

# Provider-initiated testing and counselling programmes in sub-Saharan Africa: a systematic review of their operational implementation

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**Objective:** The routine offer of an HIV test during patient–provider encounters is gaining momentum within HIV treatment and prevention programmes. This review examined the operational implementation of provider-initiated testing and counselling (PITC) programmes in sub-Saharan Africa.

**Design and methods:** PUBMED, EMBASE, Global Health, COCHRANE Library and JSTOR databases were searched systematically for articles published in English between January 2000 and November 2010. Grey literature was explored through the websites of international and nongovernmental organizations. Eligibility of studies was based on predetermined criteria applied during independent screening by two researchers.

**Results:** We retained 44 studies out of 5088 references screened. PITC polices have been effective at identifying large numbers of previously undiagnosed individuals. However, the translation of policy guidance into practice has had mixed results, and in several studies of routine programmes the proportion of patients offered an HIV test was disappointingly low. There were wide variations in the rates of acceptance of the test and poor linkage of those testing positive to follow-up assessments and antiretroviral treatment. The challenges encountered encompass a range of areas from logistics, to data systems, human resources and management, reflecting some of the weaknesses of health systems in the region.

**Conclusions:** The widespread adoption of PITC provides an unprecedented opportunity for identifying HIV-positive individuals who are already in contact with health services and should be accompanied by measures aimed at strengthening health systems and fostering the normalization of HIV at community level. The resources and effort needed to do this successfully should not be underestimated.

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## Introduction

In 2002, early advocates of provider-initiated testing and counselling (PITC) for HIV argued that the

‘exceptionalism’ that had distinguished HIV testing was no longer an adequate response to HIV in sub-Saharan Africa (SSA), especially with increasing access to antiretroviral therapy (ART) [1].

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The provider-initiated approach capitalizes on patient contacts with the medical system and consists of systematically offering HIV testing and counselling to all health facility users, unless they explicitly refuse.

In June 2007, the Joint United Nations Programme on HIV/AIDS UNAIDS and WHO issued guidance recommending PITC as a standard part of medical care in countries with generalized HIV epidemics [2].

Subsequently, concerns were raised regarding how to ensure adequate care was given to those who received a positive test result, particularly how to promote their linkage to long-term HIV services [3,4]. Other concerns included how to prevent discrimination and sex-based violence, which might result from disclosure [5–8]. Human rights and public health experts highlighted the need for informed consent to remain a cornerstone of this new approach to HIV counselling and testing [9], especially in a context of limited access to services and considerable patient–provider differences of status and power [4,10–12].

To date, 42 African countries have adopted policies recommending HIV PITC in a variety of clinical settings such as inpatient and outpatient departments, antenatal, tuberculosis (TB) and sexually transmitted infection (STI) clinics, and/or emergency and surgical departments [13].

As PITC implementation expands in SSA [5], a review of the evidence on the operational performance of PITC is essential in order to identify the main achievements and challenges, and to inform the timely adaptation of existing programmes. Two recent reviews have examined PITC programmes linked to antenatal and delivery care [14,15]. In this study we examine the operational implementation of PITC among non-pregnant adults in SSA.

## Methods

EMBASE and PUBMED databases were searched using a standard combination of terms covering the concepts ‘HIV’, ‘Testing’ and ‘Geographic location’ (Search #1, Table 1). We also searched the Global Health, JSTOR and COCHRANE databases using a more restrictive search (Search #2, Table 1). Search fields included were ‘Title’, ‘Abstract’ and ‘Subject heading word’ except for general terms such as ‘HIV’ and ‘AIDS’, where the search was limited to the title. We hand-searched the reference lists in the articles reviewed and explored the websites of international and non-government organizations working in this field.

Inclusion criteria were studies published in English, conducted in one or more SSA countries and published between January 2000 and November 2010. We excluded duplicate references, documents for which the full text was not available or was not in English, studies related to paediatric AIDS and studies that related only to prevention of mother-to-child transmission (PMTCT) and PITC in antenatal care because these had been addressed in other reviews [14,15]. Opinion documents, policy statements and guidelines were not included, but were sometimes used as background material to contextualize the discussion and conclusions.

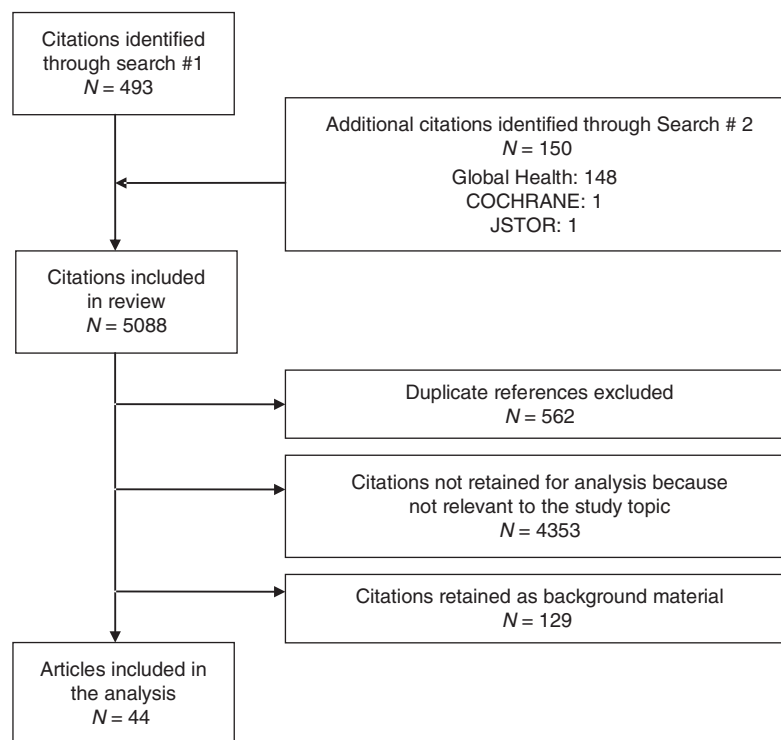
## Results

Figure 1 summarizes the results of the search and screening process. We retrieved 5088 references, which were screened by title and abstract by one of the authors (M.R.). Final decisions over inclusion were taken after reading the full text. A second researcher (T.K.) screened 10% of the references retrieved using the same process, and preliminary decisions over inclusion were compared.

**Table 1. Search strategy.**

HIV	Testing	Location
Search #1: <i>EMBASE and PubMed</i>		
HIV	Test	Each single African country
Human immunodeficiency virus	Routine	Resource-limited country
ART	Provider-initiated	Resource-limited setting
Antiretroviral	Opt-in	Africa
	Opt-out	Low-income country
	VCT	Middle-income country
	Screen	Sub-Saharan
	Diagnosis	
	Missed opportunities	
	Integration	
Search #2: <i>Global Health, Cochrane Library and JSTOR</i>		
HIV	Provider-initiated	Africa
AIDS	Opt-out	
ART	Routine testing	

Websites explored: <http://www.unaids.org>, <http://www.who.int>, <http://www.msf.org>, <http://www.aidsalliance.org>, <http://www.pathfind.org>, <http://www.pepfar.gov>.



**Fig. 1. Results of the search and screening process.**

For these 10%, there was only minor initial disagreement, which mainly related to whether to exclude a particular document from the review altogether or to keep it as ‘background material’. It was therefore deemed unnecessary for the remaining 90% to be rescreened. Final decisions were based on a thorough reading of the full text and discussion between the two researchers.

Data extraction was conducted by systematically entering information regarding study setting, design, population and main results into a standardized table (Supplementary Digital Content Table 2, <http://links.lww.com/QAD/A272>).

The majority of the studies reviewed reported on PITC experiences with TB clients, but there were also studies targeting outpatients [16–21], inpatients [22–25], patients attending STI services [26–29], and users of family planning [30] and emergency services [31,32].

### Effectiveness in identifying HIV-positive cases

Among TB patients, hospital clients and STI clinic users, the prevalence of HIV in clients tested through PITC activities has been much higher than in the general population [33] (Table 2).

Similarly, in the 32 studies that reported the prevalence of HIV in individuals tested using PITC, five studies found a prevalence of more than 70% [34–38], nine studies 50–70% [23,24,26,39–44], 13 studies 20–50% [16,18,22,25,31,32,45–51] and only five studies below 20% [19–21,28,52] (Table 3). Prevalences ranged widely from 84% in TB patients in Botswana [35] to 11% among women attending child health clinics in Kenya [52]. All the studies that documented an HIV prevalence of more than 70% were conducted amongst TB patients [34–38]. Conversely, the five studies that found a HIV prevalence below 20% were where PITC was offered to general

**Table 2. Prevalence of HIV among specific groups versus national prevalence in selected countries.**

	Prevalence in specific groups, year	National prevalence
Botswana	84% (TB patients, 2004–2005)	25% (2004)
Kenya	74% (TB patients, 2005–2007); 62% (TB suspects, 2003–2005)	6% (2005); 7% (2003)
Zambia	72% (TB patients, 2004–2006)	17% (2005)
Cameroon	68% (TB patients, 2006–2007)	5% (2005)
Malawi	77% (TB patients, 2001); 68% (hospital clients, 2003)	15% (2001); 14% (2003)
South Africa	56% (STI clinic female patients, 2005–2006)	16% (2005)
Uganda	64% (hospital clients, 2003)	4% (2003)

Based on UNAIDS/ WHO. Aids Epidemic Update, 2007. STI, sexually transmitted infection; TB, tuberculosis.

**Table 3. HIV prevalence rates reported in the studies reviewed.**

Study	Country	HIV prevalence (%)
<b>&gt;70%</b>		
TB clinics ( <i>n</i> = 5)		
Gammino <i>et al.</i> [35]	Botswana	84
Okot-Chono <i>et al.</i> [38]	Uganda	77
Chimzizi <i>et al.</i> , 2004 [34]	Malawi	77
Huerga <i>et al.</i> [36]	Kenya	74
Mwinga <i>et al.</i> [37]	Zambia	72
Other settings ( <i>n</i> = 0)		
<b>50–70%</b>		
TB clinics ( <i>n</i> = 6)		
Harris <i>et al.</i> [41]	Zambia	69
Chimzizi <i>et al.</i> [40]	Malawi	68
Njosing <i>et al.</i> [42]	Cameroon	68
Odhiambo <i>et al.</i> [43]	Kenya	62
Chakaya <i>et al.</i> [39]	Kenya	55
Sitienei, 2010 [44]	Kenya	52–44
Other settings ( <i>n</i> = 3)		
Wanyenze <i>et al.</i> (inpatients) [23]	Uganda	64
Wanyenze <i>et al.</i> 2011 (inpatients) [24]	Uganda	57
Kharsany <i>et al.</i> (STI patients) [26]	South Africa	56
<b>20–50%</b>		
TB clinics ( <i>n</i> = 5)		
Srikantiah <i>et al.</i> [50]	Uganda	42
Pope <i>et al.</i> [48]	South Africa	36
Gasana <i>et al.</i> [45]	Rwanda	29
Jerene <i>et al.</i> [46]	Ethiopia	21
Van Rie <i>et al.</i> [49]	Congo	21
Other settings ( <i>n</i> = 8)		
Nakanjako <i>et al.</i> (emergency unit) [31]	Uganda	43
Kessler <i>et al.</i> (inpatients) [22]	Botswana	43
Steen <i>et al.</i> (general population) [51]	Botswana	28–42
Arendt <i>et al.</i> (outpatients) [16]	Kenya	35
Basset <i>et al.</i> (outpatients) [18]	South Africa	33
Menzies <i>et al.</i> (hospital clients) [47]	Uganda	27
Wanyenze <i>et al.</i> (inpatients and outpatients) [25]	Uganda	25
Waxman <i>et al.</i> (emergency unit) [32]	Kenya	23
<b>&lt;20%</b>		
TB clinics ( <i>n</i> = 0)		
Other settings ( <i>n</i> = 5)		
Leon <i>et al.</i> (STI clients) [28]	South Africa	19
Topp <i>et al.</i> (outpatients) [21]	Zambia	17
Fetene and Feleke (outpatients) [19]	Ethiopia	13
Kiene <i>et al.</i> (outpatients) [20]	Uganda	13
Chersich <i>et al.</i> (women at child health clinics) [52]	Kenya	11

TB, tuberculosis.

outpatients [19–21], women in child health clinics [52] or STI clinic attenders [28].

Introduction of routine PITC rather than client-initiated or selective testing more than quadrupled HIV case-finding relative to patient-initiated Voluntary Counseling and Testing (VCT) in one South African outpatient setting [17]. In Ethiopia more than half of the HIV-positive patients identified through PITC believed that they were not at risk of HIV, underscoring the relevance of PITC to diagnose individuals who, unlike those who decide to attend a VCT centre, believe that they are at low or no risk of HIV infection [19].

### Offer and acceptance of the test

The translation of PICT policy guidance into practice has had mixed results. The proportion of the target group

who were offered an HIV test varied from 94% of TB patients in a study in South Africa [53] to 24% of outpatients in a study in Ethiopia [19]. Factors cited for not systematically offering the test included fear that patients would be offended and the perceived slowing of patient flow through the clinic [32].

Test acceptance also varied across the reviewed studies, ranging from 99% amongst inpatients in Uganda [24] to 31% in outpatients in South Africa [17]. Acceptance rates tended to be high amongst TB clients, inpatients and at emergency departments, and more moderate amongst outpatients and STI clients. However, rates in the different studies varied widely within each target group, except for the extremely high acceptance rates found in both reported emergency department studies [31,32]. Importantly, in Malawi acceptance levels above 90%

under research conditions dropped to 59% during routine care of TB patients [34,40], suggesting that the operational particularities of implementing each programme may contribute substantially to differences in acceptance rates.

Reasons given by clients for refusing the HIV test included a perception of low risk, having previously tested and feeling 'afraid' or 'not ready' [26]. In a community-based study in Botswana, 94% of the participants were in favour of routine HIV testing, but the majority of those not favouring the approach said that testing should be an individual choice and that people should not be pushed to get tested [54].

### Testing uptake by sex, age, occupation and education level

Which demographic groups were more likely to be reached through PITC was inconsistent across studies. Sex was not related to uptake of HIV testing in some studies [25,37,55], but in others males were less likely to attend health facilities, to be offered an HIV test if they did attend and to accept a test [27,54,56,57]. Similarly, HIV testing uptake was higher among the youngest groups in two studies [23,55], but lower in another [51]. The association between HIV testing uptake and educational levels was also inconsistent, with one study in Uganda finding that those with formal education were more likely to be offered a test [23], and another in Ethiopia showing that the most educated were less likely to be tested [19]. Being unemployed was associated with test acceptance in two other studies in Uganda and Ethiopia [46,55]. One Kenyan study found that higher income groups were more likely to decline the offer to test [52].

### Behavioural outcome of provider-initiated testing and counselling approaches

The behavioural outcomes of PITC, such as its impact on disclosure and self-reported sexual practices, have rarely been studied. However, a study in rural Uganda found that after receiving routine HIV testing, self-reported disclosure to a partner was above 85%, but partner uptake of testing was low, and half of the study participants, either HIV-positive or negative, reported recent risky sex at 3 months follow-up [20]. Two other Ugandan studies also suggest the need for strengthening risk-reduction post-test counselling services: only 26% of inpatients tested for HIV at a hospital in Kampala reported receiving post-test counselling [23] and 29% of TB patients tested for HIV at primary care clinics in this city did not even receive their test results [55].

### Linkage to treatment

Poor referral systems and linkage to treatment were highlighted as major areas for improvement in many of the studies [18,23,27,38,39,41,48,53,58].

Less than 40% of the HIV-positive clients identified in a study in South African TB clinics were prescribed cotrimoxazole (CTX) or referred to care [48]. Similarly, 36% of the TB patients tested in five peri-urban and rural districts of Uganda did not receive any subsequent HIV-related service [38], and fewer than one-third of HIV-positive inpatients in a South African hospital had undergone a CD4 cell count test [18]. In 16 South African clinics, only 24% of HIV-positive clients had received a follow-up medical assessment [53]. Even in clinics provided with additional financial and human resources, research identified weaknesses in referral and tracking systems leading to poor treatment access amongst HIV-positive individuals identified through TB services [39]. In a South African study, 48% of HIV-positive STI clinic clients were lost to care within 6 months of testing. The continuum of care amongst those who were not yet eligible for treatment was poor: among individuals testing at TB clinics and through VCT services, 65 and 58% of non-eligible patients, respectively, failed to have a repeat CD4 cell count test. The percentage of individuals linked to care at a 6-month follow-up visit ranged from 69 to 84% among individuals tested through PITC approaches and 53% among those testing at traditional VCT centres, suggesting that poor linkage to treatment is common with both testing modalities [27].

The proportion of HIV-positive individuals receiving treatment ranged from 12% [38] to 50% [42], but these data were only provided in some of the studies conducted with TB patients, and the number of individuals who were eligible to initiate treatment was rarely reported. From three studies where this information was available, about one-third of eligible cases had not enrolled for further HIV care within the study follow-up period [27,41,58].

Little attention has been given to the linkage of those testing HIV-positive into further screening (e.g. for TB or STIs), and, with the exception of a study assessing the behavioural outcomes of PITC, the subsequent counselling of those testing negative has hardly been addressed [20], despite worrying findings that testing HIV-negative may be associated with increased subsequent risks of HIV acquisition [59,60].

### Operational issues

Several operational challenges that have limited the effectiveness of linkages to further care for people testing HIV-positive through PITC derive from health systems weaknesses at the level of infrastructure, supplies, data registers, coordination and human resources [21,36,37,61,62].

A qualitative study in five Ugandan districts identified a range of health systems barriers that undermined the effectiveness of collaborative TB/HIV services, including the policy of routinely offering HIV testing to all TB

patients [38]. District officers had not disseminated policy guidelines to providers; no funds had been assigned for coordination meetings between the two programmes; there was virtually no follow-up nor supervision of newly trained personnel and the training curricula lacked specific modules on TB/HIV collaboration. TB registers included HIV data but most were not systematically filled in, and space for TB-related data was often lacking in HIV clinic registers. Shortages of testing kits, CTX and ART were also identified [38]. In other programmes, patient registers had to be adapted to capture HIV data [41], and infrastructure and space needed to be reassigned [21,37].

The additional workload and occupational stress experienced by nurses working within overstretched local health systems have been identified as obstacles for effective implementation of PITC [61,62]. However, few studies have attempted to estimate the additional personnel time that integration of PITC into routine care would require. In a Kenyan study, the provision of PITC added 7 min to a median consultation time of 10 min in family planning clients deciding to test [30]. In Zambia, patient-provider contact time more than doubled in a clinic when PITC was introduced [21]. As a response to this and the scarcity of medical personnel, trained lay counsellors and assistant physicians have been used by several programmes [21,51], and in a South African STI clinic, group counselling was provided together with an option for individual pre-counselling [26].

### Costs of provider-initiated testing and counselling programmes

Only three studies reported costing analyses of PITC, all of which, found that the total cost per person tested using PITC was below the cost per person tested using conventional VCT services [17,30,47]. However, in terms of costs per HIV-positive person identified, the available evidence shows conflicting results [17,47], and total costs will usually increase, as more people should be tested by PITC than with patient-initiated VCT.

### Ethical issues

In Botswana, 68% of participants felt that they could not decline HIV testing when it was proposed by a healthcare provider [57], and community-based research in the same country showed that women rarely declined the offer to test [54]. Although the national policy states that no patient should be tested against his/her wishes, clients who decline the offer were referred for 'additional counselling' if healthcare providers believed there was an important reason to test for HIV [51]. However, in a South African STI clinic, 56% of clients refused to test, of whom 32% reported that they 'felt afraid' or 'not ready' [26]. In Zambia, TB patients who initially declined testing were re-offered the test after the intensive phase of TB treatment, and again after completing therapy [41].

These examples raise concerns about how free clients might feel to repeatedly decline the test.

There are potential negative consequences to the individual who tests positive, such as sex-based violence and discrimination. However, in a cross-sectional survey in Botswana [57], few cases reported experiencing violence (1%) or discrimination (2%) related to testing. Among respondents who had received PITC services, 95% reported that confidentiality had been strictly respected [57]. Studies in other countries have not found an association between testing through PITC and being at increased risk of reporting subsequent partner violence. In a Ugandan trial that randomized medical inpatients to receive either inpatient HIV counselling and, testing or post-discharge referral for outpatient testing, there were no significant differences in terms of reported disclosure between intervention and control groups [24]. In a study in Botswana, no association was found between having tested in the past 12 months through routine testing or VCT, and reporting having experienced partner violence [54].

Finally, there was no evidence that the PITC approach had had a detrimental effect on the demand for healthcare services [51,54].

## Discussion

Systematically offering HIV tests within routine medical care is an effective strategy for identifying large numbers of previously undiagnosed HIV-positive individuals, especially in settings such as TB clinics in high HIV-prevalence countries. However, in several studies of routine PITC programmes, the proportion of patients actually offered an HIV test has been disappointingly low. This implies shortcomings in the translation of policy guidelines into practice. Similarly, many studies have found poor linkage of individuals who test HIV-positive to subsequent care and treatment services, with high proportions of newly diagnosed patients failing to access antiretroviral treatment, CTX preventive therapy, follow-up assessments and even post-test counselling in one study [23]. This is in line with the results of studies conducted in other settings, such as maternity services, which have also reported substantial patient drop-out between a pregnant woman testing HIV-positive and accessing HIV-related services for her own care [63–65], as well as for other testing modalities such as VCT [66].

There is a clear ethical and programmatic obligation for health workers to ensure that HIV-positive individuals are linked to appropriate care and treatment services. Unless a high proportion of clients who test HIV-positive are linked into the HIV services that they need, the additional costs and workload related to PITC will not reap the

expected health benefits, for the clients themselves, the health system and society as a whole.

Poor linkage to treatment after testing for HIV is not specific to PITC, and measures to improve linkage and retention such as strengthening pre-ART default monitoring need to be considered for all testing modalities. Further research should address how to track and retain individuals who are diagnosed HIV-positive before they are eligible to start treatment and how to ensure their appropriate linkage to non-HIV-related services such as STI and TB screening. The provision of post-counselling services to those testing HIV-negative through PITC also deserves greater attention.

The review was subject to the limitations of synthesizing and comparing findings from randomized, nonrandomized and qualitative studies [67]. However, the study's strengths included a systematic search of five databases supplemented by a hand-search of the reference lists in the articles identified, and inclusion of reports from key international and national organizations. The review period included some years since PITC has been widely implemented, and has resulted in a timely and comprehensive analysis of the 'real world' implementation of PITC programmes targeting non-pregnant adults in SSA.

For PITC to fulfil its potential as a gateway to HIV-related services, laboratory facilities and drug distribution systems must be strengthened and workforce shortages addressed to ensure the system has the necessary capacity to manage the additional HIV-positive cases identified through PITC. Improved infrastructure, and reallocation and/or rehabilitation of space might be required, and managerial and leadership strategies will be needed for a coordinated response. More clinicians, nurses, managers, escorts, laboratory technicians and lay counsellors may need to be recruited and trained, and recording systems improved.

The recent trend towards switching from individual pre-test counselling to a group format, and the impact of abbreviating, or removing, pre-test counselling sessions also need to be carefully evaluated. The South African experience where group counselling was provided together with an option for individual pre-test counselling [26] may be a good compromise between the individualized service required for sensitive topics and the restrictions posed by human resource constraints, but this needs to be further evaluated. The need for individual counselling may be particularly strong in the context of PITC as, having attended the health facility for non-HIV-related reasons, clients may be psychologically unprepared for an HIV-positive diagnosis.

With generally high levels of HIV test acceptance in sites adopting PITC, concerns have been raised about the extent to which the consent provided by clients is truly

informed and voluntary [4,68]. It has been argued that the social status of medical professionals, the limited availability of healthcare services and the tendency to obey authority might compromise the perceived voluntariness that should underpin informed consent procedures [10,12]. However, a recent review investigating patients' views of PITC in African countries illustrates how attitudes have shifted in the past few years to widespread acceptance of routine testing [13]. Unfortunately, the existing evidence does not tell us much about an individual's motivations to test and the possible difficulties that users might have encountered in refusing testing, and most studies omitted details about how consent was provided in practice. More information on the exact procedures is required for a thorough evaluation and development of best practice guidelines, and monitoring mechanisms are needed to ensure clients are fully aware that they can decline the offer to test without compromising their right to receive other medical care.

In theory, people might avoid going to health facilities if they fear being tested. Although the fact that attendance to services such as ante-natal care (ANC) has remained above 95% in Botswana after PITC was implemented as part of PMTCT is reassuring [51], the impact of PITC on the utilization of other services needs assessment. Similarly, whereas studies have failed to find an association between testing through PITC and reporting experiencing sex-related violence [54,57], close monitoring is required as PITC expands. If rates of testing acceptance are to be increased without compromising voluntarism, measures to tackle the underlying social norms that perpetuate HIV-related stigma as a barrier to HIV test uptake should be reinforced [69,70].

Additional costing studies need to be conducted both in general outpatient departments and in clinical settings where HIV-positive persons are likely to be over-represented, such as TB and STI clinics. However, it is expected that the number of persons testing will increase substantially as PITC expands, and given that the total cost of testing will depend on the cost per client successfully tested multiplied by the total number of clients tested, considerable additional resources will be required to implement this testing modality throughout SSA, even if the cost per HIV-positive client successfully tested is lower than in VCT programmes. In this process, it is essential that sufficient resources are allocated to ensure adequate and timely linkage to care for those testing HIV-positive. Clearly, costs per HIV-positive individual identified will be inversely related to the HIV prevalence in those tested, so PITC will be much more expensive per HIV-positive individual identified in settings where the HIV prevalence is low. Finally, as PITC programmes can only target individuals who attend health facilities, other strategies, such as community and home-based testing, will be required to reach and offer

HIV testing to individuals who do not seek healthcare services [28,71].

## Conclusion

The widespread adoption of PITC for HIV provides an unprecedented opportunity for identifying HIV-positive individuals who are already in contact with the health services, without the need for motivating them to attend a health facility for such testing. With the introduction of PITC in diverse settings, the uptake of HIV testing has increased remarkably, but there are substantial missed opportunities related to implementing the policy, with wide variations in the rates of acceptance of the test and high proportions of individuals failing to access subsequent HIV treatment and care services as well as failing to access further screening for conditions such as STIs or TB.

Acceptability of HIV PITC has largely been grounded in the potential clinical benefit to those testing, and therefore measures aimed at ensuring access to treatment after testing HIV-positive should be central to its implementation.

To reap the expected health benefits, PITC programmes should incorporate measures aimed at strengthening health systems and fostering the normalization of HIV at community level. However, the resources and effort needed to do this successfully should not be underestimated.

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## Conflicts of interest

The authors declare no conflict of interest.

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