–1.50)	1.27 (0.99–1.63)
Age<30 years	1	1	1	1
Age≥30 years	**2.42 (1.03–5.68)**	2.00 (0.92–4.35)	1.10 (0.68–1.78)	**1.40 (1.07–1.82)**
Tested in 2004–2006	1	NA	1	1
Tested in 2007–2009	1.32 (0.57–3.08)	NA	1.18 (0.75–1.85)	0.94 (0.74–1.19)

ANC = antenatal care, STI = sexual transmitted infections, TB = tuberculosis, VCT = voluntary counseling and testing.
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This study shows that men and younger adults fail to access health services efficiently. Only 30% of clients tested for HIV were men. This is consistent with studies showing that HIV-infected men are less likely to access treatment [22,23], present with more advanced stages of HIV disease [24] and have a higher mortality risk during ART [25,26,27,28,29,30,31,32]. Repeated CD4 counts were less likely in individuals under 30 years of age as also reported elsewhere[33].

It is important to note that less than half of patients whose first CD4 count was above the ART eligibility threshold came back for a repeat test. One way of improving ART uptake, and thus reduce mortality among patients who are otherwise lost to care, might be to change the CD4 threshold to 350 cell/μl in line with the latest World Health Organization recommendations [34].

Our overall finding that 33% of patients eligible for ART were lost to care is consistent with several reports from elsewhere in southern Africa. In a programme report from South Africa, only 55% of patients had a CD4 count measurement within 8 weeks of HIV diagnosis and 81% of eligible patients were on ART at 3 months follow-up [6,7]. Out of 2483 patients eligible for ART in Uganda 637 (26%) did not start ART; a third of these patients died before ART initiation and another quarter were alive but not taking ART [25]. In Mozambique only 57% of patients testing HIV positive entered HIV care and 31% of patients eligible for ART started ART within 3 months [35].

In our study only 63% of patients testing positive for HIV attended for a CD4 count measurement within 6 months. These outcomes are worse than those recently reported by a public-sector clinic in Johannesburg where 84.6% of patients who tested positive for HIV had a CD4 count measurement. The majority of these patients did not return for their CD4 result within 12 weeks [36]. Data from the same clinic in Johannesburg showed that among patients not yet eligible for ART only 26% returned for a scheduled pre-ART medical visit within one year compared to 43% of our patients not yet eligible for ART returning for a repeat CD4 count [37].

Substantial improvement in linkage to HIV care for TB and VCT patients was observed in more recent years in this study and yet this was not accompanied by improvements in linkage to ART. Failure of linkage to HIV and ART services translates into incomplete ART coverage at population level, seriously undermining the potential for reductions in mortality, morbidity, TB incidence and HIV transmission.

The study has several strengths and limitations. Strengths include that the study was conducted in a routine clinical program where CD4 count testing and ART were provided free. Thus, the results should be generalisable to similar settings. The study was conducted over a prolonged period with increasing ART availability. Among the limitations is the fact that patients might have been misclassified as failing to link to care if they accessed care with a service provider other than the primary health care clinic or hospital. Thus, linkage to care might be underestimated. However the nearest other ART site is more than 10 km away, and residents of this poor community are unlikely to have sought care in such a distant ART site unless they had moved away. Second, we did not assess if patients who had a CD4 count measurement actually returned to receive the result. Thirdly, we did not investigate reasons for not linking to care. Studies that have ascertained outcomes among patients lost to care have reported that up to a third of patients who failed to initiate ART had died [7,8,25]. Time cut-offs for linkage to care for both timely CD4 count and ART initiation are somewhat arbitrary. When no time cut-offs were used 75.3% (95% CI 70.3–80.3) of eligible individuals who had a CD4 count at some point during the study period eventually initiated ART.

In conclusion, while considerable attention has been paid to loss to follow-up and mortality among patients receiving ART [32,38,39,40], data on losses at earlier stages of the care pathway are scarce. As our study shows, a focus only on outcomes of those patients fortunate enough to initiate treatment fails to account for a substantial number of patients who are eligible for ART but do not receive it or not yet eligible but fail to reappear. Pre-ART defaulting should be encouraged in programme reporting. Programme adaptation to ensure retention in care between testing and ART should consider point of care CD4 count testing at time of HIV diagnosis as well as provision of integrated TB and HIV.

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Author Contributions

Analyzed the data: KK. Wrote the paper: KK. Designed the study and collected data: KK. Oversaw the field site and collected data, was involved in writing the paper: JZ. Oversaw the field site and collected data, contributed to and approved the final version of the paper: PG CO NK. Gave input on writing the paper, contributed to and approved the final version of the paper: SL. Responsible for the research infrastructure, contributed to and approved the final version of the paper: LGB. Responsible for the research infrastructure, gave input on writing the paper, contributed to and approved the final version of the paper: RW.

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11 Treatment interruption – systematic review

Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review

1. For a 'research paper' already published
   1.1. Where was the work published? ***Tropical Medicine and International Health***
   1.2. When was the work published? ***2011***
   1.3. Was the work subject to academic peer review? ***Yes***
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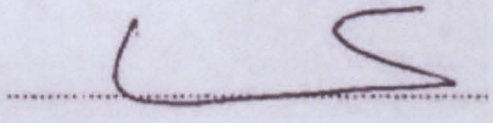
   The candidate designed the study, developed the search strategy, conducted the search and screening of abstracts and titles, performed the data extraction and analysis and wrote the publication.



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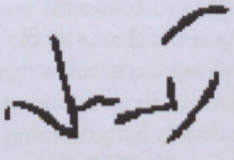

Dr. Nathan Ford
Co-Author

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Systematic Review

Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review

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Summary

OBJECTIVE To characterize the frequency, reasons, risk factors, and consequences of unstructured anti-retroviral treatment interruptions.

METHOD Systematic review.

RESULTS Seventy studies were included. The median proportion of patients interrupting treatment was 23% for a median duration of 150 days. The most frequently reported reasons for interruptions were drug toxicity, adverse events, and side-effects; studies from developing countries additionally cited treatment costs and pharmacy stock-outs as concerns. Younger age and injecting drug use was a frequently reported risk factor. Other risk factors included CD4 count, socioeconomic variables, and pharmacy stock outs. Treatment interruptions increased the risk of death, opportunistic infections, virologic failure, resistance development, and poor immunological recovery. Proposed interventions to minimize interruptions included counseling, mental health services, services for women, men, and ethnic minorities. One intervention study found that the use of short message service reminders decrease the prevalence of treatment interruption from 19% to 10%. Finally, several studies from Africa stressed the importance of reliable and free access to medication.

CONCLUSION Treatment interruptions are common and contribute to worsening patient outcomes. HIV/AIDS programmes should consider assessing their causes and frequency as part of routine monitoring. Future research should focus on evaluating interventions to address the most frequently reported reasons for interruptions.

keywords HIV, unstructured treatment interruption, antiretroviral therapy

Introduction

Antiretroviral therapy (ART) has dramatically reduced HIV-associated mortality and morbidity in high- and low-income countries (Palella *et al.* 1998; Egger *et al.* 2002; Jahn *et al.* 2008; Floyd *et al.* 2010; Mahy *et al.* 2010). Treatment outcomes reported from cohort studies and clinical trials have improved over time as a result of improved drug efficacy, reduced toxicity, and simplified treatment through reduced pill burden and dosing intervals (Boyd 2009). Despite these improvements, consistent adherence and uninterrupted treatment remain major challenges (Lazo *et al.* 2007; Byakika-Tusiime *et al.* 2009; Lima *et al.* 2009; Glass *et al.* 2010; Bastard *et al.* 2011).

Ensuring high levels of adherence is desirable for the treatment of any chronic conditions (Jackevicius *et al.* 2002; Kopjar *et al.* 2003; Cramer 2004; Osterberg & Blaschke 2005) but is particularly important for treatment of HIV in resource-limited settings, where less robust regimens are used and an extremely high level of adherence (>95%) is required to prevent the development of drug resistance (Bangsberg *et al.* 2006). There are many challenges to maintaining such high levels of adherence (Mills *et al.* 2006; Nachega *et al.* 2010). Among these, treatment interruptions are an inconsistently reported yet common phenomenon in clinical practice, often occurring as a result of treatment fatigue or in an attempt to minimize side-effects. Common toxicities such as lipodystrophy and metabolic side-effects related to prolonged use of ART may improve when treatment is stopped (Tuldra *et al.* 2001; Mocroft *et al.* 2005; Mussini *et al.* 2005; Calmy *et al.* 2007). However, the majority of individuals who discontinue treatment only do so temporarily, as they experience a rapid decline in CD4 count and increase in viral load

following discontinuation of therapy (Poulton *et al.* 2003; Skiest *et al.* 2004; El-Sadr *et al.* 2006; Sungkanuparph *et al.* 2007).

The potential for provider-directed, structured treatment interruptions as a way to limit antiretroviral exposure (and therefore both toxicities and costs) was abandoned after randomized trials and cohort studies found an increased risk of opportunistic infection and death (El-Sadr *et al.* 2006; Mugyenyi *et al.* 2008; Seminari *et al.* 2008). Nevertheless, patient-initiated unstructured treatment interruptions are a reality of routine clinical care and have been reported in both developed (Holkmann Olsen *et al.* 2007) and developing country settings (Kranzer *et al.* 2010).

To better characterize the frequency, reasons, risk factors, and consequences of unstructured treatment interruptions in routine clinical practice, we conducted a systematic review of available studies reporting on unstructured treatment interruptions.

Methods

Criteria for selection of studies

We aimed to identify studies reporting on unstructured ART treatment interruptions in clinical practice. Unstructured treatment interruption was defined as discontinuation of all ART drugs for any period of time, after which treatment was resumed. We considered that any interruption was undesirable, and thus did not limit our search to specific causes or durations. We excluded studies reporting on structured treatment interruptions, defined as physician-initiated, cyclical interruptions guided by CD4 count or viral load. We also excluded studies only reporting on patients experiencing virologic failure. We included both cross-sectional and cohort studies, but excluded editorials, case studies, case reports, and reviews.

Search strategy

We searched three electronic databases for primary studies: Medline, Embase, and Global Health using the compound search strategy summarized in Table S1 and searched the bibliographies of retrieved articles for additional studies. Our search was limited to studies published and conducted from 1996 (the time when highly active ART became available) until the end of the search period (March 2011). We also searched for conference abstracts from all conferences of the International AIDS Society (April, 1985–July, 2010), and all Conference on Retroviruses and Opportunitistic Infections (January, 1997–February, 2010) and the PEPFAR implementers meeting 2007–2009. No language restriction was applied.

Study selection and data extraction

Studies were entered into an electronic database (EndNote X1) to screen potentially eligible studies by title and abstract according to our pre-defined inclusion and exclusion criteria. Full-length articles of all studies considered eligible upon initial screening were obtained and reviewed for eligibility; conference abstracts were screened first by title, then by full abstract. All reviews were carried out independently, in duplicate. After agreeing on eligibility, we abstracted the following information using a standardized extraction form: definitions of treatment interruption, frequency and duration of interruption, reasons, risk factors, consequences of treatment interruption, and proposed interventions. Whenever required, we attempted to contact study authors for clarification by email.

Finally, we assessed full articles for determinants of methodological quality using a pre-defined assessment framework. The following factors were assessed: definition and objectivity of treatment interruption provided, appropriateness of the statistical analysis. Studies investigating consequences or treatment failure (e.g. mortality or viral rebound) were assessed for adjustment for potential confounding and use of objective outcome measures.

Results

Characteristics of included studies

The study selection process is summarized in Figure 1. Our initial search yielded 813 potentially relevant publication and 577 potentially relevant conference abstracts, from which 47 publications and 23 abstracts were considered eligible for inclusion. Three studies considered potentially eligible were excluded because it was unclear whether patients restarted treatment (i.e. interruption) or not (i.e. discontinuation); authors were contacted but did not provide clarification (Berenguer *et al.* 2004; Braitstein *et al.* 2007; Ayuo *et al.* 2008). Sixteen studies were from Africa, 14 from North America, two from Australia, one from South America, two from Eastern Europe, three from Asia, and 32 from Europe. The majority of studies (63) reported results of treatment interruptions in adults from the general population; of the remainder, two studies were among children, one was among adolescents, one was among injecting drug users, one was among men who have sex with men, one was among recurrent prisoners, and one was among women. We judged the methodological quality of studies included as full-length articles to be moderate: a third of studies (15/47) provided a definition and objectivity of treatment interruption; almost all (46/47) used an appropriate statistical analysis approach, and where

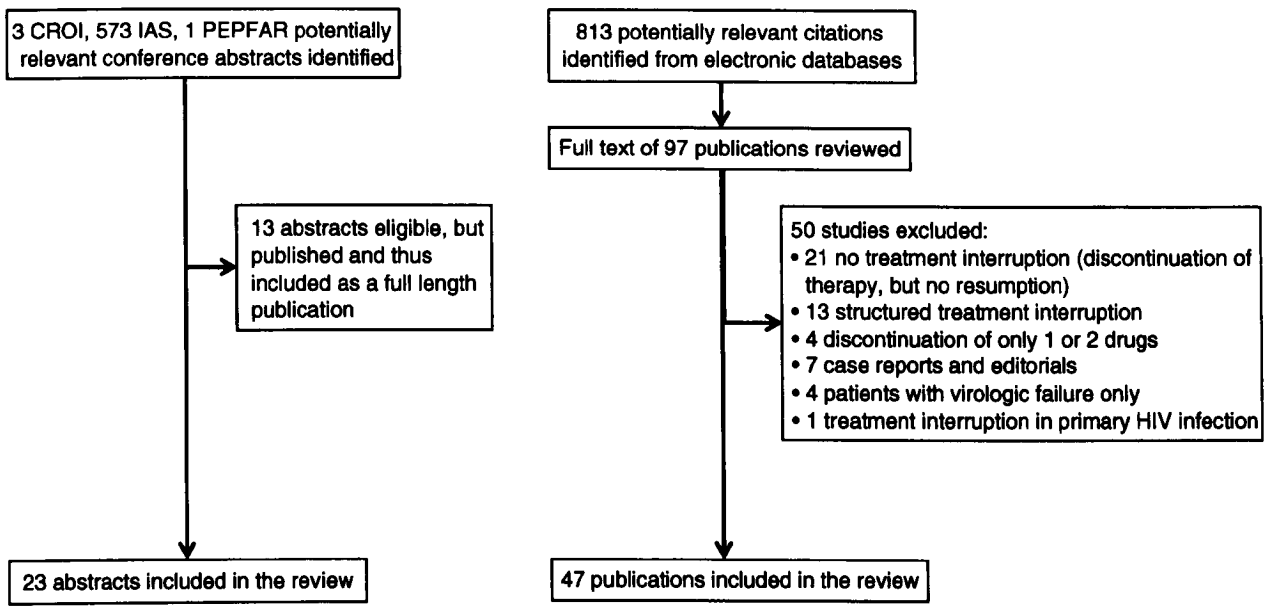

Figure 1 Study selection process.

appropriate the majority (23/25) adjusted for confounders and used an objective outcome measure (29/30).

Definition of treatment interruption and measurement

We found substantial variation and uncertainty in the definition of treatment interruption applied by the individual studies. Twenty-eight did not define the duration of treatment interruption, while of the 42 studies that did specify a definition, duration ranged from 24 h to 1 year (Figure 2). Two cross-sectional studies investigating self-reported treatment interruptions defined interruption as discontinuation of all drugs for more than 24–48 h in the 4 weeks preceding the survey (Glass *et al.* 2006; Marcellin *et al.* 2008). Two studies investigating short interruptions defined a maximum duration of treatment discontinuation of 1 month (Oyugi *et al.* 2007) and 3 months (Taffe *et al.* 2002).

The methods used to determine treatment interruptions varied: self-report (21/70), electronic medication monitoring (4/70) data, prospectively collected by clinicians (7/70), information extracted from clinical records (7/70), pharmacy prescriptions in combination with clinical records (3/70), pharmacy prescriptions only (2/70),

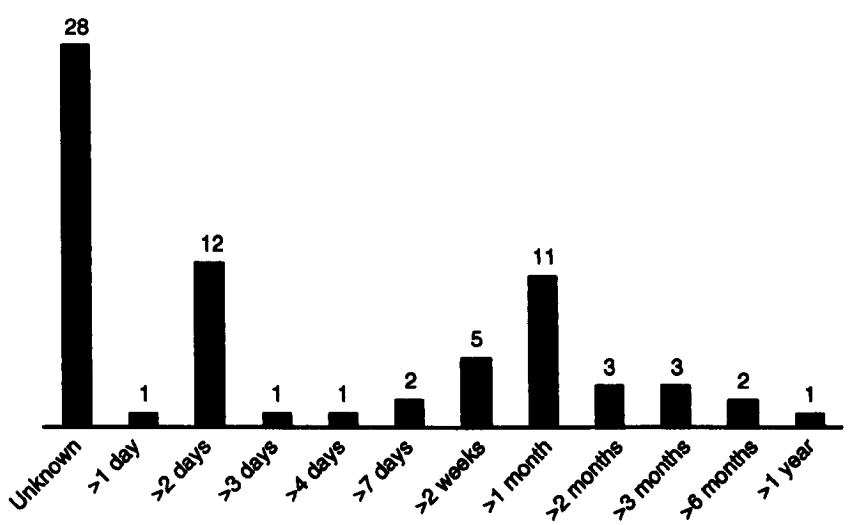

Figure 2 Definition of treatment interruption and their frequencies.

combination of data collected by clinicians and/or self-report and/or prescriptions (4/70). Twenty-two studies did not describe the method used to identify treatment interruptions.

Frequency and duration of treatment interruption

Forty-two studies reported frequencies of treatment interruptions, either as proportions (35), rates (1), or proportions and rates (3) of interruption, or as rates or proportions of discontinuation and resumption (3) (Table 1). The proportion of treatment interruptions ranged from 5.8% [adults in Switzerland (Glass *et al.* 2006)] to 83.1% [recurrent prisoners in the USA (Pai *et al.* 2009)]; the median proportion of patients interrupting treatment was 23.1% (IQR 15.0–48.0). Rates of treatment interruptions ranged from 2.0 per 100 person-years in the United Kingdom (Bansi *et al.* 2008), to 6.0 in the EuroSIDA study (Holkmann Olsen *et al.* 2007). Eleven studies reported on the mean or median duration of treatment interruptions, with durations ranging from 11.5 days (Oyugi *et al.* 2007) to 18 months (Holkmann Olsen *et al.* 2007) (median 150 days). Treatment interruptions were frequently reported as recurrent events, with up to three interruptions per person reported in South Africa (Kranzer *et al.* 2010) and Senegal (Uhagaze *et al.* 2006), five in Switzerland (Taffe *et al.* 2002), six in the EuroSIDA study (Holkmann Olsen *et al.* 2007), and an average of two in Uganda (Oyugi *et al.* 2007).

Reasons for treatment interruption

Twenty-two studies, 18 from developed countries and four from Africa, investigated reasons for treatment interruptions (Table 2). Toxicity, adverse events, and side effects were the most frequently reported reasons, with between 6% (Saitoh *et al.* 2008) and 80% of patients reporting these reasons (Chen *et al.* 2002). Other reasons included pill burden (Moore *et al.* 2009), intercurrent illness (Wolf *et al.* 2005), patient's decision (Krentz *et al.* 2003; Sommet *et al.* 2003; Gibb *et al.* 2004; Pavie *et al.* 2005; Saitoh *et al.* 2008; Moore *et al.* 2009), treatment fatigue (Saitoh *et al.* 2008), social and psychiatric issues (Uhagaze *et al.* 2006; Saitoh *et al.* 2008), perceived lack of benefits (Tarwater *et al.* 2003; Gibb *et al.* 2004) and physician's decision (Wolf *et al.* 2005) because of drug interactions, surgery, or other reasons. A study from Australia found that 38% of patients interrupted treatment for solely clinical reasons and 29% for solely lifestyle reasons (Grierson *et al.* 2004). Costs were the main reason for treatment interruptions (>60%) in two studies from Nigeria (Adeyemi & Olaogun 2006; Wenkel *et al.* 2006). Pharmacy stock outs and poor access to drugs were reported in three of the four studies from developing countries (Adeyemi & Olaogun 2006; Wenkel *et al.* 2006; Pasquet *et al.* 2010).

Risk factors for treatment interruption

Sixteen studies (12 from developed countries) reported on risk factors for treatment interruption. The most commonly reported risk factors were younger age (Mocroft *et al.* 2001; Gandhi *et al.* 2004; Li *et al.* 2005; Nacher *et al.* 2006; Holkmann Olsen *et al.* 2007; Moore *et al.* 2009; Kranzer *et al.*2010) and injecting drug use (Taffe *et al.* 2002; Compostella *et al.* 2005; Touloumi *et al.* 2006; Kavasery *et al.* 2009; Moore *et al.* 2009) (Table 3). The effect of gender and CD4 count on treatment interruption was inconsistent across studies: a high CD4 count (baseline or current) was associated with interruptions in some studies (Taffe *et al.* 2002; Touloumi *et al.* 2006; Holkmann Olsen *et al.* 2007; Moore *et al.* 2009; Kranzer *et al.* 2010) while others reported an association between low CD4 count and treatment interruptions (Li *et al.* 2005; Touloumi *et al.* 2006; Kavasery *et al.* 2009). Socioeconomic variables such as employment, income, education, and being homeless were also identified as risk factors for interruption in some studies (Taffe *et al.* 2002; Oyugi *et al.* 2007; Marcellin *et al.* 2008; Das-Douglas *et al.* 2009; Kavasery *et al.* 2009). One study reported that the odds of treatment interruption among homeless and marginally housed patients was six times higher if their health care plan included consumer cost-sharing (Das-Douglas *et al.* 2009). Finally, a study from Cameroon reported that pharmacy stock shortages were identified as a major risk factor for treatment interruption (Marcellin *et al.* 2008).

Consequences of treatment interruption

Thirty-eight studies reported on various consequences of treatment interruption, comprising mortality, opportunistic infections, immunological and virologic changes, the development of resistance mutations, neurocognitive impairment, and decreased health-related quality of life.

Consistent with the findings of structured interruption studies, unstructured treatment interruptions were commonly associated with a higher risk of death and opportunistic infection and a lower probability of increased CD4 cell counts (Hogg *et al.* 2002; Taffe *et al.* 2002; Schrooten *et al.* 2004; Holkmann Olsen *et al.* 2007; Pai *et al.* 2009; Zhang *et al.* 2010; Kaufmann *et al.* 2011). Furthermore, a high prevalence of neurocognitive impairment (Munoz-Moreno *et al.*2010) and lower health-related quality of life

Table 1 Frequency of treatment interruptions

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Adeyemi and Olaogun (2006)	Adults	Nigeria	2005	Cross-sectional study	Self-report	–	560	22.0	–	–	–	–
Ahonkhai *et al.* (2011)	Adults	South Africa	2004–2008	Prospective cohort study	Unknown	–	11 397	11.0	–	–	–	–
Ammassari *et al.* (2004)	Adults	Italy	–	Cross-sectional study	Self-report	–	116	15.0	–	–	–	–
Bansi *et al.* (2008)	Adults	UK	1996–2005	Prospective cohort study	Unknown	>2 weeks	12 977	21.7	4.4 months	2.0	–	–
Boileau *et al.* (2008)	Adults	Burkina Faso, Mali	2005	Cross-sectional study	Self-report	–	606	22.3	–	–	–	–
Compostella *et al.* (2005)	Adults	Italy	–	Cross-sectional study	Self-report	–	119	56.3	–	–	–	–
Das-Douglas *et al.* (2009)	Homeless and marginally housed	USA	2006	Cross-sectional study	Self-report	>48 h	125	11.2	–	–	–	–
Ekstrand *et al.* (2010)	Adults	India	–	Prospective cohort study	Self-report	>48 h	552	20.0	–	–	–	–
Ekstrand *et al.* (2008)	Adults	India	–	Prospective cohort	Self-report	>48 h	229	48.0	–	–	–	–
Ekstrand *et al.* (2008)	Adults	India	–	Cross-sectional study	Self-report	>48 h	93	31.0	–	–	–	–
Gandhi *et al.* (2004)	Women	USA	–	Prospective cohort	Self-report	>48 h	120	27.2	–	–	–	–
Glass *et al.* (2006)	Adults	Switzerland	2003	Cross-sectional study	Self-report	>24 h in the 4 weeks pre-survey	3607	5.8	–	–	–	–
Grierson *et al.* (2005)	Adults	Australia	2003	Cross-sectional national survey	Self-report	–	1059	47.0	87 days	–	–	–
Grierson *et al.* (2004)	Adults	Australia	2001/2002	Cross-sectional national survey	Self-report	–	640	71.7	–	–	–	–
Holkmann Olsen *et al.* (2007)	Adults	Europe (EuroSIDA)	Until September 2005	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	>3 months	3811	23.1	18 months	6.0	–	–
Kaptue *et al.* (2002)	Adults	Cameroon	–	Prospective cohort study	Unknown	–	50	30.0	–	–	–	–
Kaufmann *et al.* (2011)	Adults	Switzerland	1996–2008	Prospective cohort study	Recorded by clinician	>1 month	2491	51.0	9 months	–	–	–
Kavasery *et al.* (2009)	Injecting drug users	USA	Until July 2005	Prospective cohort study	Self-report	>6 months	335	77.6	12 months	–	–	–

Table 1 *(Continued)*

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	N	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Knobel *et al.* (2009)	Adults	Spain	Until July 2007	Prospective cohort study	Computer assisted pharmacy dispensing system and self-report	>3 days	540	42.8	–	–	–	–
Knobel *et al.* (2002)	Adults	Spain	1998/ 1999	Cross-sectional survey with self-reported TI	Self-report with validation of a subset	>2 days	3004	15.0	–	–	–	–
Kouanfack *et al.* (2008)	Adults	Cameroon	2006/ 2007	Cross-sectional survey	Unknown	–	427	9.6	–	–	–	–
Kranzer *et al.* (2010)	Adults	South Africa	2004– 2009	Prospective cohort study	Pharmacy record and clinical records	>30 days	1154	–	228 days	–	12.8/ 100 PY	21.4/ 100 PY
Lazar *et al.* (2010)	Adolescents	Romania	–	Cross-sectional survey	Self-report	–	96	51.60	–	–	–	–
Li *et al.* (2005)	Homosexual men	USA	Until March 2002	Prospective cohort study	Self-report	–	687	10.5 – 1997 5.2 – 1999 7.7 – 2001	61 days	–	–	–
Marcellin *et al.* (2008)	Adults	Cameroon	2006/ 2007	Cross-sectional national survey	Self-report	>2 days in the 4 weeks pre-study	533	12.8	–	–	–	–
Martsinovskaya *et al.* (2010)	Adults	Ukraiine	2008	Cross-sectional survey	Unknown	–	3133	22.0	–	–	–	–
Mbanya (2003)	Adults, self-paying	Cameroon	–	Prospective cohort study	Unknown	–	50	8.0	–	–	–	–
Mocroft *et al.* (2001)	Adults	UK	Until December 1998	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	–	556	–	7 months	–	26.0%	56.1%
Moore *et al.* (2009)	Adults, outpatients	British Columbia	2000– 2006	Prospective cohort study	Recorded by clinician	>3 months	1707	37.7	–	–	–	–
Murri *et al.* (2002)	Adults	Italy	2001	Cross-sectional survey	Self-report	–	80	26.0	–	–	–	–
Murri *et al.* (2009)	Adults	Italy	2006	Cross-sectional survey	Self-report	–	359	24.7	–	–	–	–

Table 1 *(Continued)*

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Nacher *et al.* (2006)	Adults, hospital based cohort	French Guiana	1992–2003	Prospective cohort study	Unknown	>1 year	1213	–	–	4.3	–	–
Oyugi *et al.* (2007)	Adults, self-paying	Uganda	2002–2004	Prospective cohort study	Electronic medication monitor, self-report, pill count	>48 h ≤30 days	97	65.0	11.5 days	–	–	–
Pasquet *et al.* (2010)	Adults	Ivory Coast	2006–2008	Prospective cohort study	Clinical records	>1 month	1554	53.4	–	–	–	–
Pai *et al.* (2009)	Recurrent prisoners	USA	1996–2005	Prospective cohort study	Dispensing pharmacy and community provider	Not taking antiretroviral therapy while outside of jail	467	83.1	–	–	–	–
Protopopescu *et al.* (2010)	Adults	France	–	Prospective cohort study	Clinical records	>60 days	832	11.5	109 days	2.9	–	–
Saitoh *et al.* (2008)	Children	USA	2000–2004	Prospective cohort study	Unknown	>3 months	405	–	16 months	–	17.8%	66.6%
Taffe *et al.* (2002)	Adults	Switzerland	Until May 2001	Prospective cohort study	Self-report	>1 month <3 months	4720	27.5	–	–	–	–
Touloumi *et al.* (2006)	Adults	Europe, Cascade study	Until August 2003	Prospective cohort study	Unknown	>2 weeks	1551	19.3	–	–	–	–
Uhagaze *et al.* (2006)	Adults	Senegal	2004–2005	Cross-sectional survey	Unknown	–	602	7.0	150 days	–	–	–
Wenkel *et al.* (2006)	Adults, user fees	Nigeria	June 2005	Cross-sectional national survey with self-reported TI	Self-report	–	122	72.0	189 days	–	–	–
Zhang *et al.* (2010)	Adult	the Netherlands	Until February 2008	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	Any duration	3321	15.4	3.1 months	–	–	–

Table 2 Reasons for treatment interruption

Author	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Reasons
Adeyemi and Olaogun (2006)	Nigeria	2005	Cross-sectional study	Self-report	–	123	Cost (69%), side effects (22%), missing of clinic days (12%), poor access to drug (urban 52%, rural 87%)
Bedimo *et al.* (2006)	USA	1996–2001	Prospective cohort study	Unknown	>180 days	71	Complete viral suppression (1%), treatment failure (4%), non-adherence and adverse events (94%)
Chen *et al.* (2002)	USA	–	Prospective cohort study	Clinical records	>30 days	75	Side effects (80%), new opportunistic infection (1%), virologic failure (12%), non-adherence (7%), financial (15%)
Gibb *et al.* (2004)*	UK, Ireland	1999–2002	Prospective cohort study	Clinical records	>4 weeks	71	Poor adherence (23%), parent or child request (24%), adverse drug reactions (9%), perceived lack of virologic and immunologic benefits (21%)
Gonzalez *et al.* (2003)	Spain	–	Prospective cohort study	Unknown	–	64	Drug-related adverse events (55%), patient or physician decision (45%),
Grierson *et al.* (2004)	Australia	2001/2002	Cross-sectional national survey	Self-report	–	263	Solely clinical reasons (38%), both/neither lifestyle and clinical reasons (33%), solely lifestyle reason (29%)
Krentz *et al.* (2003)	Canada	1999–2002	Prospective cohort study	Unknown	>2 months	50	Virologic failure and a drug resistance (41%), adverse effects or toxicity (36%), patient decision (14%)
Landman *et al.* (2003)	France	1998–2002	Retrospective cohort study	Unknown	>2 months	80	Patient's request (19%), lipodystrophy (21%), other drug toxicity (23%), pregnancy or post-partum (11%), high CD4 count (20%), early therapy (6%)
Lazar *et al.* (2010)	Romania	–	Cross-sectional survey with self-reported TI	Self-report	–	50	Neglect (59%), boredom (14%), the wish that other do not know that one is ill (10%), lack of medication (10%)
Moore *et al.* (2009)	Canada	2000–2006	Prospective cohort study	Recorded by clinician	>3 months	74	Medication associated adverse event (7%), pill burden (2%), interaction with methadone (0.3%), pregnancy (0.2%), patient-initiated (2%), treatment failure (0.3%), unknown (88%)
Munoz-Moreno *et al.* (2010)	Spain	2006–2008	Cross-sectional study	HIV database, clinical records	>15 days	27	Structured TI (42%), toxicity (22%), individual decision (36.%)
Murri *et al.* (2002)	Italy	2001	Cross-sectional survey	Self-report	–	23	Side effects (43%) – particularly vomiting and gastrointestinal symptoms, other reasons included being bored of therapy and being in holiday
Pasquet *et al.* (2010)	Ivory Coast	2006–2008	Prospective cohort study	Clinical records	–	830	Drug stock outs (9%), travel/funeral/adverse events/ traditional medicine/inability to pay (12%), not recorded (79%)
Pavie *et al.* (2005)	France	1999–2003	Retrospective chart review	Unknown	–	30	Patient initiated (50%), side effects (50%)
Saitoh *et al.* (2008)	USA	2000–2004	Prospective cohort study	Unknown	>3 months	72	Medical fatigue (69%), toxicity (14%), adverse events (6%), social and behavior issues (6%), social issues (11%), behavior issues (7%), psychiatric disease (3%)
Sanchez *et al.* (2007)	Spain	–	Prospective cohort study	Pharmacy prescriptions	>4 weeks	20	Toxicity (65%)

Table 2 *(Continued)*

Author	Country	Time period	Study description	Measure of TI	Definition of TI	N	Reasons
Sommet *et al.* (2003)	France	1998–2001	Prospective cohort study	Unknown	>30 days	163	Virologic failure (43%), side effects (33%), patient initiated (24%)
Uhagaze *et al.* (2006)	Senegal	2004–2005	Cross-sectional survey	Unknown	–	42	Fear of side effects (72%), having forgotten to take the drugs (26%), the illness (33%), falling asleep (15%), depression (17%)
Tarwater *et al.* (2003)	USA	–	Prospective cohort study	Clinical records, clinician, self-report	–	105	Perceived lack of an indication for therapy on the part of the clinician (44%), drug toxicity (15%), non-adherence (14%), performance of resistance testing (15%), failure (8%)
Van Valkengoed *et al.* (2003)	Europe	–	Prospective cohort study	Unknown	>7 days	201	Toxicity (43%), patient's decision (29%)
Wolf *et al.* (2005)	Germany	1999–2002	Prospective frequency matched cohort study	Recorded by clinician	>2 weeks	133	Toxicity and/or side effects (39%), physician's decision or recommendation (20%), intercurrent illnesses (5%), other reasons (3%)
Wenkel *et al.* (2006)	Nigeria	2006	Cross-sectional survey	Self-report	–	88	Financial constraints (61%), ARVs out of stock (14%), side effects (6%), others (19%)

*Children.

(Krentz *et al.* 2003) were reported in individuals interrupting therapy.

All studies investigating CD4 and viral load response during treatment interruption reported a substantial drop of CD4 count and increase in viral load compared with pre-interruption levels (Gonzalez *et al.* 2003; Sommet *et al.* 2003; Tarwater *et al.* 2003; Gibb *et al.* 2004; Achenbach *et al.* 2005; Burton *et al.* 2005; Giard *et al.* 2005; Pavie *et al.* 2005; Wolf *et al.* 2005; Bedimo *et al.* 2006; Hull *et al.* 2006; Sanchez *et al.* 2007; Saitoh *et al.* 2008; Mussini *et al.* 2009; Sarmati *et al.* 2010). The influence of nadir CD4 counts, CD4 counts, and viral load levels prior to treatment interruption on CD4 decay was inconsistent, with some studies reporting an effect (Gonzalez *et al.* 2003; Wolf *et al.* 2005; Hull *et al.* 2006; Mussini *et al.* 2009) while others reported no effect (Saitoh *et al.* 2008).

CD4 counts rose after resumption of therapy (Chen *et al.* 2002; Sommet *et al.* 2003; Gibb *et al.* 2004; Giard *et al.* 2005; Wolf *et al.* 2005; Sanchez *et al.* 2007; Touloumi *et al.* 2008; Mussini *et al.* 2009). The increase was biphasic with a steeper slope in the first months after re-initiation of therapy (Touloumi *et al.* 2008; Mussini *et al.* 2009). However, CD4 recovery was incomplete: in studies reporting CD4 recovery, the proportion of patients experiencing an increase in CD4 counts to levels before treatment interruption at 24 months ranged from 28% to 69% (Chen *et al.* 2002; Giard *et al.* 2005). One study that investigated the effect of treatment interruption in a prison setting found that patients with continuous ART treatment gained on average 0.67 CD4 cells per months compared with intermittently treated patients who lost cells at an average of 0.93 CD4 cells per month (Pai *et al.* 2009).

The majority of studies reported that patients experienced virologic suppression once treatment was restarted (Chen *et al.* 2002; Yozviak *et al.* 2002; Gibb *et al.* 2004; Wolf *et al.* 2005; Touloumi *et al.* 2008; Mussini *et al.* 2009). However, treatment interruptions were associated with an increased risk of rebound and virologic failure in developed and developing countries (Murri *et al.* 2002; Parienti *et al.* 2004, 2008; Spacek *et al.* 2006; Laher *et al.* 2007; Oyugi *et al.* 2007; Bansi *et al.* 2008; Boileau *et al.* 2008; Kouanfack *et al.* 2008; Knobel *et al.* 2009; Datay *et al.* 2010; Ekstrand *et al.* 2010). A study from Spain differentiated treatment interruptions because of patients' choice and adherence difficulties or physician's advice for toxicity, severe side effects, or intercurrent illness. After adjusting for drug regimen and adherence level, the risk of a detectable viral load (>500 copied/ml) or death was 3.62 for the former and 1.36 for the latter, compared with continuous treatment (Knobel *et al.* 2009). A study among adults receiving boosted protease inhibitors (PI) reported

Table 3 Risk factors for treatment interruptions

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Risk factors for TI
Compostella *et al.* (2005)	Adults	Italy	–	Cross-sectional study	Self-report	–	119	Older age Injecting drug use Time lag between HIV diagnosis and treatment initiation Anxiety related to therapy Subjective antiretroviral therapy (ART) intolerance Experience of more than four regimens
Das-Douglas *et al.* (2009)	Homeless and marginally housed	USA	2006	Cross-sectional study	Self-report	>48 h	125	Consumer cost-sharing Emergency department visits in the past year Being homeless Depression
Gandhi *et al.* (2004)	Women	USA	–	Prospective cohort study	Self-report	>48 h	120	Younger age Reduced adherence Alcohol use Higher viral load
Holkmann Olsen *et al.* (2007)	Adults	Europe (EuroSIDA)	Until September 2005	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	>3 months	3811	Higher current log viral load Higher current CD4 count Women Younger age
Kavasery *et al.* (2009)	Injecting drug users	USA	Until July 2005	Prospective cohort study	Self-report	>6 months	335	Younger age Lower CD4 count Higher HIV RNA level Daily injecting drug use Unemployment ART initiation in later calendar years Using crack and alcohol
Kranzer *et al.* (2010)	Adults	South Africa	2004–2009	Prospective cohort study	Pharmacy record and clinical records	0>30 days	1154	Men* Higher baseline CD4 count* Shorter time on ART* ART initiation in later calendar years*
Li *et al.* (2005)	Homosexual men	USA	Until March 2002	Prospective cohort study,	Self-report	–	687	Younger age Black race Lower CD4 count Higher HIV RNA level Shorter time on ART Not taking 3TC
Marcellin *et al.* (2008)	Adults	Cameroon	2006/2007	Cross-sectional national survey	Self-report	>2 days in the 4 weeks preceding the study	533	Men Low educational level Low monthly household income Treatment with 3TC Binge drinking Number of symptoms Pharmacy stock shortages

Table 3 (*Continued*)

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Risk factors for TI
Mocroft *et al.* (2001)	Adults	UK	Until end of 1998	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	–	556	Younger age* Men* Higher viral load*
Moore *et al.* (2009)	Adults, outpatients	British Columbia	2000–2006	Prospective cohort study	Recorded by clinician	>3 months	1707	History of IDU Higher baseline CD4 count Hepatitis C pos Women Younger age No AIDS diagnosis at baseline Less experienced physician
Murri *et al.* (2009)	Adults	Italy	2006	Cross-sectional survey	Self-report	–	359	Suboptimal adherence Higher viral load Smokers NNRTIs
Nacher *et al.* (2006)	Adults, hospital based cohort	French Guiana	1992–2003	Prospective cohort study	Unknown	>1 year	1213	Younger age Initial CD4 count >500 cells/μl
Oyugi *et al.* (2007)	Adults, self-paying	Uganda	2002–2004	Prospective cohort study	Electronic medication monitor, self-report, pill count	>48 h ≤30 days	97	Financial difficulties
Protopopescu *et al.* (2010)	Adults	France	–	Prospective cohort study	Clinical records	>60 days	832	Good patient-provide relationship No social support from their main partner No prior history of viral rebound Fewer HIV-related clinical events
Taffe *et al.* (2002)	Adults	Switzerland	Until May 2001	Prospective cohort study	Self-report	>1 month <3 months	4720	High baseline viral load High baseline CD4 count Injecting drug use Low education
Touloumi *et al.* (2006)	Adults	Europe, Cascade study	Until August 2003	Prospective cohort study	Unknown	>2 weeks	1551	Women Injecting drug use High baseline viral load High baseline CD4 count Low current CD4 count

*Associated with discontinuation (not TI).

that average adherence predicted viral suppression, whereas treatment interruption did not in multivariate analysis (Parienti *et al.* 2010).

Four studies investigated the development of resistance mutations (Parienti *et al.* 2004; Spacek *et al.* 2006; Oyugi *et al.* 2007; Sanchez *et al.* 2007). In a study from France, interrupting treatment more than once was significantly associated with the development of resistance to the non-nucleoside-reverse-transcriptase inhibitors (NNRTI) class (hazard ratio 22.5, 95% CI 2.8–180.3) (Parienti *et al.* 2004). Among 19 treatment interrupters in Spain, nine had mutations in the reverse transcriptase gene and 17 had polymorphism in the protease gene, with L63P being the most commonly found (Sanchez *et al.* 2007). In Uganda, none of the patients with continuous treatment had evidence of resistance mutations, but 13% of patients with a history of treatment interruption had resistance mutations: all of them had mutations conferring nevirapine resistance, five had mutations conferring lamivudine resistance, and three had mutations conferring stavudine resistance (Oyugi *et al.* 2007). Another study from Uganda showed resistance to NNRTI class in 26 of 36 patients with detectable viral load with the most common mutation being K103N. Twenty-three of the 36 patients had the M184V/I mutation and three had genotypic resistance to PIs (Spacek *et al.* 2006).

Interventions

We only identified one intervention study. This randomized controlled trial from Kenya showed that short message service reminders either daily or weekly reduced the prevalence of treatment interruptions exceeding 48 h from 19% to 10% ($P = 0.03$) (Pop-Eleches *et al.* 2011).

Six studies investigating risk factors associated with treatment interruptions discussed possible interventions. Studies from developed countries suggested appropriate counseling on the consequences of drug discontinuation, encouragement of optimal adherence, offering of mental health services, addressing addictions, and providing services specifically engaging women and ethnic minorities (Li *et al.* 2005; Moore *et al.* 2009; Murri *et al.* 2009). Studies from Uganda and Cameroon emphasized the importance of steady and reliable access to medication, as well as free access to ART and possibly food supply programs (Oyugi *et al.* 2007; Marcellin *et al.* 2008). A study from South Africa concluded that interventions should be targeted at men and during the first 6 months on ART (Kranzer *et al.* 2010).

When patients were asked to give at least one suggestion how to improve adherence and reduce treatment interruptions: 46% suggested reduction in daily doses, 28% more detailed information about therapy, 27% more attention to side effects, 20% more time dedicated to adherence-related issues, 19% supervised treatment interruptions, and 16% psychological help (Ammassari *et al.* 2004).

Conclusions

Recent research has highlighted the importance of non-adherence to and defaulting from antiretroviral care in contributing to poor program outcomes (Garcia De Olalla *et al.* 2002; Nieuwkerk & Oort 2005; Mills *et al.* 2006; Maggiolo *et al.* 2007; Rosen *et al.* 2007; Brinkhof *et al.* 2009). Our review highlights that unstructured treatment interruptions, while far less frequently reported, are an important phenomenon both in developed and in developing countries and may result in excess mortality and opportunistic infections, increased risk of virologic failure, and poor immunological recovery.

Medication-taking behavior is characterized by adherence which is defined as 'extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen' and persistence defined as 'the duration of time from initiation to discontinuation of treatment' (Cramer *et al.* 2008). Persistence emphasizes the concept of continuous therapy and is influenced by both defaulting from antiretroviral care and treatment interruption' (Bae *et al.* 2011). Adherence and persistence are both important for optimal treatment outcomes, but their impact may vary dependent on the type of regimen prescribed and the duration and frequency of treatment interruptions.

We found that the characterization of treatment interruption in the literature to date is confused by heterogeneous definitions. A quarter of studies provided no definition, while for those that did definitions varied from more than 24 h to more than 1 year of discontinuation of treatment. Only half of studies reported on median duration of interruption. Similar problems with regard to uniformity of definitions have been encountered in studies investigating loss to follow-up where definitions ranged from 1 to 6 months late for a scheduled consultation or medication pick-up (Rosen *et al.* 2007). In addition, the method of determination of treatment interruption varied considerably: over a quarter of studies using self-report, while a similar number did not specify the method used to identify treatment interruptions.

The reported causes of treatment interruption are multidimensional and context-specific. However, research to date has largely assessed risk factors and reasons for treatment interruption, few in developing country settings. Studies from developing countries highlighted pharmacy stock outs and costs as important factors for treatment

interruptions. While several interventions have been proposed, only one has been formally assessed.

Data synthesis is a desirable goal for systematic reviews. However, in view of the substantial degree of heterogeneity between studies with regard to definitions of treatment interruption and methods used to identify treatment interruptions, we decided against providing a data synthesis. In addition, because treatment interruptions depend on duration of ART, incidence would be a more informative measure, but few studies provided incidence estimates. Another limitation of our review, reflecting a limitation of the published evidence, is that only four studies investigated the association between treatment interruption and genotypic resistance. The sample size of these studies was small. One of these studies relied on self-report to identify treatment interruptions. Larger studies using objective measures of treatment interruptions are needed to confirm the association between treatment interruption and genotypic resistance. Finally, although our search strategy was extensive, yielding a high number of studies, we cannot exclude the possibility that our search strategy may not have captured all reports of treatment interruption.

Our study highlights several directions for future research and practice. First, reporting on treatment interruptions should be encouraged, both to improve the quality of program outcome reports, and support better characterization and quantification of the problem. Second, more uniform reporting of treatment interruption should be encouraged to support comparability across studies, as has been proposed for treatment defaulting. The range of proposed interventions in the literature does not reflect the range of causes reported, with a notable absence of attention on some of the most frequently reported drivers of treatment interruption, including drug toxicity, adverse events, and side effects. This suggests that a first step to minimizing treatment interruptions in many settings is simply to provide better care to patients. Finally, intervention studies should be planned to determine the effectiveness of approaches to minimize treatment interruption and encourage treatment resumption.

In conclusion, treatment interruptions are common both in developed and in developing countries and are associated with increased morbidity, mortality, and possibly genotypic resistance. Future research should focus on evaluating interventions to address the most frequently reported reasons for interruptions to support patients in a way that maximizes the chances of continuous and effective treatment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy.

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12 Treatment interruption in a South African ART cohort

Treatment Interruption in a Primary Care Antiretroviral Therapy Program in South Africa: Cohort Analysis of Trends and Risk Factors

1. For a 'research paper' already published
   1.1. Where was the work published? ***Journal of Acquired Immune Deficiency Syndrome***
   1.2. When was the work published? ***2010***
   1.3. Was the work subject to academic peer review? ***Yes***
   1.4. Have you retained the copyright for the work? ***Yes***
   If yes, attach evidence of retention
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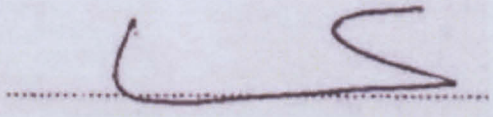
2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published?
   2.2. List the paper's authors in the intended authorship order
   2.3. Stage of publication – Not yet submitted/Submitted/Undergoing revision from peer reviewers' comments/In press

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, wrote the ethics, cleaned the data, linked the data, performed the data analysis and wrote the publication.



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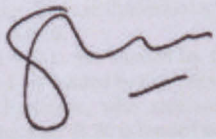
Supervisor or senior author's signature to confirm role as stated in (3)



Dr. Stephen D. Lawn
Supervisor and Co-Author

Treatment Interruption in a Primary Care Antiretroviral Therapy Program in South Africa: Cohort Analysis of Trends and Risk Factors

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Objective: To investigate antiretroviral treatment (ART) interruption in a long-term treatment cohort in South Africa.

Methods: All adults accessing ART between 2004 and 2009 were included in this analysis. Defaulting was defined as having stopped all ART drugs for more than 30 days. Treatment interrupters were patients who defaulted and returned to care during the study, whereas loss to follow-up was defined as defaulting and not returning to care. Kaplan–Meier estimates and Poisson regression models were used to analyze rates and determinants of defaulting therapy and of treatment resumption.

Results: Overall rate of defaulting treatment was 12.8 per 100 person-years (95% confidence interval: 11.4 to 14.4). Risk factors for defaulting were male gender, high baseline CD4 count, recency of ART initiation, and time on ART. The probability of resuming therapy within 3 years of defaulting therapy was 42% (event rate = 21.4 per 100 person-years). Factors associated with restarting treatment were female gender, older age, and time since defaulting.

Conclusions: Defaulting treatment need not be an irreversible event. Interventions to increase retention in care should target men, less immunocompromised patients, and patients during the first 6 months of treatment. Resumption of treatment is most likely within the first year of interrupting therapy.

Key Words: antiretroviral, Africa, HIV, loss to follow-up, unstructured treatment interruption

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INTRODUCTION

Access to antiretroviral therapy (ART) has improved substantially in resource-limited settings in Africa, Asia, and South America where 90% of people with HIV/AIDS reside. According to World Health Organization (WHO) estimates, more than 4 million people with HIV/AIDS in low-income and middle-income countries had initiated treatment by the end of 2008.[1] Despite this success, ensuring that patients remain in care over time remains one of the major challenges in resource-limited settings. Much attention has been paid to patient adherence,[2–5] loss to follow-up, and mortality in ART programs in resource-limited settings.[6–9] A systematic review of 33 patient cohorts from 13 African countries reported that only between 46% and 85% of patients remained in care at 2 years.[8]

The realization that a substantial proportion of patients reported as lost to follow-up may have died has led to concern that there may be significant biases in program outcome reports of survival.[10] Another potential source of bias is the fact that a proportion of patients may only transiently default, returning to care at a later stage. Such unstructured treatment interruption has been reported to occur in around 20% of patients in industrialized settings.[11–14] The proportion of patients who transiently interrupt treatment in resource-limited settings is largely unreported.

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No conflicts of interest to declare.

The authors K.K. designed the study, collected the data, and wrote the article with input from N.F., J.L., J.Z., C.O., S.D.L. and R.W.; K.K. designed and did the statistical analyses with input from J.L. and N.F; J.Z. and C.O. oversaw the field site; and R.W. was responsible for research infrastructure. All authors contributed to and approved the final version of the article.

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Treatment interruptions, planned or otherwise, have been found to increase the risk of opportunistic infection and death,[15–17] with viral load increase and associated CD4 decline most pronounced in the first 2 months.[16,18–20] Interruptions raise similar concerns with respect to drug resistance and increased mortality as suboptimal adherence.[11,15,21–23] However, few studies have addressed the issue of unstructured treatment interruptions in resource-limited settings. The aim of this study was to investigate the frequency and risk factors of defaulting treatment and identify factors associated with subsequent return to care in a long-term treatment cohort in South Africa.

METHODS

Study Site and Data Collection

The study was based in a periurban township in the greater area of Cape Town, with a population of approximately 15,000 people and an estimated adult HIV prevalence of 23% in 2005.[24] The community is served by a single public-sector primary care clinic which provides ART free of charge.

ART provision began in 2004. From 2005 to 2009, ART services were partly provided according to the antiretroviral treatment protocol of the Western Cape and partly through a study funded by the National Institutes of Health (NIH). Patients enrolled in the NIH-funded study could access ART with a CD4 count below 350 cells per microliter or WHO stage 3 disease as compared with 200 cells per microliter or WHO stage 4 disease in the provincial program. The NIH-funded study completed enrollment in 2007 after which all patients were treated in the provincial ART program.

Initial evaluation for ART eligibility included medical history, physical examination, and CD4 cell count. A follow-up appointment was scheduled 1–2 weeks later when the laboratory results were reviewed, and ART eligibility was determined. Patients eligible for ART underwent 3 adherence counseling sessions before starting treatment.

The initial follow-up schedule for those starting ART included 1 visit 2 weeks after ART initiation, followed by monthly visits until month 3. Patients who were stable on ART and did not experience any adherence problems were thereafter seen every 3 months. Three attempts were made to contact patients who had missed appointments.

All patients aged ≥15 years accessing ART in the primary health care clinic between March 01, 2004, and December 31, 2009, were included in the analysis.

Sociodemographic and clinical data at baseline and laboratory data were collected prospectively using a standardized data form. All laboratory tests were performed by the National Health Laboratory Services in Cape Town.

Definitions

"Patients defaulting treatment" were defined as those who had not presented at the pharmacy for ART refills for more than 30 days. This category included patients who subsequently returned to care and restarted ART (treatment interrupters) and patients who had not returned to care at the time of censoring (loss to follow-up) (Fig. 1).

Treatment interruption was defined as a patient-initiated episode of more than 30 days of stopping ART (same definition as defaulting) but who subsequently resumed treatment (Fig. 1).

"Patients lost to follow-up" were those who stopped ART for more than 30 days and had not returned to care at the time of censoring (Fig. 1).

Study Design

In-program data on death, transfers outs, and loss to follow-up were collected prospectively. Death on ART was defined as any death within 3 months of drug refill. If the exact date of death was not recorded, it was estimated to be the 15th of the month after the last clinic appointment.

Patients who had stopped ART for more than 30 days and resumed therapy were identified using the pharmacy dispensing data. The electronic pharmacy dispensing system records each time medication is dispensed to a patient. Treatment interruption was verified through folder reviews.

The first endpoint was the time from ART initiation to the first time at which all drugs were stopped for a period of at least 30 days (default). Follow-up of patients on continuous therapy was censored at the date of death, date of transfer, or study end (December 31, 2009).

The second endpoint was treatment resumption, defined as the time from defaulting treatment for the first time to the time of restarting ART. Follow-up of patients for whom therapy was not resumed was censored at the date of death, date of transfer, date of migration, or study end. For a proportion of these patients (48%) vital status, date of death, date of transfer, and date of migration was determined by home visits.

Statistical Analysis

All analyses were carried out using Stata version 10.0 (Stata Corp LP, College Station, TX). Frequency tables were produced for all categorical baseline characteristics. For continuous baseline characteristics, the median and interquartile ranges were reported. Standard survival analysis methods, including Kaplan–Meier estimates and Poisson regression models, were used to analyze the rate and determinants of defaulting therapy and of treatment resumption after defaulting treatment for the first time. The proportional hazards assumption for potential interaction between each variable and time was tested using the likelihood ratio test. A univariate Poisson regression model was used to determine risk for time-to-event outcomes for each exposure variable. Multivariate models were built through backwards elimination. Sensitivity analyses were conducted excluding individuals with unascertained vital status. All reported P values are exact and 2-tailed, and for each analysis, $P < 0.05$ was considered significant.

Ethical Approval

The study was approved by the University of Cape Town Ethics Committee and the London School of Hygiene and Tropical Medicine Ethics Committee. Written informed consent was obtained from all patients at enrollment.

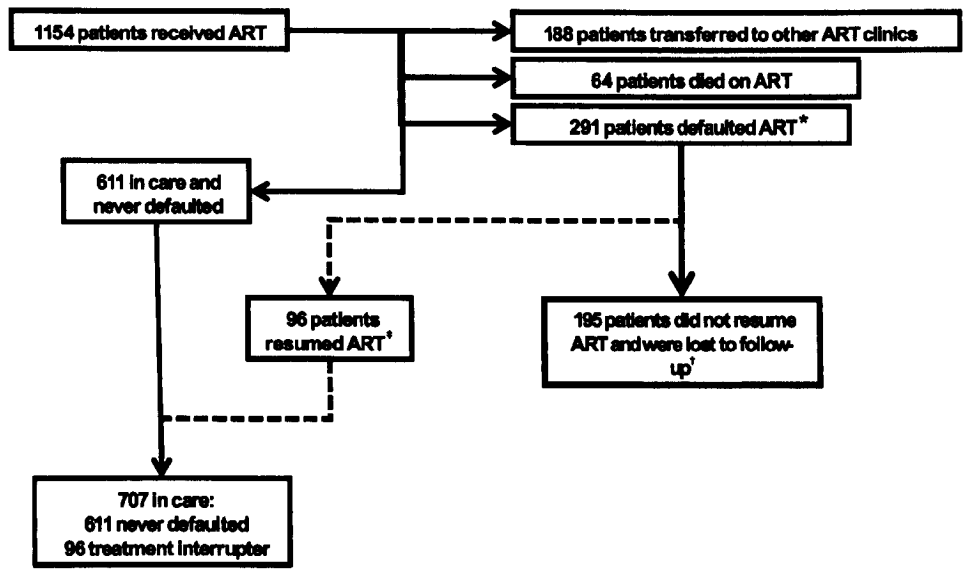

FIGURE 1. Flow chart of patients in care, first time defaulters and treatment interrupters. *Defaulting treatment was defined as having stopped all ART drugs for more than 30 days. This category included patients who subsequently returned to care and restarted ART (treatment interrupters) and patients who had not returned to care at the time of censoring (loss to follow-up). †Loss to follow-up was defined as stopping ART for more than 30 days and not returning to care at the time of censoring. ‡Treatment interruption was defined as a patient-initiated episode of more than 30 days of stopping ART and subsequently resuming treatment.

RESULTS

Patient Characteristics

A total of 1154 patients were included in the analysis (Table 1), and the median time of follow-up was 1.45 years [interquartile range (IQR): 0.48–3.24]. The majority of patients were young women (65.2%) and residents in the township (95.5%). Before treatment initiation, the majority of patients were in WHO clinical stage 3 (51.1%) and 4 (25.1%), and median CD4 count was 122 cells per microliter (IQR: 54–190). The number of patients initiating ART per year doubled from 137 in 2004 to 279 in 2006 and declined thereafter.

TABLE 1. Baseline Characteristics of Patients (n = 1154) Who Enrolled in the ART Program Between 2004 and 2009

Variable	n (%)	Median (IQR)
Gender		
Women	752 (65.2)	
Men	402 (34.8)	
Age (yrs)	—	31.9 (27.3–37.5)
Residents in the study township		
Yes	1102 (95.5)	
No	40 (3.5)	
Unknown	12 (1.0)	
Transferred in from another ART service		
No	1046 (90.6)	
Yes	108 (9.4)	
Year of initiating ART		
2004	137 (11.9)	
2005	242 (21.0)	
2006	279 (24.2)	
2007	153 (13.3)	
2008	155 (13.4)	
2009	188 (16.3)	
WHO clinical stage*		
1	106 (9.3)	
2	166 (14.5)	
3	585 (51.1)	
4	287 (25.1)	
Baseline CD4 (cell/μL)†	—	122 (54–190)

*Ten missing values.
†One-hundred fourteen missing values.

A total of 291 patients defaulted treatment at least once (Fig. 1). Among these, 96 resumed therapy (treatment interruption), whereas 195 did not resume therapy during follow-up (lost to follow-up). Of the 96 individuals resuming therapy, 75 individuals had 1 episode of treatment interruption, 19 had 2, and 2 had 3. The median time patients failed to receive ART was 228 days (IQR: 126–409) during the first episode of treatment default and 194 days (IQR 121-278) during the second episode. Thirty-five patients who had stopped treatment underwent rescreening that included clinical assessment, laboratory tests, and adherence counseling and yet did not resume therapy during the period of the study.

Subsequent analyses investigated first episode of treatment interruption by analyzing the time to stopping treatment for the first time and resuming therapy thereafter.

Factors Associated With the Probability of Defaulting Treatment

The overall rate of treatment default for the first time was 12.8 per 100 person-years [95% confidence interval (CI): 11.4 to 14.4]. The Kaplan–Meier estimate of the probability of defaulting treatment for at least 30 days was 14.9% (95% CI: 12.7 to 17.4) by 1 year, 25.6% (95% CI: 22.7 to 28.8) by 2 years and 41.0% (95% CI: 37.0 to 45.3) by 5 years from ART initiation (Fig. 2).

Factors associated with increased risk of defaulting therapy in univariate analysis were male gender, higher baseline CD4 count, recency of ART initiation, and shorter duration on ART (Table 2). Defaulting rate was highest in the first 6 months of ART (18.2 per 100 person-years, 95% CI:

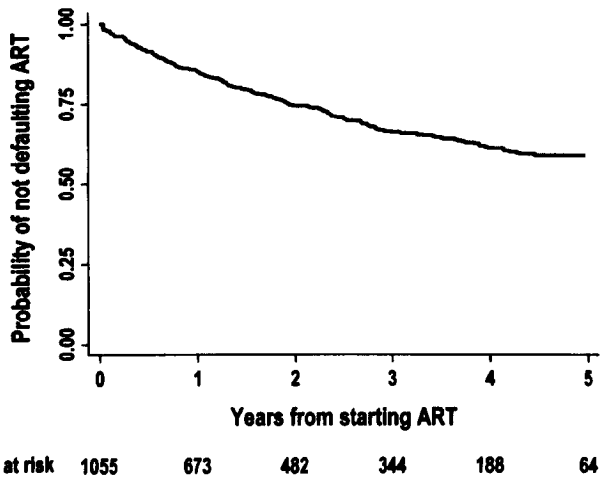

FIGURE 2. Kaplan–Meier plot showing the probability of not defaulting ART from the time of initiating ART up to the end of the fifth year of treatment.

14.7 to 22.5) but decreased thereafter and had more than halved after 2 years (8.8 per 100 person-years, 95% CI: 7.0 to 11.0).

Gender, baseline CD4 count, time on ART, and date of initiation remained significantly associated with defaulting in the multivariate model. Men were 1.51 (95% CI: 1.18 to 1.93) times more likely to default treatment compared to women, as were those patients with a higher baseline CD4 count. The adjusted risk of defaulting treatment increased by 1.30 (95% CI: 1.17 to 1.44) for each calendar year. Patients on treatment for more than 2 years had a lower risk of 0.69 (95% CI: 0.48 to 0.98) of defaulting compared with patients during the first 6 months of treatment. Similar results were found in a sensitivity analysis that excluded individuals whose vital status could not be ascertained.

Factors Associated With the Probability of Resuming Therapy

A total of 291 patients defaulted treatment at least once. The overall rate of treatment resumption after defaulting treatment for the first time was 21.4 per 100 person-years (95% CI: 17.5 to 26.2) (Fig. 3). The Kaplan–Meier cumulative

TABLE 2. Risk Factors for Defaulting Treatment

Variable	Number Defaulting Treatment	Person-Years at Risk	Rate of Default of Treatment per 100 Person-Years (95% CI)	Unadjusted HR of Default of Treatment (95% CI)	*P*	Adjusted HR of Default of Treatment (95% CI)	*P*
Gender							
Women	172	1544	11.1 (9.6 to 12.9)	1	—	1	—
Men	115	692	16.6 (13.9 to 20.0)	1.49 (1.17 to 1.89)	<0.01	1.51 (1.18 to 1.93)	<0.01
Age (yrs)							
≤30	196	1473	13.3 (11.6 to 15.3)	1	—	—	—
>30	91	762	11.9 (9.7 to 14.7)	0.90 (0.70 to 1.15)	0.40	—	—
Residents in the study township							
Yes	271	2168	12.5 (11.1 to 14.1)	1	—	—	—
No	10	65	15.4 (8.3 to 28.7)	1.23 (0.66 to 2.32)	0.52	—	—
Transferred from another ART service							
No	268	2110	12.7 (11.3 to 14.3)	1	—	—	—
Yes	19	127	15.0 (9.6 to 23.5)	1.18 (0.74 to 1.88)	0.48	—	—
WHO stage							
1 or 2	57	499	11.4 (8.8 to 14.8)	1	—	—	—
3 or 4	209	1608	13.0 (11.4 to 14.9)	1.14 (0.85 to 1.53)	0.37	—	—
Baseline CD4 count (cells/μL)							
≤100	89	823	10.8 (8.8–13.3)	1	—	1	—
101–200	103	716	14.4 (11.9 to 17.3)	1.33 (1.00 to 1.77)	0.05	1.32 (0.99 to 1.76)	0.06
>200	73	530	13.8 (10.9 to 17.3)	1.27 (0.83 to 1.73)	0.13	1.39 (1.02 to 1.91)	0.04
Year of initiating ART*							
2004	24	434	5.5 (3.7 to 8.2)	1.36 (1.24 to 1.48)	<0.01	1.30 (1.17 to 1.44)	<0.01
2005	76	703	10.8 (8.6 to 13.5)				
2006	83	599	13.9 (11.2 to 17.2)				
2007	47	247	19.0 (14.3 to 25.3)				
2008/2009	57	253	22.6 (17.4 to 29.3)				
Time on ART							
<6 months	84	462	18.2 (14.7 to 22.5)	1	—	1	—
6 months to 2 years	130	939	13.8 (11.7 to 16.4)	0.76 (0.58 to 1.00)	0.05	0.86 (0.65 to 1.15)	0.31
>2 years	73	834	8.8 (7.0 to 11.0)	0.48 (0.35 to 0.66)	<0.01	0.69 (0.48 to 0.98)	0.04

*The *P* value for test for departure from linear trend 0.35.
HR, hazard ratio.

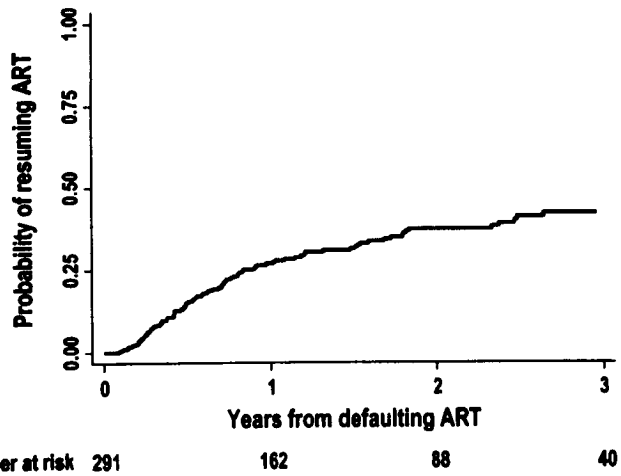

FIGURE 3. Kaplan–Meier plot showing the probability of resuming ART from the time of defaulting therapy up to 3 years after defaulting treatment.

estimate of the probability of treatment resumption was 26.7% (95% CI: 21.7 to 32.7) in the first year, 37.1% (95% CI: 31.1 to 43.9) in the second year, and 42.1% (95% CI: 35.2% to 49.7%) in the third year after stopping treatment.

In univariate analysis a greater likelihood of resuming ART was associated with older age and shorter time since defaulting (Table 3); gender, residency, calendar year of defaulting, and CD4 count nearest to the time of defaulting was not associated with resuming treatment.

In multivariate analysis, men were less likely to resume treatment compared with women (incidence risk ratio [IRR]: 0.67, 95% CI: 0.43 to 1.04, $P = 0.07$); whereas patients >30 years old were more likely to restart treatment (IRR: 1.80, 95% CI: 1.13 to 2.89). The likelihood of resuming treatment decreased significantly beyond one year of defaulting treatment (IRR: 0.40, 95% CI: 0.25 to 0.63).

Of the 96 patients resuming therapy, 86 had a CD4 count measurement while receiving therapy and before the treatment interruption; the majority of these (80) responded to ART with an increase in CD4. Patients who resumed therapy were found to have a median CD4 count (150.5 cells/μL, IQR: 73–266) comparable to their baseline CD4 count before initiating therapy (138.5 cells/μL, IQR: 73–188). The median time between the measurement of CD4 count and resuming therapy was 13 days (IQR: 0–28 days).

Excluding individuals with unascertained vital status revealed similar results with regards to parameter estimated, but the association with male gender became nonsignificant (incidence risk ratio: 0.81, 95% CI: 0.52 to 1.26, $P = 0.35$).

DISCUSSION

To our knowledge, this is the first study from sub-Saharan Africa to report on unstructured treatment interruptions in a routine program setting. Our analysis shows that treatment interruption is a common phenomenon. The probability of ART defaulters to resume therapy within 3 years was 42%. Most ART cohorts report on loss to follow-up, defined as not attending the clinic for more than 3 months,[8]

TABLE 3. Risk Factors for Resuming Treatment After Defaulting

Variable	Number Resuming Treatment	Person-Years at Risk	Rate of Restarting Treatment per 100 Person-Years (95% CI)	Unadjusted IRR of Restarting Treatment (95% CI)	P	Adjusted IRR of Restarting Treatment (95% CI)	P
Gender							
Women	61	253	24.1 (18.7 to 31.0)	1	—	1	—
Men	32	182	17.6 (12.5 to 24.9)	0.73 (0.48 to 1.12)	0.15	0.67 (0.43 to 1.04)	0.07
Age (yrs)							
≤30	26	174	15.0 (10.2 to 22.0)	1		1	
>30	67	261	25.7 (20.2 to 32.6)	1.72 (1.09 to 2.70)	0.02	1.80 (1.13 to 2.86)	0.01
Residents							
Yes	87	405	21.5 (17.4 to 26.5)	1	—	—	—
No	5	14	34.5 (14.4 to 82.9)	1.60 (0.65 to 3.96)	0.30	—	—
CD4 count at time of defaulting (cells/μL)							
≤200	36	155	23.4 (16.8 to 32.4)	1	—	—	—
>200	57	280	20.3 (15.7 to 26.3)	0.87 (0.57 to 1.32)	0.52	—	—
Year of defaulting treatment							
2004/2005	9	60	15.0 (17.8 to 28.9)	1	—	—	—
2006	23	122	18.8 (12.5 to 28.3)	1.25 (0.58 to 2.70)	0.57	—	—
2007	29	127	22.7 (15.8 to 32.6)	1.51 (0.72 to 3.19)	0.28	—	—
2008	32	93	21.4 (13.8 to 33.2)	1.42 (0.65 to 3.13)	0.38	—	—
2009	12	31	38.5 (21.9 to 67.8)	2.57 (1.08 to 6.09)	0.03	—	—
Time off ART							
<1 year	68	222	31.6 (24.2 to 38.9)	1	—	1	—
>1 year	25	213	11.7 (7.9 to 17.4)	0.38 (0.24 to 0.61)	<0.01	0.40 (0.25 to 0.63)	<0.01

and assume that loss to follow-up is an irreversible event. Our study shows that patients who fulfill the widely used definition of loss to follow-up at one time point might resume therapy later. In this cohort, the median duration of the first treatment interruption was 7.5 months.

The median CD4 count of those resuming therapy was similar to their initial CD4 count before starting treatment, which underscores the potentially negative impact of interruption leading to a reversal in immunological recovery made although on treatment. Data from industrialized settings suggest that treatment interruption has detrimental effects on CD4 count, viral load suppression, and clinical progression.[11,12,19] Programs that report patient attrition and the number of patients in care will not account for the potential that up to 14% of patients in care have interrupted treatment at least once.

We were able to determine risk factors for defaulting ART and factors associated with resuming therapy. Male gender, high baseline CD4 count, recency of ART initiation, and the first 6 months of treatment were associated with a higher risk of defaulting. Treatment resumption was more likely in women, patients elder than 30 years and within the first year of stopping therapy.

Our finding that men were at higher risk of defaulting treatment and less likely to resume treatment is consistent with studies showing that HIV-infected men are less likely to access treatment,[25,26] have an increased risk for loss to follow-up in the pretreatment period,[27] present with more advanced stages of HIV disease,[28] and have a higher mortality risk on ART.[2,9,29–33] Strategies to diagnose HIV in men earlier and to link and to retain them in care might include the following: (1) extending clinic hours into evenings and weekends, (2) training male health care staff and counsellors, (3) offering additional adherence sessions to men, and (4) initiating male support groups.

Individuals initiating treatment in more recent years were more likely to default, suggesting that programatic factors might influence retention in care. A study including data from 15 treatment cohorts from Africa, Asia, and South America showed that early patient losses were increasingly common when programs were scaled up.[6] Increasing cohort size in an environment of scarce human resources for health has been suggested to influence both the scale-up capacity and the long-term retention in ART programs.[34] In the study, clinic resources and staffing were further reduced when enrolment for the NIH-funded study finished in 2007. In contrast, year of defaulting was not associated with resumption of treatment, suggesting that patient tracing was less influenced by cohort size (although this would vary according to tracing procedures).

Treatment defaulting was more likely in patients with less advanced immunodeficiency at baseline. This may be explained by the fact that individuals who default treatment and stay alive do so because they feel better on treatment, a phenomenon that has been reported by other studies.[35] This finding is particularly important in view of the 2009 WHO guidelines recommending ART initiation at CD4 counts below 350 cells per microliter[36] and when considering initiation of ART regardless of CD4 count as proposed in the "test and treat" strategy.[37] Initiating ART at the time of HIV diagnosis will result in increased numbers of relatively immunocompetent individuals on ART who may have a higher risk of defaulting treatment. Specific interventions aimed at these individuals need to be developed to ensure optimal retention in care.

This study has several limitations. First, ascertainment of vital status for treatment defaulters was incomplete, which may have led to a misclassification of deaths as defaulters. However, sensitivity analysis excluding individuals with unascertained vital status did not influence our overall findings. Second, resumption of therapy was not ascertained in patients who moved to other communities, possibly resulting in underestimation of treatment resumption. Third, the clinical and immunological consequences of treatment interruption were not analyzed due to lack of laboratory data, in particular, the lack of capacity to perform routine viral load, and the small number of individuals resuming therapy. However it has been shown in industrialized settings that treatment interruption impacts negatively on CD4 count, viral load suppression, and clinical progression.[11,12,19]

We consider that the main finding of this study that a considerable proportion of treatment defaulters return to care is likely to be generalizable to similar settings. Nevertheless, risk factors for defaulting and resuming therapy might differ with regards to eligibility criteria and resources available for patient tracing.

A strength of this study is that the relatively large sample size and follow-up time. This allows for an assessment of risk factors for defaulting and treatment interruption that in turn allows for several proposals to be made to limit defaulting and treatment interruption in similar programme settings. In particular, interventions to keep patients in care should be targeted at men, patients with higher CD4 counts and during the first 6 months of ART. Moreover, the finding that the probability of resuming therapy was highest in the first year after treatment defaulting suggests that efforts to bring patients back into care might be most successful early into defaulting treatment.

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13 Time-updated CD4 analysis

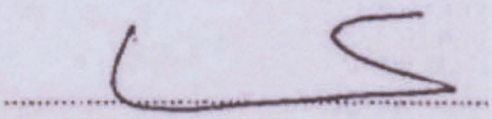
Antiretroviral treatment cohort analysis using time-updated CD4 counts: assessment of bias with different analytic methods

1. For a 'research paper' already published
   1.1. Where was the work published?
   1.2. When was the work published?
      1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion
   1.3. Was the work subject to academic peer review?
   1.4. Have you retained the copyright for the work?
   If yes, attach evidence of retention
   If no, or if the work is being included in its published format, attach evidence of permission from copyright holder (publisher or other author) to include work

2. For a 'research paper' prepared for publication but not yet published
   2.1. Where is the work intended to be published? ***PLos One***
   2.2. List the paper's authors in the intended authorship order? List the paper's authors in the intended authorship order **Katharina Kranzer, James J. Lewis, Richard G. White, Judith R. Glynn, Stephen D. Lawn, Keren Middelkoop, Linda-Gail Bekker, Robin Wood**
   2.3. Stage of publication ***in press***

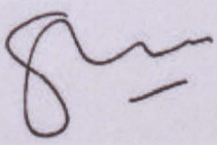
3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

   The candidate designed the study, wrote the ethics, cleaned the data, linked the data, performed the data analysis and wrote the publication. The candidate did not develop the mathematical model.



Candidate's signature

Supervisor or senior author's signature to confirm role as stated in (3) _



Dr. Stephen D. Lawn
Supervisor and Co-author

Antiretroviral treatment cohort analysis using time-updated CD4 counts: assessment of bias with different analytic methods

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World Count: Abstract = 250; Text =2607; Tables = 4; Figures = 1; References = 33

13.1 Abstract

Background: Survival analysis using time-updated CD4+ counts during antiretroviral therapy is frequently employed to determine risk of clinical events. The time-point when the CD4+ count is assumed to change potentially biases effect estimates but methods used to estimate this are infrequently reported.

Methods: This study examined the effect of three different estimation methods: assuming i) a constant CD4+ count from date of measurement until the date of next measurement, ii) a constant CD4+ count from the mid-point of the preceding interval until the midpoint of the subsequent interval and iii) a linear interpolation between consecutive CD4+ measurements to provide additional midpoint measurements. Person-time, tuberculosis rates and hazard ratios by CD4+ stratum were compared using all available CD4+ counts (measurement frequency 1-3 months) and 6 monthly measurements from a clinical cohort. Simulated data were used to compare the extent of bias introduced by these methods. A literature review was conducted to identify methods used for time-updated CD4+ count analysis.

Results: The midpoint method gave the least biased estimates for person-time spent with low CD4+ counts and for hazard ratios for outcomes in both the clinical dataset and the simulated data. The majority of studies (11 out of 21) conducting survival analysis with time-updated CD4+ counts did not specify the method used to estimate the time-point of change.

Conclusion: The midpoint method presents a simple option to reduce bias in time-updated CD4+ analysis, particularly at low CD4 cell counts and rapidly increasing counts after ART initiation.

13.2 Introduction

Observational prospective cohort data of patients on ART are often used to estimate the relationship between time-varying CD4+ counts and incident clinical events such as TB, death, opportunistic infections and malignancies. While within-subject CD4+ count variability [1,2,3] will inevitably introduce measurement error, measurement frequency and the choice of when to split time attributed to a certain CD4+ count value might also introduce bias. Measurement frequencies are either determined by the study protocol which specifies time intervals at which individuals are followed (interval cohort) or by prevailing guidelines within the health care service (clinical cohort) [4]. In the latter the frequency of visits and laboratory measurements may also be influenced by the severity of illness, access to and utilization of health care which might increase the bias.

Differences in measurement frequency between two exposure groups have been shown to introduce bias when time to a specific biomarker level is used as a surrogate outcome [5]. The time-point when the CD4+ count is assumed to change might bias effect estimates especially when measurement intervals are wide or CD4+ counts are rapidly changing. Possible methods used assume that (i) the CD4+ count remains constant until the date of the next measurement or (ii) the CD4+ count remains constant from the mid-point of the preceding interval until the

midpoint of the subsequent interval or (iii) uses linear interpolation between two consecutive CD4+ count measurements to provide a midpoint measurement.

We aimed to assess how these 3 different methods of dealing with time points influence effect estimates and rates using data from a clinical ART cohort with frequent measurements. The clinical ART cohort was based in Cape Town, South Africa and CD4 counts were measured monthly for the first 3 months and 3 monthly thereafter. We further investigated the direction of bias using a simulated dataset.

13.3 Methods

13.3.1 Data collection

Data collected in a peri-urban township in the greater area of Cape Town as part of the CIPRA-SA trial were used for this analysis [6]. The trial randomized patients to nurse or doctor-monitored HIV care and showed equivalence of the two monitoring strategies for treatment failure over 2 years. A total of 363 HIV-positive ART-naïve patients with a CD4 cell count of ≤ 350 cell/uL or WHO stage 4 disease from this study community were enrolled in the trial in Cape Town. All patients received a standard ART regimen and were managed according to the South African National Guidelines [7].

CD4+ counts were measured at weeks -4, 0, 4, 8, 12 (relative to the start of ART) and then every 12 weeks. Incident TB was used as the outcome of interest. Start and end of TB treatment were determined by merging the ART register with the

electronic TB register on first name, surname, medical record number, date of birth, truncation of names and switching of first name and surname. This method was validated by clinical folder review in a similar dataset of 585 patients from a different study and revealed 96.1% sensitivity and 97.4% specificity. All identifiers were removed from the data after merging.

Individuals who did not live in the study community and individuals who were on TB treatment at ART initiation and died or were lost to follow-up before they completed treatment were excluded from the analysis.

13.3.2 Definition of study variables

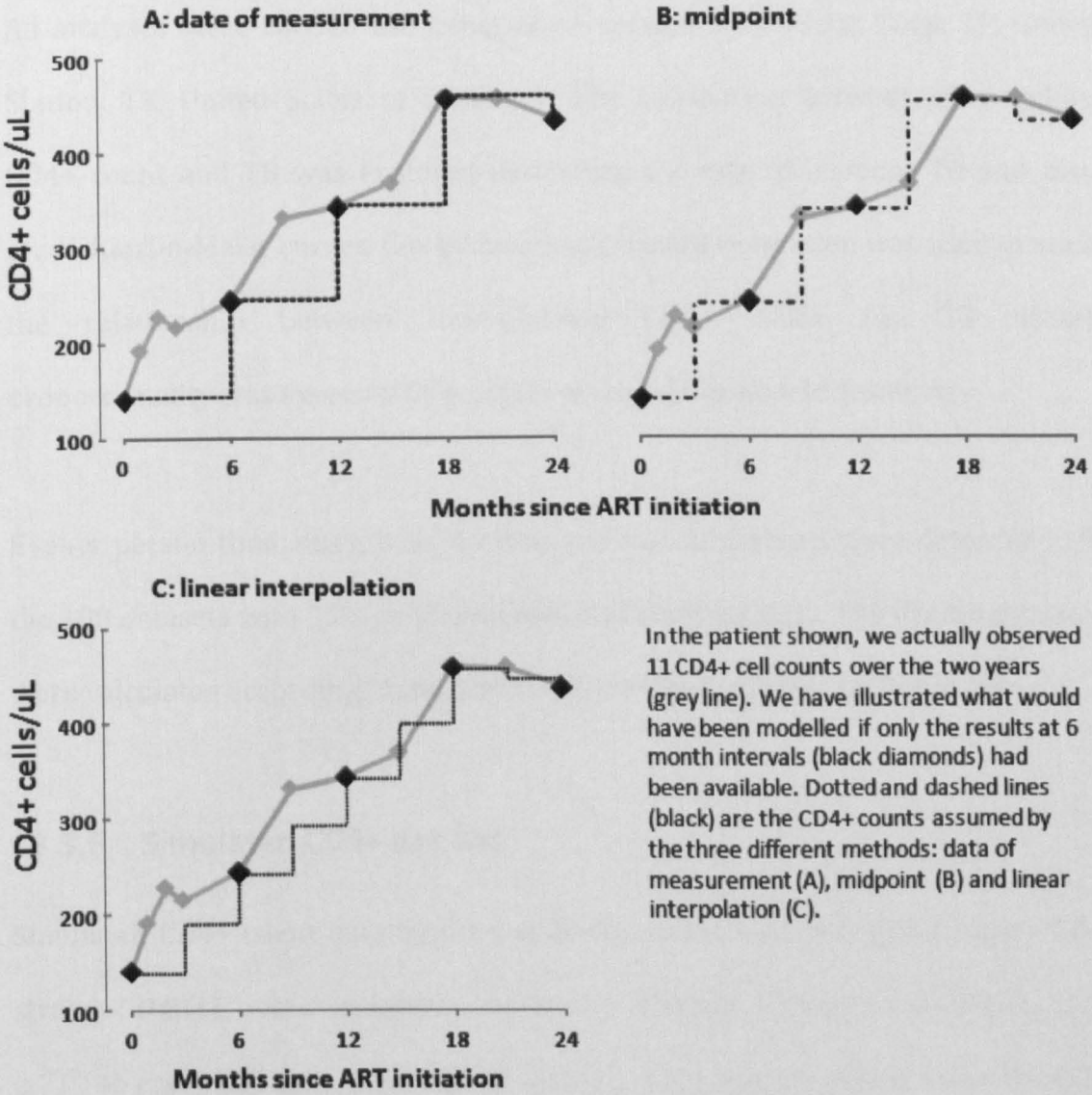
The exposure was time-updated CD4+count and the outcome was incident TB defined as starting TB treatment. Person-time accrued from ART initiation to the date of TB disease, death, becoming lost to follow-up or the 31st December 2008 was calculated. Individuals who were on TB treatment at time of ART initiation were only included in the analysis after they had completed TB treatment. Individuals who developed incident TB were re-included in the analysis after completing TB treatment. Individuals only contributed time while they were on ART and person-time during treatment interruptions was excluded from the analysis.

13.3.3 Time-updated CD4 count

The data were analyzed in three different ways: the first analysis assumed that the CD4+ count changed at the date when the blood sample for CD4+ count measurement was drawn (*date of measurement analysis*) (Figure 13.1A); the

second assumed a change of CD4+count at the midpoint between two measurements (*midpoint analysis*) (Figure 13.1B); and the third calculated an additional CD4+ count using a linear interpolation between two consecutive CD4+ measurements and used the date when the blood samples were drawn and the midpoint between the two dates as the time point of change of CD4+ count (*linear interpolation analysis*) (Figure 13.1C).

Figure 13.1: Illustration of the three different methods of modelling CD4+ count



In the patient shown, we actually observed 11 CD4+ cell counts over the two years (grey line). We have illustrated what would have been modelled if only the results at 6 month intervals (black diamonds) had been available. Dotted and dashed lines (black) are the CD4+ counts assumed by the three different methods: data of measurement (A), midpoint (B) and linear interpolation (C).

13.3.4 Newly generated datasets

A dataset including baseline CD4+ counts and 6 monthly CD4+ counts only was generated. From this dataset 15% of the follow-up CD4+ counts were randomly selected and removed to simulate the reality of missing data in clinical cohorts. A total of 100 datasets with 15% randomly missing follow-up CD4+ counts were generated.

13.3.5 Statistical analysis

All analyses were carried out using Stata version 11.0 (Stata Corp. LP, College Station, TX, United States of America). The association between time-updated CD4+ count and TB was explored describing the rate of incident TB and using crude Kaplan-Meier curves. Cox proportional hazard regression was used to model the relationship between time-updated CD4+ count and TB. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals.

Events, person-time, rates, hazard ratios and standard errors were determined for the 100 datasets with 15% randomly missing follow-up data. The overall estimates were calculated according to the combination rules described by Rubin [8].

13.3.6 Simulated CD4+ dataset

Simulated CD4+ count data by time since treatment initiation and baseline CD4+ strata, $CD4_i(t)$, were generated by fitting $CD4_i(t) = CD4_i(t_0) + CD4_i(t_m)(1 - e^{-r_i t})$ to empirical data from Nash et al.[9] by least-squares, where i was the CD4+ stratum at treatment initiation, t was time since treatment initiation, $CD4_i(t_0)$ was

the average CD4+ level in strata i at treatment initiation, $CD4_i(t_m)$ was a parameter determining the increase in CD4+ count in strata i after 5 years of treatment, and r_i was a parameter determining the rate of CD4+ count increase in strata i. Each CD4+ stratum i was simulated separately and the results were also combined to generate a 'mixed' cohort of 25%, 17%, 18%, 15%, 25% of patients with baseline CD4+ of 25-50 cells/μl, 51-100 cells/μl, 101-150 cells/μl, 151-200 cells/μl and 201-300 cells/μl respectively, to represent a mix of patients seen in a typical clinic. A clinical South African ART cohort was used to determine the proportions of patients in different CD4+ count strata for the mixed cohort [10].

The areas under the CD4+ curve (AUC) were calculated using date of measurement, midpoint or linear interpolation methods with either 6 monthly or 3 monthly measurements. The AUC measures CD4 exposure. It is derived from the actual CD4+ values and the time spent with these values. Rates were calculated assuming constant rates within CD4+ count strata using TB rate estimates from published literature [11,12].

13.3.7 Ethical approval

All patients in the CIPRA-SA trial signed informed consent forms. The trial was approved by the University of Cape Town Ethics Committee and Partners Human Subjects Institutional Review Board. The London School of Hygiene and Tropical Medicine Ethics Committee and the University of Cape Town Ethics Committee and Partners Human Subjects Institutional Review Board gave approval for the analysis of the anonymised data.

13.3.8 Literature review

A literature review was undertaken to identify studies conducting survival analysis with time-updated CD4+ counts as either exposure variable or confounder to see which methods were used. The search was conducted in Medline and restricted to English literature published between January 2006 and August 2010. The search strategy included "CD4 lymphocyte count", "HIV", "proportional hazard model", "survival analysis", "cohort studies" as Mesh terms and text words and "current", "risk ratio", "repeated measurements", "hazard ratio", "updated" and "time-updated" as text words. Abstracts of identified studies were screened to assess if they fulfilled the inclusion criteria. Potentially relevant studies were further assessed by reading the full-text publication.

13.4 Results

13.4.1 TB incidence and hazard ratios by time-updated CD4+ count using clinical cohort data

Overall TB incidence was 4.9/100 person-years (PY) (95% confidence interval (CI) 3.6-6.8). TB incidence rates were 14.7 in the lowest CD4+ count stratum (≤200 cells/μl), 3.1 in the middle CD4+ count stratum (201-350 cells/μl) and 2.9 in the highest CD4+ count stratum (>350 cells/μl) when using all available CD4+ counts and performing a date of measurement analysis (Table 13.1). The midpoint analysis revealed TB incidence rates of 16.0, 3.1 and 2.8 for the three different CD4+ count categories. The total person-time spent at low CD4+ counts was less in the midpoint analysis compared to the date of measurement analysis.

TB incidence rates and hazard ratios (HRs) were different when using a dataset with 6 monthly CD4+ counts as compared to analysis using all available CD4+ counts (Table 13.1). With all three estimation methods, compared to the results with more frequent measures, rates were underestimated at low and high CD4+ counts, and overestimated at moderate CD4+ counts, with most marked overestimation in the midpoint analysis.

Analyses using a dataset with 6 monthly CD4+ counts and 15% randomly missing follow-up CD4+ counts revealed more extreme variations in rates, but with the same pattern of underestimation at low and high counts, and overestimation at moderate counts (Table 13.1). The differences in rates and HRs compared to the analysis using all available data were most pronounced using the date of measurement analysis, and least pronounced using the midpoint analysis.

13.4.2 Area under the CD4+ curve using simulated data

The midpoint analysis estimated the AUC most accurately for cohorts with low (25-50 cell/uL), high (151-200 cells/μl) and mixed baseline CD4+ counts (Table 13.2). The date of measurement analysis underestimated the AUC for all cohorts and time-points. The relative difference was most pronounced in cohorts with low baseline CD4 counts and short follow-up (1 year). The date of measurement analysis was less accurate with 3 monthly measurements than the midpoint analysis with 6 monthly measurements.

Table 13.1: Person-time, rates of tuberculosis and hazard ratios for tuberculosis using clinical cohort data and different methods to estimate the time-point of change of CD4+ count

CD4 strata (cells/μl)	Date of measurement analysis				Midpoint analysis				Linear interpolation analysis			
	Events	PY	Rate	HR	Events	PY	Rate	HR	Events	PY	Rate	HR
Survival and Cox regression analysis using all available CD4+ counts												
≤200	19	128.9	14.7	1	19	119.0	16.0	1	*Not performed*			
201-350	8	261.2	3.1	0.26 (0.11-0.61)	8	255.4	3.1	0.25 (0.11-0.55)				
>350	11	378.7	2.9	0.34 (0.15-0.75)	11	394.5	2.8	0.29 (0.13-0.65)				
Survival and Cox regression analysis using 6 monthly CD4+ counts only												
≤200	22	176.6	12.5	1	18	140.2	12.8	1	20	152.1	13.2	1
201-350	10	256.4	3.9	0.41 (0.19-0.88)	13	246.2	5.3	0.52 (0.25-1.08)	12	261.9	4.6	0.45 (0.22-0.95)
>350	6	335.7	1.8	0.25 (0.06-0.66)	7	382.3	1.8	0.24 (0.09-0.62)	6	354.7	1.7	0.22 (0.08-0.60)
Survival and Cox regression analysis using 6 monthly CD4+ counts and 15% randomly missing												
≤200	16.1	184.7	8.7	1	18.7	145.9	12.8	1	16.1	158.6	10.2	1
201-350	14.5	255.8	5.7	0.86 (0.42-1.77)	12.7	245.9	5.2	0.51 (0.24-1.05)	14.5	262.9	5.5	0.73 (0.35-1.510
>350	7.4	326.2	2.3	0.49 (0.19-1.25)	6.6	374.5	1.8	0.23 (0.09-0.59)	7.4	344.8	2.1	0.40 (0.15-1.02)

*Linear interpolation analysis was not performed for the analysis using all available CD4+ counts, as the result was not expected to differ greatly compared to the date of measurement and midpoint analysis.

Table 13.2: Estimated area under the CD4+ count curve using simulated data and different methods to estimate the time-point of change of CD4+ count

Baseline CD4+ count of the cohort	Time	Cumulative area under the CD4+ count curve				
		True	Date of measurement method 6 monthly CD4+ counts	Date of measurement method 3 monthly CD4+ counts	Linear interpolation method 6 monthly CD4+ counts	Midpoint method 6 monthly CD4 counts
25-50 cells/μl	1 year	145	99	123	120	142
	5 years	1348	1272	1311	1307	1342
51-100 cells/μl	1 year	180	138	160	157	177
	5 years	1435	1368	1403	1399	1430
101-150 cells/μl	1 year	228	186	208	205	225
	5 years	1662	1597	1631	1627	1657
151-200 cells/μl	1 year	282	238	261	258	278
	5 years	1862	1801	1833	1829	1856
201-300 cells/μl	1 year	345	305	326	323	342
	5 years	2180	2121	2152	2148	2274
Mixed	1 year	237	194	216	213	233
	5 years	1704	1639	1673	1669	1699

13.4.3 TB rates using simulated data

Both the date of measurement and midpoint analysis underestimated TB rates for low CD4+ count strata (<200 cell/uL). Rates were less accurately estimated using the date of measurement analysis compared to the midpoint analysis (Table 13.3). Rates for some CD4 count+ strata could not be determined as no time was spent in those strata. For example a cohort with a baseline CD4 count of 151-200 did not accumulate any person-time in the CD4+ count strata ≤50 and 51-100. In addition cohorts with baseline CD4+ counts of 25-50 and 51-100 did not improve their CD4+ count beyond 400 over the 5 year period and thus did not accumulate any time in higher CD4+ count strata.

Table 13.3: Estimated rates of tuberculosis using simulated data and different methods to estimate the time-point of change of CD4+ count

CD4+ strata	True rates	Cohort with baseline CD4+ count 25-50 cells/μl		Cohort with baseline CD4+ count 51-100 cells/μl		Cohort with baseline CD4+ count 151-200 cells/μl		Mixed cohort	
		Date of measure-ment method	Midpoint method	Date of measure-ment method	Midpoint method	Date of measure-ment method	Midpoint method	Date of measure-ment method	Midpoint method
≤50	21.7	11.25	13.2						
51-100	12.8			9.69	10.12				
101-200	9.27	6.65	9.27	6.24	8.13	5.93	6.39	7.38	9.27
201-300	5.48	5.42	5.73	5.39	5.48	4.75	5.18	5.48	5.48
301-400	4.61	4.61	4.61	4.61	4.65	4.51	4.59	4.61	4.66
401-500	4.23					4.23	4.23		

13.4.4 Literature review

Titles and abstracts of 199 studies were screened for inclusion in the review. 25 publications were identified for full-text review. A total of 21 studies fulfilled the inclusion criteria. Eight studies [11,13,14,15,16,17,18,19] performed a date of measurement analysis and 2 studies [20,21] performed a linear interpolation analysis (Table 13.4). The remaining 11 studies [22,23,24,25,26,27,28,29,30,31,32] did not specify the method of analysis.

Table 13.4: Studies conducting analysis using time-updated CD4+

Author	Journal	Outcome	CD4+ count	Description of how time-updated CD4+ counts were determined.
Dunn[14]	JID	AIDS or death	exposure	Follow-up time from the time that each measurement was obtained was censored at the date of the next measurement.
Guiguet[21]	Open AIDS J	AIDS or death	exposure	CD4+ counts were modeled using linear interpolation between two measurements.
Lawn[13]	AIDS	Death	exposure	Person time was divided into intervals each of which was defined by the CD4+ count measurement at the start of the interval.
Lawn[11]	AIDS	Tuberculosis	exposure	Person-time was subdivided into 4-month intervals for analysis. Each interval was defined by theCD4 cell count measurement at the start of the interval.
Reekie[22]	Cancer	Non-AIDS-defining malignancies	exposure	
d'Arminio Monforte[15]	AIDS	death from malignancies	exposure	Each person's follow-up was divided into a series of consecutive 1-months periods, and the individual's status (most recent CD4+ count) was determined.
Lodi[23]	J Natl Cancer Inst	Kaposi sarcoma	exposure	
Engels[16]	JAIDS	Non-Hodgkin Lymphoma	exposure	We considered the most recent laboratory result "current" until the next measurement.
Crum-Cianflone[24]	Arch Intern Med	Cutaneous malignancy	exposure	
Guiguet[20]	Lancet Oncology	Malignancies	exposure	Follow-up was divided into consecutive 1-month periods, and time-varying covariables were updated at the beginning of every month. The CD4+ count was linearly interpolated unless ART was started between 2 measurements.
Podlekareva[26]	Sand J Infec Dis	Fungal infections	exposure	
Prosperi[27]	CID	Malignancies	exposure	
Seyler[28]	AIDS Res Human Retroviruses	Severe morbidity	exposure	
Sogaard[17]	PLoS one	Death from pneumonia	confounder	CD4+ counts were estimated between measurements by carrying forward the value from the most recent measurement
Walker[29]	Lancet	Effect of Co-trimoxazole	confounder	
Crum-Cianflone[25]	AIDS	Malignancies	exposure	
Phillips[18]	AIDS	Death	exposure	Person time was counted from the time of each qualifying CD4+ count until the next CD4+ count.
Beaudrap[30]	BMC Infect Dis	AIDS defining illness	exposure	
Mocroft[31]	AIDS	Clinical disease progression	exposure	
Bohlius[32]	Antivir Ther	Non-Hodgkin Lymphoma	exposure	
Bruyand[19]	CID	Malignancies	exposure	We assumed that the value of the measurement reported at a given follow-up visit remained stable until the next follow-up visit

13.5 Discussion

This study shows that the time-point when a CD4+ count is assumed to change influences incidence rates of clinical events during ART and effect estimates in time-updated CD4+ count analysis. The analysis using modeled CD4+ count data showed that the midpoint method gives the least biased estimates both for person-time and rates. The choice of time-point when a CD4+ count is assumed to change had the greatest impact in cohorts with low baseline CD4+ counts and during the first year after ART initiation. While the absolute difference in effect estimates was small when analyzing data with frequent measurements, the choice of time-point was important in data with less frequent and missing measurements. Thus the frequency of measurement and the method used to determine the time-point of change in CD4+ count need to be taken into account when comparing effect estimates from different studies. However the majority of studies performing survival or Cox regression analysis with time-updated CD4+ count as exposure or confounder variable failed to describe how the time-point of change in CD4+ count was determined.

The rate of change in CD4+ count is highest in the first months after initiation of ART [9]. The dataset including all CD4+ counts had a particularly high frequency of measurements in the first 3 months on ART, with testing done at 0, 4, 8 and 12 weeks. Person-time spent with low CD4+ counts was overestimated in all analyses conducted on a dataset with only 6 monthly CD4+ counts compared to analysis using a dataset with all available CD4+ counts. As a result TB incidence rates were underestimated in the low CD4+ count strata. The difference in person-time spent

with low CD4+ counts was smallest in the midpoint analysis, but rates and hazard ratios were nevertheless strongly biased using the dataset with 6 monthly CD4+ counts. The bias was due to a smaller number of events estimated to occur in the low CD4+ count strata, which was probably due to chance and small sample size. The midpoint analysis produced the least biased estimates for both rates and hazard ratios using a dataset with 6 monthly CD4+ counts and 15% missing follow-up CD4+ counts. The analysis using modeled CD4+ count data confirmed that the midpoint analysis estimated person-time and rates most accurately.

Our study confirms and extends the findings of a study from Côte d'Ivoire [33]. In this study by Deuffic-Bruban et al., person-time spent at low CD4+ counts (<50 cells/μl) was highest in the date of measurement analysis and lowest in the analysis assuming that the CD4+ count changed immediately to the level of the next measurement [33]. Estimates of rates of opportunistic infections were highest (249/100 PYs) in the analysis assuming an immediate change, followed by the linear interpolation (210/100 PYs) and date of measurement analysis (130/100 PYs). However this study is not comparable to our study or to routine programmatic data because of the very high frequency of CD4+ counts (median time between the last CD4+ measurements 1-1.8 months) throughout the study (compared to a median of 3 months in our study) which means that the differences between methods will be less pronounced. Deufic-Burban et al. did not compare the results from the original dataset and datasets with less frequent measurements and thus they were unable to assess the extent of bias that would be seen in those situations. In contrast, we used the dataset with frequent measurements as a gold standard and compared it to a generated dataset with only 6 monthly

measurements (a dataset comparable to most clinical cohort data). Another further important addition in our study was that we used the mid-point method, which appeared to produce the least biased estimates.

Limitations of the clinical cohort analysis are the small sample size, the small number of events and the relatively high baseline CD4+ count. The effect estimates calculated in full analysis were imprecise and the extent of bias due to different methods was uncertain from the clinical cohort analysis alone. However the analysis using modeled data confirmed that person-time at higher CD4+ counts and rates were more profoundly underestimated using the date of measurement method compared to the midpoint method. TB rates within CD4+ count strata were assumed constant in the modeled dataset which might not accurately reflect the reality. Thus estimated TB rates might be even more biased if true TB rates differ according to CD4+ count within CD4+ count strata.

Analysis using time-updated CD4+ counts as exposure or confounder should consider using the midpoint method as a simple way to reduce bias. In addition authors should be encouraged to clearly describe the assumption underlying the time-point of change in CD4+ count and researchers conducting meta-analyses should contact authors to determine the method used.

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14 Association between TB risk and ART coverage in a South African ART cohort

14.1 Introduction

Observational studies have demonstrated a reduction of TB risk by 54-92% in HIV infected individuals receiving ART [1]. The risk of TB decreases with rising CD4 cell counts and increasing duration of treatment [2,3]. However whether ART has an impact on TB incidence at a population level will not only depend on the efficacy of ART in preventing TB disease, but also on population ART coverage, patient compliance and transmission dynamics. Mathematical modelling suggests that the effect of ART may be limited due to the high burden of TB that occurs prior to ART initiation and the persistence of higher TB risk in patients on long-term ART compared to HIV-negative patients [4].

Observational data from a peri-urban community in the Western Cape, South Africa have shown decreased TB prevalence and TB notification rates in the HIV-infected population after ART roll-out [5,6]. Further stratification according to ART status showed that while TB notification rates decreased significantly in HIV infected individuals on ART, TB notification rates remained relatively stable in HIV-infected individuals not on ART. Thus the decrease in TB notification rates might have been entirely due to immune recovery resulting in decreased risk of progression to TB disease. Decreased TB notification rates after ART roll-out have also been reported in a before-and-after study from Malawi [7]. Before-and-after studies lack a concurrent control group. Thus other factors such as migration,

mortality, changes in the national TB control program and changes in the notification system might have resulted in reduced TB notification rates.

Mathematical models investigating the effect of ART on TB incidence do not take into account the effect of active TB case finding in ART programs, nosocomial transmission in clinics and non-random mixing of populations. HIV infections are likely to cluster in households and social networks [8], and the same is probably true for ART [9,10]. We therefore hypothesized that ART might have an impact on TB risk over and above the improvement of CD4 counts in individuals receiving ART. This study aimed to assess the impact of community ART coverage on TB risk in a cohort of HIV infected individuals receiving ART.

14.2 Methods

14.2.1 Study community

The study was conducted in a peri-urban township in the greater area of Cape Town, with a population of approximately 17,000 people and a measured adult HIV prevalence of 23% in 2010 [11]. The community is served by a single public-sector primary care clinic which provides ART and TB treatment free of charge. A nearby hospital (5 km away) provides all secondary care for the population, including inpatient and antenatal services. The hospital also provides ART for some HIV infected individuals from the community.

The clinic manages all TB patients resident in the community according to the National TB control program guidelines [12]. All patients initiating ART were

screened for active TB with symptom screening followed by smear and cultures for patients with symptoms suggestive of TB. The screening did not include testing for latent TB infection. Isoniazid preventive therapy has not been implemented in this community.

ART provision began in 2004. From 2005 to 2008 ART services were partly provided according to the Antiretroviral Treatment Protocol of the Western Cape [13] and partly through a study funded by the NIH [14]. Patients enrolled in the NIH-funded study could access ART with a CD4 count below 350 cells/μl or WHO stage 3 disease as compared to 200 cells/μl or WHO stage 4 disease in the provincial program. The NIH-funded study completed enrollment at the end of 2006 after which all patients were initiated in the provincial ART program.

14.2.2 ART cohort

Data on clinical variables, outcomes and laboratory records were routinely collected in all patients at the primary health care clinic and hospital. Data were entered in prospectively maintained ART cohort databases.

14.2.3 CD4 counts

Patients seen as part of the provincial program had a baseline CD4 count prior to initiating ART followed by 6 monthly measurements. CD4 counts were measured at weeks -4, 0, 2, 4, 8, 12 and then every 12 weeks for patients participating in the NIH funded study. CD4 count measurements were performed by the NHLS and prospectively entered into the ART database. These data were supplemented with CD4 counts from a direct download of the NHLS.

14.2.4 Number of patients in care by calendar period

The ART cohort database allowed for multiple entries and exits. Patients joined the cohort as a result of one of the following events: ART initiation, transfer in and restarting ART after defaulting. Exit events were deaths, loss to follow-up or transfer outs. A patient was defined to be in care at the end of a calendar year if the current treatment episode was ongoing.

14.2.5 Incident TB

Incident TB was defined as a TB episode starting with the start of TB treatment whether or not the individual had had previous TB. TB data were obtained from the local TB clinic and clinical folders from 2002 to 2010. The data were entered into an electronic TB register. The electronic TB register was merged with the ART register by first name, second name, truncation of names, switching of first name and second name, date of birth and gender. A total of 585 (40.4%) clinical folders of ART patients were reviewed and the incident TB information retrieved. This information was used to validate the merging process. The merging was 96% sensitive and 97% specific.

14.2.6 ART coverage using mathematical modelling

ART coverage was estimated using a mathematical model of HIV in the community, described in detail elsewhere [15]. Briefly, the growth of the community over time was projected using a cohort component projection model stratified by age and sex, with migration assumptions set to ensure model consistency with the change in population size and age distribution observed in regular community censuses.

Annual age-specific HIV incidence rates in males and females were estimated from a national model [16], and were scaled in order to ensure consistency between model estimates of HIV prevalence and levels of HIV prevalence measured in the community in 2005 and 2008 [5,17]. Untreated HIV infected adults were assumed to progress through a four-stage model of CD4 decline (CD4 >500, 350-500, 200-349 and <200), with AIDS death or ART initiation occurring in either of the last two stages. Rates of transition between untreated CD4 categories were estimated by fitting a separate model to data from South African surveys of CD4 distributions in HIV-positive adults [18,19,20], and these estimates were validated by comparing the modelled distribution of CD4 counts in untreated adults with the results of a CD4 survey conducted in the community in 2010.

Rates of ART initiation, ART default, ART resumption, transfer in, transfer out and mortality after ART initiation were estimated from ART programme data routinely collected in the community. ART coverage in each year was calculated as the number of adults receiving ART at the middle of each year, divided by the sum of the number of treated adults, the number of ART-naïve adults with CD4 counts below a defined threshold (200 or 350) and the number of untreated adults who had defaulted ART.

14.2.7 ART coverage in the community in 2010

A population-based HIV sero-prevalence survey was conducted between September and December 2010 which has been described in detail elsewhere [11]. In brief a house-to-house enumeration of the community in August 2010 provided a database of 12520 residents 15 years or older of whom 1300 residents were

randomly selected for inclusion in the study (10% of the community). Field workers invited the selected individuals to attend a mobile HIV testing service. Consent forms, questionnaires and HIV testing were all completed at the mobile HIV testing service. Individuals were asked if they were taking ART, they were tested for HIV and all HIV positive individuals had CD4 count measurement with a point of care test (Alere™Pima™ CD4 Analyser, Waltham, MA, USA) using venous blood samples. Participation rate in the survey was 88%.

14.2.8 Analysis

All data were analysed using Stata 11.2 (StataCorp, College Station, USA). Analysis was restricted to adult (≥15 years of age) residents receiving ART treatment. Descriptive statistics were used to characterize the demographic, clinical and laboratory variables of the ART cohort at baseline.

The CD4 count distribution at the end of each calendar year was calculated on per patient bases. All CD4 count measurements between the 1st of May of the respective calendar year and the 28th of February of the next calendar year were included in the analysis to ensure that each patient in ART care in a given year contributed at least one CD4 count to the analysis. For most patients CD4 counts were measured 6 monthly, thus a period of 10 months starting on the 1st of May guaranteed the availability of at least one CD4 count per patient. If a patient had more than one CD4 count in that period the mean of all CD4 counts was calculated.

Time from initiation of ART was used as the timeline for survival analysis. Cox proportional hazard analysis adjusted for age at initiation, sex and time-updated

CD4 count was used to assess the effect of ART coverage on TB risk. We assumed that the CD4 count remained constant until the midpoint between two measurements and then changed to the subsequent CD4+ count. The endpoint of the analysis was the time from ART initiation to incident TB. Follow-up of patients on continuous therapy was censored at the date of death, date of transfer, date of default or study end (31st December 2009). Patient-time of patients on TB treatment at time of ART initiation was excluded from denominator until they completed TB treatment. Patients developing incident TB during ART were again included in the analysis after they completed TB treatment. Patients' episodes were censored when they defaulted ART, but they were again included in the analysis when they restarted ART. The analysis was adjusted for multiple episodes of TB by using robust standard errors. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals.

The exposure variable was ART coverage as estimated by the mathematical model. Yearly ART coverage estimates were used in the analysis and assumed to be constant within one calendar year. ART coverage was used in the model as a time-updated exposure variable. Thus patient time was split according to CD4 counts and ART coverage. ART coverage was measured as a proportion and included as a linear variable. The hazard ratio therefore describes the decrease in TB risk for an increase in ART coverage from 0% to 100%.

14.3 Results

14.3.1 Baseline characteristics and retention in care

A total of 1444 adult residents received ART between 2004 and 2009 (Table 14.1). The majority of patients were women (66.7%) and median age was 31.7 years

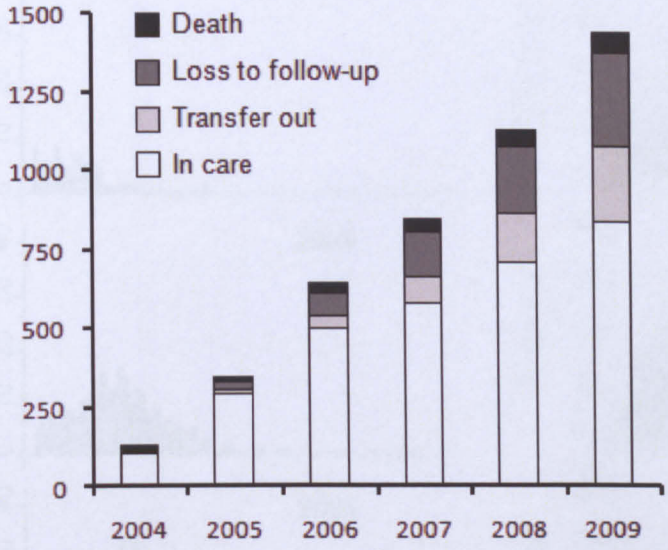
(IQR) 27.2-37.0). Median CD4 count at initiation of ART was 132 cell/μL (IQR 60-201) and 70.6% were in WHO clinical stage 3 and 4. Median CD4 counts at initiation of ART were 80 (IQR 36-140), 146 (IQR 74-220), 153 (IQR 67-254), 122 (IQR 50-187), 136 (IQR 62-196), 135 (IQR 76-191) in 2004, 2005, 2006, 2007, 2008 and 2009 respectively. By the end of 2009, 841 patients were still receiving ART at the clinic or hospital, 239 had been transferred out, 299 had defaulted and 65 had died (Figure 14.1)

Table 14.1: Adult residents ever receiving ART (2004-2009) (N=1444)

Variable	N (%) Median (IQR)
Women	962 (66.7)
Age (years)	31.7 (27.2-37.0)
Transfer-in	101 (7.0)
Year joining the cohort	
2004	119 (8.2)
2005	228 (15.8)
2006	297 (20.6)
2007	204 (14.1)
2008	285 (19.7)
2009	311 (21.5)
*WHO clinical stage**	
1	167 (12.7)
2	220 (16.7)
3	609 (46.2)
4	321 (24.4)
CD4# (cells/μl)	132 (60-201)

*26 missing values for WHO clinical stage, WHO clinical stage was not available for patients transferred into the service
#58 missing values for CD4 count

Figure 14.1: Cumulative number of adults in the ART cohort who were dead, lost to follow-up and transferred-out by calendar year



14.3.2 CD4 count distribution in the ART cohort by calendar year

The CD4 count distribution shifted to the right in more recent calendar years (Figure 14.2). While almost 90% of the cohort had a CD4 count ≤ 200 cells/μl in 2004, the percentage of individuals with CD4 count ≤ 200 cells/μl decreased to one third in 2005 (Table 14.2). The percentage of individuals with CD4 count ≤ 200 cells/μl remained constant between 2007 and 2009 (22.3-23.4%). The median CD4 count of the cohort increased from 119 cells/μl (IQR 60-161) in 2004 to 366 cells/μl (IQR 213-546) in 2009.

Figure 14.2: CD4 count distribution in the ART cohort by calendar year

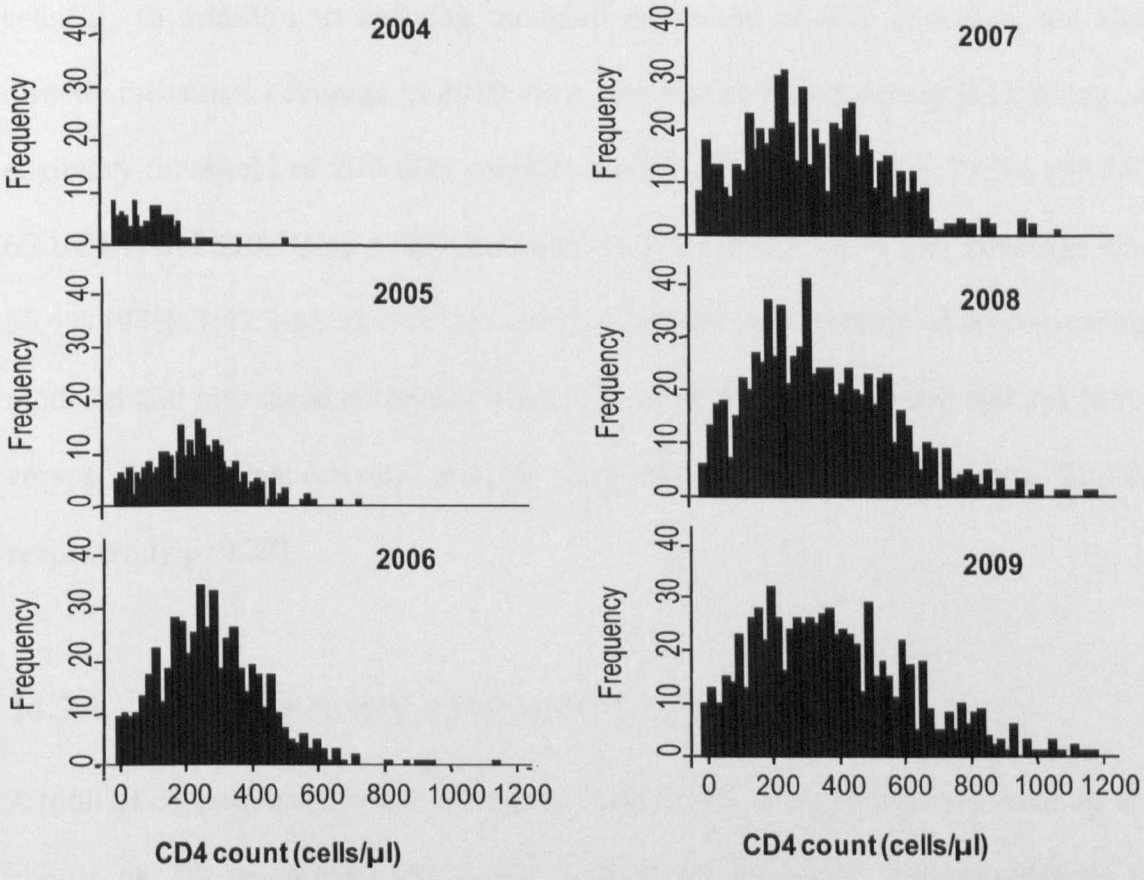


Table 14.2: CD4 count distribution in the ART cohort by calendar year

CD 4 count(cells/µl)	2004	2005	2006	2007	2008	2009
Median (IQR)	119 (60-161)	250 (154-328)	282 (185-389)	336 (210-492)	338 (212-511)	366 (213-546)
≤200	89.4%	34.3%	29.4%	23.4%	22.3%	22.4%
201-350	8.9%	45.2%	37.3%	28.5%	30.1%	24.7%
>350	1.8%	20.5%	33.3%	48.1%	47.6%	53.0%

14.3.3 ART coverage in the community

Estimated adult ART coverage based on the CD4 threshold of 200 cells/µl increased from 18% in 2004 to 84% in 2009 (Figure 14.3). After a rapid increase from 2004-2006, ART coverage slowed down after 2007. ART coverage estimates

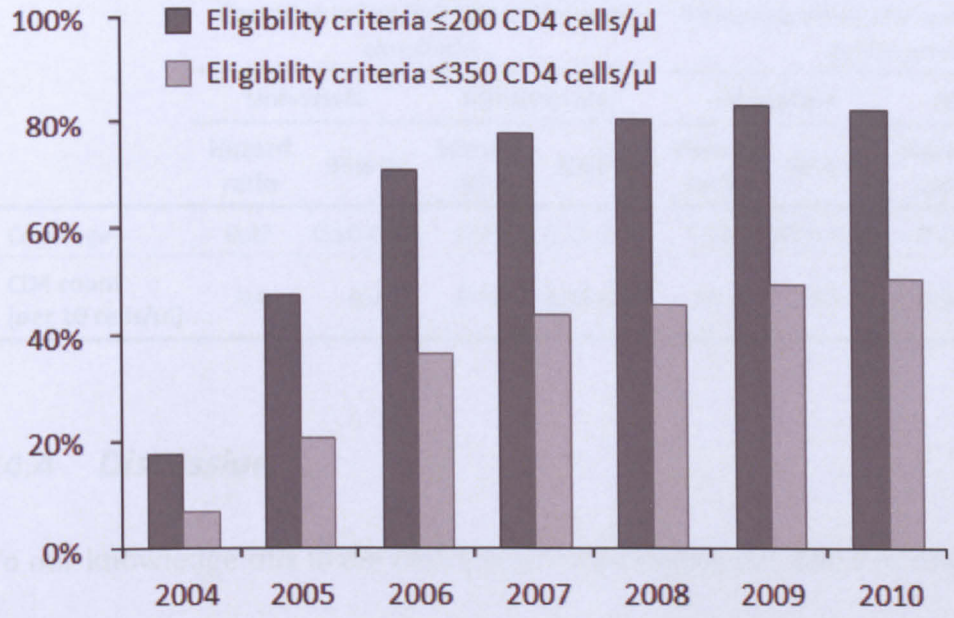
were 7% in 2004 and 50% in 2009 using an ART eligibility threshold of 350 cells/μL. In addition to deriving modeled estimates of ART coverage, we also directly measured coverage in 2010 via a community-based survey [11]. Using an eligibility threshold of 200 CD4 cells/μl, adult ART coverage was 77.0% (95%CI 68.1-84.4) in 2010. Using a CD4 threshold of 350 cells/μl, adult ART coverage was 55.4% (95%CI 47.3-63.3). Overall coverage in 2010 was similar when comparing modeled and measured estimates with CD4 count thresholds of 200 cells/μl (83% versus 77.0%, respectively p=0.13) and 350 cells/μl (51% versus 55.4%, respectively p=0.27).

14.3.4 TB incidence in the ART cohort

A total of 67 patients did not contribute time to the analysis, as they entered the cohort on TB treatment and exited before TB treatment was completed: 17 defaulted, 11 died and 8 were transferred out while on TB treatment. The remaining 31 patients did not complete TB treatment before the censoring date (31 December 2009)

Mean follow-up time was 1.85 years per patient. Overall TB incidence was 5.4 per 100 person-years (PYs) (95%CI 4.6-6.4). TB incidence was 21.3 (95%CI 15.5-29.1), 8.4 (95%CI 6.0-11.8), 3.9 (95%CI 2.7-5.6), 3.4 (95%CI 2.2-5.2) and 2.6 (95%CI 1.6-4.3) per 100 PYs for time-updated CD4 counts ≤100, 101-200, 201-350, 351-500 and >500 cells/μl.

Figure 14.3: ART coverage estimates derived from a mathematical model



14.3.5 Association between TB risk in the ART cohort and ART coverage in the community

Univariate analysis showed a 73% (95%CI 25%-90%) decreased risk of TB when increasing ART coverage from 0 to 100% using a CD4 threshold of 200 cells/µl. The risk was decreased 82% (95%CI 19%-96%) using a CD4 threshold of 350 cells/µl.

Multivariate analysis adjusted for current CD4 count revealed a hazard ratio (HR) of 0.36 (95%CI 0.13-0.98) for ART coverage at 200 cells/µl and 0.25 (95%CI 0.05-1.12) for ART coverage at 350 cells/µl (Table 14.3). Further adjustment for age and sex did not change the effect estimates (HR 0.37 for ART coverage at 200 cells/µl and 0.26 for ART coverage at 350 cells/µl). There was no association between TB risk and calendar year after adjusting for current CD4 count, age and sex (HR 0.92; 95%CI 0.81-1.04, p=0.17).

Table 14.3: Effect of ART coverage on TB risk

	Coverage using 200 CD4 cells/μl as threshold				Coverage using 350 cells CD4 cells/μl as threshold			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Coverage	0.27	0.10-0.79	0.36	0.13-0.98	0.18	0.04-0.88	0.25	0.05-1.12
CD4 count (per 10 cells/μl)	*NA*	*NA*	0.98	0.96-0.99	*NA*	*NA*	0.98	0.96-0.99

14.4 Discussion

To our knowledge this is the first study investigating the effect of community ART coverage on TB risk in an ART cohort. Increasing ART coverage from 0 to 100% decreased TB risk by 64% using CD4 eligibility criteria of ≤200 cells/μl. TB risk was even further reduced (75%) when using the new WHO eligibility criteria of CD4 count ≤350 cells/μl [21]. These results were adjusted for time-updated CD4 count. Thus they represent the additional benefit of ART coverage beyond the positive effect of ART on the individual's CD4 count recovery.

The additional benefit of ART might be explained by three mechanisms. First high ART coverage reduces the probability of contacts between individuals on ART and individuals with high risk for TB disease (HIV infected individuals with low CD4 counts not yet on ART). Second active TB case finding conducted as part of the routine ART visit reduces the duration of infectiousness in HIV infected individuals with TB disease. Third ART effects nosocomial transmission in clinics due to active TB case finding and improved immune status of individuals attending the clinics.

Some studies indicate that access to ART care is facilitated if an individual knows somebody who is already on ART [9,10]. Therefore it is likely that both HIV and ART are clustered in households, partnerships and social networks [8,22,23]. Thus the improvement of the CD4 count distribution of the ART cohort in more recent calendar years might not only impact on nosocomial transmission in individuals on ART [24], but also on transmission in the community.

Furthermore individuals on ART are regularly seen by health care professionals. Active TB case finding through symptoms screening was implemented at the start of the ART clinic in 2004. There was a significant reduction in untreated prevalent TB in the HIV infected population in this township between 2005 and 2008 as measured in two TB prevalence surveys [5]. The case detection rate among HIV infected individuals increased from 44% in 2005 to 64% in 2008, but remained stable in the HIV negative individuals over the same time period. This increase in case detection rate was entirely due to increased case detection among HIV infected individuals on ART. Increased TB case detection and timely diagnosis through active TB case finding followed by TB treatment will reduce the number of infectious individuals and the duration of infectiousness which potentially results in decreased transmission.

In this study TB risk was assessed within an ART cohort. This allowed calculating TB rates and risks based on precise denominators and times at risk. TB incidence rates stratified by time-updated CD4 counts were comparable to rates reported from other South African ART cohorts [2,3].

A major limitation of this study is the level of uncertainty regarding the variable "ART coverage". The study was conducted in a community where almost a third of the adult population (27%) had migrated into the community within the previous 3 years [11]. Highly mobile populations are difficult to model, as there is substantial uncertainty regarding both the demographic profile and the HIV disease profile of individuals moving into and out of the community. Estimates of ART coverage are very sensitive to assumptions about rates of CD4 decline [25], which are difficult to quantify accurately and may differ between populations [26]. However, the fact that two different definitions of coverage were found to be similarly associated with TB incidence provides some assurance that inaccuracies in the estimated coverage levels did not substantially bias the results. In addition ART coverage estimates derived from a mathematical model correlated well with estimates from a population-based cross-sectional survey.

Observational studies are prone to residual confounding both due to known and unknown confounders. CD4 counts were performed every 3-6 months. More frequent CD4 count measurement would have captured immune recovery more accurately. CD4 count is one of the strongest predictors for TB disease. It is therefore plausible that the effect of ART coverage on TB risk is entirely due to residual confounding by CD4 count. Misclassification of CD4 counts in observational cohorts with infrequent measurements is a well recognized problem. Misclassification of confounders introduces bias. In view of the high likelihood of residual confounding and bias due to confounder misclassification it is difficult to argue that there is true effect of ART coverage on TB risk.

ART coverage was associated with calendar year and therefore other factors such as migration and changes in the TB control program might have resulted in reduced burden of TB disease. The possibility that the time effect might be explained by factors other than ART coverage that were not measured cannot be excluded.

Mathematical modelling suggests that the population CD4 count distribution in this community has not changed since rollout of ART (Dr Leigh Johnson personal communication). ART rollout prevented a further left shift of the population CD4 count distribution, but did not lead to any improvement. Thus the effect of ART coverage on TB risk cannot be explained by improving overall immunity in the population. If indeed there is an effect of ART on TB transmission it might be confined to the ART cohort only. This is supported by unchanged TB notification rates in children in this community (Dr Keren Middelkoop personal communication) indicating stable TB transmission.

In summary this study gives some evidence that increases in ART coverage were associated with reduced risk of TB in an ART cohort even when controlling for time-updated CD4 count, suggesting an additional effect of ART on TB incidence. Starting individuals even earlier might reduce TB incidence even further. Studies investigating antiretroviral treatment as an HIV prevention strategy should investigate potential impact on TB control.

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15 Conclusions

15.1 Main findings

We reported a high uptake and diagnostic yield of community-based active TB case finding linked to a mobile HIV testing service. Treatment outcomes of actively found cases were as good as outcomes reported from primary health care clinics. A considerable proportion of TB cases did not start TB treatment ('early defaulters'), either because we were unable to contact them or they failed to start treatment. However the 'early defaulter' rate was comparable to reported rates from primary health clinics in South Africa which used passive TB case finding. We found that the costs of the active TB case finding program were USD 1,177 per TB case diagnosed and USD 2,458 per successfully treated TB case. A recent report from South Africa estimated the cost of passive case finding with USD 766 per successfully treated TB case assuming a smear positivity rate of 10% [1]. Our active case finding program was only three times more expensive than passive case finding. This is somehow surprising, as the smear positivity rate in our program was much lower than the assumed 10% in the passive case finding program. In addition tracing patients and contacting clinics was time consuming and therefore expensive. Thus, overall cost-effectiveness of mobile active TB case finding compares favourably to passive case finding. These results provide evidence for the feasibility and cost-effectiveness of community-based active TB case finding as a TB control strategy. Feasibility assessment and cost-effectiveness data are important to inform wide-spread implementation of community-based active case finding programs.

Despite challenges regarding early diagnosis, linkage to HIV and ART care and retention in care ART coverage in a township in Cape Town was high. TB risk in the ART cohort decreased with increasing ART coverage even after controlling for time-updated CD4 count suggesting that as ART coverage increased, TB transmission was reduced. We hypothesise, that reduction in transmission was probably due to a combined effect of ART and routine active TB case finding in the ART program. ART improved CD4 counts resulting in an effect similar to herd immunity; and routine active TB case finding in the ART program decreased duration of infectiousness. TB risk reduction was even higher when using coverage estimates based on the new WHO eligibility threshold of 350 CD4 cells/μl [2]. This study is the first to show an association between risk of TB and ART coverage, and the potential impact of the new WHO eligibility threshold.

The ultimate goal of HIV programmes is to achieve universal access as defined by current guidelines; however, the in depth analysis of test uptake, linkage, retention and coverage in this South African community highlights the challenges encountered in achieving this. Therefore although mathematical modelling has show that a 'test and treat' strategy with high coverage of HIV testing and immediate initiation of ART regardless of the CD4 count would reduce HIV transmission and providing high impact on TB transmission [3,4], many obstacles are going to have to be overcome if this is to be achieved.

15.2 Limitations

The community-based active TB case finding study and the ART coverage analysis did not investigate the impact on population TB incidence, as this was beyond the scope and time-frame of these studies. Direct measurement of TB incidence requires large sample sizes and are associated with major logistic and financial challenges [5]. As a result, there are few studies directly measuring TB incidence [6]. Tuberculin skin surveys have been used in the past to derive TB incidence estimates, but are deemed unreliable [7]. TB prevalence measured in repeated population-based surveys is at present the best indicator to assess impact of any TB control measures.

A study from Zimbabwe showed that community-based active TB case finding using smear microscopy decreased population TB prevalence in a before-and-after design [8]. A similar design was used in a South African study showing a decrease in TB prevalence after ART roll-out [9]. While these studies provide some evidence for the effect of these TB control measures, they are limited by the lack of concurrent control groups due to coincidental time trends. Further evidence for the effectiveness of ART comes from mathematical modelling and studies reporting decreased TB notification rates after ART roll-out [4,10,11]. Overall, evidence on the impact of ART and active TB case finding on TB control is at best limited, with even less data available to inform operational and strategic questions.

15.3 Future research – community-based active TB case finding

The best strategy and diagnostic algorithm for community-based active TB case finding is unknown. Diagnostic considerations include the number and sequence of tests, the choice of diagnostic tests such as chest X-ray, smear, culture or the new geneXpert MTB/RIF assay and symptom screens. Strategic questions relate to (i) timing and frequency of testing (ii) setting such as mobile services or work-places (iii) and additional services provided for example testing for other chronic or infectious diseases.

The majority of studies report on one round of active TB case finding conducted over a relatively short time-span. Repeated rounds of case finding will be necessary for TB control and elimination to be achieved. Shorter intervals between rounds of case finding reduce the yield and cost-effectiveness of the programme, whereas longer intervals prolong duration of infectiousness resulting in less effect on transmission. The optimal interval to balance maximal yield and minimal duration of infectiousness is not known. A study in Czechoslovakia in the 1960s showed a decreasing yield of active TB case finding programmes conducting serial mass radiography [12]. However, in a study in Zimbabwe, the yield did not significantly decrease in six rounds of active TB case finding over a period of 3 years [8]. Difference in follow-up and baseline TB incidence might explain the difference in results. In order to achieve acceptable yield, intervals will need to be adapted over the course of a screening programme and in line with the local setting.

Community-based active TB case finding studies comparing screening strategies such as temporary screening camps, mobile clinics utilizing existing community sites, fully mobile vans and home-based screening are rare. The Zimbabwean study compared mobile vans and home-based screening and found a higher overall yield when using mobile vans. However, the study was underpowered to show a difference in effect between the two screening strategies [8]. Unfortunately the study did not attempt to assess cost-effectiveness of the two screening strategies. Cost-effectiveness is an important parameter when considering widespread implementation of programs.

TB care is often delivered by vertical programs [13]. Integration with other services such as HIV has only recently received attention [14,15,16]. It is therefore hardly surprising that most population-based active TB case finding studies offer TB screening as stand-alone service [6,8,17,18,19,20]. Feasibility, acceptability and costs of integrating TB screening with chronic disease and HIV screening in population-based programs are currently unknown. In the Zimbabwean active case finding study over two thirds of those diagnosed with TB who consented to diagnostic HIV testing were HIV positive. These data highlight the need to consider integration of TB and HIV services, not only within health centres [16], but also at the level of community-based interventions. Combining active HIV and TB case finding in high HIV-prevalence settings would have several benefits. First, testing for both diseases will support prioritization of resources according to need given that people infected with TB are at greater risk of death if they are HIV-positive. Second a combined approach will be less demanding for patients provided issues

of stigma and confidentiality are carefully addressed. Finally, providing integrated, dual testing may allow a more efficient use of scarce community-level resources.

Number and sequence of diagnostic tests, the choice of test and symptom algorithms widely differ between studies [21]. Ultimately decisions need to be informed by yield, laboratory capacities, cost and diagnostic delays. One might argue that smear microscopy detects the most infectious patients and thus cuts the transmission chain. However, a more sensitive diagnostic test such as liquid culture detects TB cases earlier in the course of disease and increases the diagnostic yield of screening, which might allow for longer intervals between subsequent rounds of active TB case finding.

Treatment initiation rates and treatment outcomes of actively detected TB cases are rarely reported [22,23,24,25,26]. Some studies suggested higher treatment refusal and default rates in actively compare to passively detected case [25,26]. These findings raise concerns regarding the emergence of drug resistance. Furthermore if actively detected TB cases do not start treatment the impact of active TB case finding on transmission will be limited and ultimately active TB case finding will be less cost-effective. Reporting of treatment initiation and outcome rates should therefore be encouraged in any active TB case finding study.

15.4 Future research – antiretroviral therapy

Cluster randomized trials designed to investigate the 'test and treat' strategy are an opportunity to assess the effect of ART not only on HIV, but also on TB

incidence provided TB prevalence and notification data are collected. The success of 'test and treat' both for HIV and TB control will rely on high and frequent test uptake and good linkage and retention in care. Resources, interventions, infrastructure and staffing will be plentiful in a trial setting. Widespread implementation of ART early in the course of HIV disease will probably be more challenging under operational conditions. If a positive effect of high ART coverage early in the course of disease is shown under trial conditions, impact evaluation needs to be performed in routine settings.

While waiting for results of cluster randomized trials trends in TB notification rates might provide some insight of the effect of ART. Time-trends of TB notification rates in well described populations such as demographic surveillance sites with relatively precise ART coverage estimates should be analysed to provide more evidence for the effect of ART on TB control.

15.5 Concluding remarks

The studies presented in this thesis reported on feasibility, outcomes and costs of population-based active TB case finding and the losses along in the continuum of HIV care. The studies did not assess the impact of these control strategies on population TB incidence. The ideal study design to investigate the impact of community-based active TB case finding and ART would be a cluster randomized trial assessing TB prevalence using population-based surveys, MDR prevalence, treatment initiation and default rates and TB mortality preferably with long term (several years) follow-up [27,28,29].

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