Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review

Darshini Govindasamy\textsuperscript{a}, Nathan Ford\textsuperscript{b,c} and Katharina Kranzer\textsuperscript{d}

**Objective:** To characterize patient and programmatic factors associated with retention in care during the pre-antiretroviral therapy (ART) period and linkage to ART care.

**Design:** Systematic literature review.

**Methods:** An electronic search was conducted on MEDLINE, Global Health, Google Scholar and conference databases to identify studies reporting on predictors, barriers and facilitators of retention in care in the pre-ART period, and linkage to care at three steps: ART-eligibility assessment, pre-ART care and ART initiation. Factors associated with attrition were then divided into areas for intervention.

**Results:** Seven hundred and sixty-eight citations were identified. Forty-two studies from 12 countries were included for review, with the majority from South Africa (16). The most commonly cited category of factors was transport costs and distance. Stigma and fear of disclosure comprised the second most commonly cited category of factors followed by staff shortages, long waiting times, fear of drug side effects, male sex, younger age and the need to take time off work.

**Conclusion:** This review highlights the importance of investigating interventions that could reduce transport difficulties. Decentralization, task-shifting and integration of services need to be expedited to alleviate health system barriers. Patient support groups and strategic posttest counselling are essential to assist patients deal with stigma and disclosure. Moreover, well tolerated first-line drugs and treatment literacy programmes are needed to improve acceptance of ART. This review suggests a combination of interventions to retain specific groups at risk for attrition such as workplace programmes for employed patients, dedicated clinic and support programmes for men and younger individuals.

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**Keywords:** AIDS, antiretroviral therapy, attrition, continuity of patient care, HIV, lost to follow-up, retention, sub-Saharan Africa

**Introduction**

Scale-up of antiretroviral therapy (ART) over the last decade has been impressive, with 6.6 million receiving ART in low and middle-income countries \cite{1}. But, overall ART coverage in sub-Saharan Africa remains low, at 49\%, with major disparities between the eastern and southern region (56\%) compared with the western and central region (30\%), which is largely attributable to the difference in economic stability, effectiveness of HIV/AIDS programmes and domestic and donor support \cite{2}. HIV-positive patients continue to delay entry to care, and consequently almost a quarter of patients die in their first year of treatment \cite{3}. Hence, identification of interventions that can enrol more patients into care, earlier in their disease progression, is essential \cite{3}.

Data on the number of patients lost to follow-up prior to ART-initiation is not routinely collected and thus, it is challenging for national HIV/AIDS control programmes to provide accurate data on the extent of this problem \cite{4}. However, one recent systematic review quantified the...
losses occurring between HIV testing and ART initiation in sub-Saharan Africa [5]. This study showed that patient attrition was highest in the pre-ART phase, with under half (46%) of individuals not yet eligible for ART retained in pre-ART care and just over two-thirds (68%) of ART-eligible individuals initiating ART [5]. Although such attrition is widely acknowledged as a major problem, risk factors for attrition are less well described, and few interventions have been evaluated to improve linkage to care. Given the current economic crisis, international AIDS donors need to invest strategically, particularly in areas with a potentially high economic return [6] such as linkage and retention in care [7]. This review summarizes the characteristics of patient and programme level factors associated with retention in care during the pre-ART period and linkage to ART care in sub-Saharan Africa.

Methods

We sought all studies reporting on risk factors, barriers and facilitators of retention (number of patients remaining in care), attrition (number of patients reported dead, lost to follow-up or who discontinued care) in the pre-ART period and linkage to care at three steps: ART eligibility assessment, pre-ART care, and ART initiation. Studies were omitted if they exclusively examined steps downstream from ART initiation such as retention or adherence, were done in the private healthcare sector, reported un systemctl observations (case reports and case series), or were secondary data sources (editorials and viewpoints). Studies were also excluded if they were of poor quality (i.e. outcome definition unclear, no adjustment of confounders, unreliable measurement tool used and no discussion of potential limitations). The search was limited to quantitative and qualitative studies conducted within sub-Saharan Africa, published in English between 01 January 2000 (the time when ART first became available in this region) [2] and 31 May 2011.

Two electronic databases (MEDLINE and Global Health) were searched using a compound search strategy (Web Appendix 1, http://links.lww.com/QAD/A239). Keywords were also searched in Africa-Wide Information and Google Scholar. Bibliographies of potentially eligible full text publication were searched. Conference abstracts were sought only for the years that abstract databases were available online [i.e. Conference on HIV Pathogenesis and Treatment of the International AIDS Society (IAS, 2001–2011), the Conference on Retroviruses and Opportunistic Infections (CROI, 2006–2011), the International AIDS Conference (AIDS, 2001–2008) and AIDS Education Global Information System (AEGIS)]. Finally, experts in the field were contacted for recommended literature.

Potentially eligible studies were downloaded into RefWorks, and titles and abstracts were searched by two reviewers (D.G. and K.K.) according to the pre-defined inclusion and exclusion criteria. Screening of articles taken through to full review was also performed in duplicate (D.G., K.K.). Conference abstracts were screened by title and full text. The data extraction and quality assessment form was adapted from the STROBE statement checklist [8].

Results

The search yielded a total of 768 citations, among which 32 were retained for review (Web Appendix 2, http://links.lww.com/QAD/A239). The majority of studies were conducted in South Africa (n = 16); the remainder were conducted in Uganda (n = 7), Kenya (n = 5), Malawi (n = 3), Ethiopia (n = 2), Tanzania (n = 2), Zambia (n = 2), Rwanda (n = 1), Swaziland (n = 1), Mozambique (n = 1), South Africa and Zimbabwe (n = 1) and South Africa and Kenya (n = 1). Most were semi-qualitative studies (n = 19); the remainder used either purely quantitative (n = 17) or qualitative (n = 6) methods.

Twenty studies examined predictors for retention and linkage in the pre-ART period (Table 1) [9–31]. These studies were conducted among home-based testers [9], female sex workers [10], patients accessing a mobile HIV testing service [15] and patients accessing public healthcare facilities [11–14, 16–18, 21–29, 31]. The most common predictors for enrolling into HIV care were disclosing one’s HIV-positive status [9, 15], perceived poor health [9], and low CD4 count [15]. Commonly reported correlates for attrition between CD4 count testing and ART initiation included distance to a testing centre [13, 16], cost of transport [29], male sex [16–18, 23, 24, 27, 31], younger age [18, 19, 22, 25, 31], having advanced immunodeficiency [20, 22, 24, 26, 27] and having lower levels of education [21, 28].

Twenty-five studies examined barriers to accessing and remaining in HIV care (Web Appendix 3, http://links.lww.com/QAD/A239 [32]), which were categorized into psychosocial, economic, health systems and medical barriers. The main reported psycho-social barriers were stigma and fear of disclosure [9, 15, 27, 33–43], and fear of drug toxicities [15, 27, 34, 36, 39, 41, 42] (Table 2). Transport costs [14, 27, 34, 35, 37, 38, 40, 42, 44–47], distance to health facility [14, 15, 36, 38, 42, 44, 48], food shortage [36, 37, 39, 41, 44], patient-related time constraints [14, 38] and employed patients unable to take time off work for clinic appointments [14, 15, 38, 40, 47, 49] were the main reported economic barriers. Long clinic waiting times [33–36, 38, 44, 45] and shortage of healthcare workers (HCWs) [36, 43, 44] were the main reported health systems
Table 1. Factors influencing the patient continuum of HIV care.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Setting</th>
<th>Year of the study</th>
<th>Study design</th>
<th>Eligible (N)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1: Initiation of ART eligibility assessment</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amolloh [9]</td>
<td>Kenya</td>
<td>Asembo, home based testing service</td>
<td>2008–09</td>
<td>Household survey/Prospective cohort</td>
<td>737</td>
<td>Enrolling in care: Older age, female, HIV disclosure, perceived poor health, testing as a couple/family, having another household member enrolled in care</td>
</tr>
<tr>
<td>Braunstein [10]</td>
<td>Rwanda</td>
<td>Kigali, FSWs</td>
<td>2007–08</td>
<td>Prospective cohort</td>
<td>141</td>
<td>Not enrolling in HIV care: Breastfeeding, known HIV+ sexual partner, reported condom use in the last sex act</td>
</tr>
<tr>
<td>Losina [13]</td>
<td>South Africa</td>
<td>Durban, semi-private hospital</td>
<td>2006–2007</td>
<td>Prospective cohort</td>
<td>454</td>
<td>Not having a timely CD4 count: Distance from clinic (≥10 km), history of TB treatment, referred by healthcare provider for HIV testing</td>
</tr>
<tr>
<td>Naidoo [14]</td>
<td>South Africa</td>
<td>Johannesburg, clinic</td>
<td></td>
<td>Survey of HIV+ patients that had bloods taken for a CD4 count test</td>
<td>225</td>
<td>CD4 count collection: Age (25-36 years), secondary schooling, perception that people do not care what their CD4 count result is, CD4 count does not matter if you are HIV+ Enrolling into care: Low CD4 count (&lt;350 cells/μl), disclosure, presence of TB symptoms, unemployment; Receiving result telephonically: Low CD4 count (&lt;350 cells/μl), female, the availability of a phone number</td>
</tr>
<tr>
<td>Ingle [16]</td>
<td>South Africa</td>
<td>Free State, public sector clinics</td>
<td>2004–07</td>
<td>Prospective cohort</td>
<td>44844</td>
<td>No recorded pretreatment CD4 count: Male, enrolled in 2007, no national ID number</td>
</tr>
<tr>
<td>Nakigozi [17]</td>
<td>Uganda</td>
<td>Rakai community cohort study</td>
<td>2004–07</td>
<td>Follow-up of HIV+ participants that accepted VCT</td>
<td>1145</td>
<td>Not enrolling in HIV care: Male, younger age (15–24 years), having 1–2 co-residents, married, CD4 &gt; 250 cells/μl</td>
</tr>
<tr>
<td><strong>Step 2: Pre-ART care</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Evangelii [19]</td>
<td>South Africa</td>
<td>Rural Kwa-Zulu Natal, HIV treatment and care programme</td>
<td>2009–10</td>
<td>Prospective cohort</td>
<td>456</td>
<td>HIV treatment and care programme attrition: not being eligible for ART, greater reliance on family and friends, more time spent with friends, younger age</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Setting</th>
<th>Year of the study</th>
<th>Study design</th>
<th>Eligible (N)</th>
<th>Risk factors</th>
<th>Predictors for retention</th>
<th>Predictors for attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karcher [21]</td>
<td>Kenya</td>
<td>Nyanza, district hospital</td>
<td>2004–05</td>
<td>Retrospective cohort</td>
<td>159</td>
<td>Not initiating ART: age (&lt;35 years), severe malnutrition, active pulmonary TB, severe bacterial infection and prolonged unexplained fever</td>
<td>Not initiating ART: male, patients with no family/friends who were HIV-infected</td>
<td></td>
</tr>
<tr>
<td>Tayler-Smith [22]</td>
<td>Kenya</td>
<td>Kibera slum, clinics</td>
<td>2005–08</td>
<td>Retrospective cohort</td>
<td>2471</td>
<td></td>
<td>Not initiating ART: male, unemployed, baseline CD4 &lt; 100 cells/µl</td>
<td></td>
</tr>
<tr>
<td>Bassett [23]</td>
<td>South Africa</td>
<td>Durban, semi-private hospitals</td>
<td>2006–08</td>
<td>Prospective cohort</td>
<td>1474</td>
<td>Not initiating ART: male, patients with no family/friends who were HIV-infected</td>
<td>Not initiating ART: male, enrolled in a rural clinic, clinic with low staffing levels, distance from clinic</td>
<td></td>
</tr>
<tr>
<td>Ingle [16]</td>
<td>South Africa</td>
<td>Free state, public sector clinics</td>
<td>2004–07</td>
<td>Retrospective cohort</td>
<td>44844</td>
<td>Not initiating ART: male, enrolled in a rural clinic, clinic with low staffing levels, distance from clinic</td>
<td>Not initiating ART: male, unemployed, baseline CD4 &lt; 100 cells/µl</td>
<td></td>
</tr>
<tr>
<td>Bassett [24]</td>
<td>South Africa</td>
<td>Durban, semi-private hospitals</td>
<td>2006</td>
<td>Retrospective cohort</td>
<td>501</td>
<td>Not initiating ART: male, enrolled in a rural clinic, clinic with low staffing levels, distance from clinic</td>
<td>Not initiating ART: male, unemployed, baseline CD4 &lt; 100 cells/µl</td>
<td></td>
</tr>
<tr>
<td>Lawn [26]</td>
<td>South Africa</td>
<td>Cape Town, primary care clinic</td>
<td>2002–05</td>
<td>Retrospective cohort</td>
<td>1235</td>
<td>Not initiating ART: advanced immunodeficiency</td>
<td>Not initiating ART: advanced immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Amuron [27]</td>
<td>Uganda</td>
<td>Jinja, clinic</td>
<td>2004–06</td>
<td>Prospective cohort</td>
<td>2182</td>
<td>Incomplete screening: male, low CD4 count (&lt;50 cells per 10³/µl)</td>
<td>Not initiating ART: less education, difficulty dressing, more delayed ART initiation appointment, mid-upper arm circumference &lt; 22 cm</td>
<td></td>
</tr>
<tr>
<td>McGrath [28]</td>
<td>Malawi</td>
<td>Karango, rural, district hospital</td>
<td>2005–06</td>
<td>Prospective cohort</td>
<td>659</td>
<td>Not initiating ART: less education, difficulty dressing, more delayed ART initiation appointment, mid-upper arm circumference &lt; 22 cm</td>
<td>Nonacceptance to ART: cost of transport to ART site</td>
<td></td>
</tr>
<tr>
<td>Zacharash [29]</td>
<td>Malawi</td>
<td>Thyolo, district hospital, TB patients</td>
<td>2003–04</td>
<td>Retrospective cohort</td>
<td>742</td>
<td>Not initiating ART: less education, difficulty dressing, more delayed ART initiation appointment, mid-upper arm circumference &lt; 22 cm</td>
<td>Nonacceptance to ART: cost of transport to ART site</td>
<td></td>
</tr>
<tr>
<td>Nolan [30]</td>
<td>Kenya</td>
<td>m2m programme, pregnant HIV+ women</td>
<td>2003–04</td>
<td>Retrospective cohort</td>
<td>4070</td>
<td>Antiretroviral uptake: Disclosure, m2m visits</td>
<td>Antiretroviral uptake: Disclosure, m2m visits</td>
<td></td>
</tr>
<tr>
<td>Pepper [31]</td>
<td>South Africa</td>
<td>Cape Town, primary care clinic</td>
<td>2008–2009</td>
<td>Retrospective cohort</td>
<td>100</td>
<td>Not initiating ART: male, older age (&lt;36 years)</td>
<td>Not initiating ART: male, younger age (&lt;36 years)</td>
<td></td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; FSW, female sex workers; HIV+, HIV-infected; ID, identification; m2m, mothers to mothers; TB, tuberculosis; VTC, voluntary counselling and testing.
barriers. The main medical barrier was having to complete TB therapy. Only one study, from Tanzania, examined facilitators to care and showed that the provision of referral letters to patients together with transport vouchers, community escorts and supportive counselling facilitated their linkage to care [37,50].

**Discussion**

There is a clear need to implement and evaluate interventions to retain patients in the period before they have started treatment, yet to date few such studies have been published. This literature review identified three major areas that are amenable to intervention and thus provide direction for future research for the exploration or validation of interventions to support patient retention along the care cascade.

We found that transport costs and distance were the main factors that impeded on a patient's continuity in HIV care. Transport vouchers, transport re-imbursements and a free patient transport system are viable methods to avert out-of-pocket payments for travel [14,27,29,34,35,37,38,40,42,44–47]. Integration [54,55] and decentralization [56–62] of ART care has been shown to be beneficial for patients receiving ART and may also improve access to care for pre-ART patients. In particular, the use of mobile units providing pre-ART services such as CD4 count monitoring and home-delivered ART [63] have been found to improve linkage to care.

The current study also found that lack of human resources was both a predictor and barrier to care and was reported by several studies. Task-shifting [56,57,64–68] has been shown to be effective in resource-constrained settings and thus may partially address staff shortages. Furthermore, financial incentives, career development programmes, enhanced management, personal recognition and improved working conditions are critical for retaining and sustaining HCWs in the public-sector in order to have the human resources to retain patients in care [69,70]. This review showed that long waiting times was a commonly reported barrier to care. These could be potentially eliminated through a systematic patient appointment system, less frequent patient visits, and less frequent dispensing schedules, including community-based dispensing which has been found to reduce patient attrition on ART [71]. Results from several studies have shown that most patients who undergo CD4 count testing fail to return to their healthcare facility for their results [11–14] and this is mainly to avoid accruing transports costs and waiting in long clinic queues [38,44]. Recent data has shown that point-of-care (POC) CD4 count technology is effective in reducing losses associated with CD4 count testing completion in both South Africa [72] and Mozambique [73] as this reduces the number of visits a patient has to make to the healthcare facility. Moreover, a study conducted in a mobile clinic setting in South Africa showed that patients receiving rapid CD4 count results were more likely to link to care in comparison to those who did not [74].

Disclosure was positively associated with enrolment into HIV care and uptake of ART in two studies conducted in Kenya [9,30]. Of note, stigma and fear of disclosure was the most commonly reported psycho-social barriers to care. These findings highlight the need for stronger...
posttest counselling, community escorts, patient support groups and empowerment programmes for people living with HIV/AIDS to improve linkage to care. Fear of drug toxicity was the second most commonly reported psycho-social barrier which underscores the need for newer drugs with better safety profiles such as switching from stavudine to tenofovir-based first-line regimens [75–77] and for improving treatment literacy programmes to assist in patient acceptance and compliance of ART.

The results from this review indicate that multiple interventions are required to cater to various groups of individuals at risk for attrition. Inconvenient clinic hours make it difficult for the working population to access public healthcare facilities, underscoring the need for scale-up of after-hour clinics or workplace programmes [78]. Men and younger patients were shown to be at risk for attrition in the pre-ART period, with similar results reported from ART programs [79–81], and point to the need for dedicated clinics and support programmes for men and adolescents. The possibility of expanding ART initiation criteria in the coming years could result in large numbers of ART-eligible patients being added onto an already weakened HIV care pathway and consequently higher rates of attrition [4], thus strengthening of the cascade is fundamental [82]. Universal testing and treatment yields large long-term dividends [83]. However, the benefits of this strategy have been shown to double by increasing linkage to care and preventing patient attrition [84]. Furthermore, strategies to prevent loss to follow-up such as transport reimbursements and improving HCW training has been shown to be cost-effective [85]. In light of the global financial crisis, it is evident that investment in these strategies could possibly result in substantial savings in the long-run [7].

There are several limitations to the evidence base. Considerable variability in outcome definitions made it challenging to compare data between studies. The sample size of some studies was small [15,21,22]. The majority of studies were from South Africa, potentially limiting generalizability of some findings. It was difficult to amalgamate data as some were focused on specific groups (i.e. female sex workers [10], home-based testers [9], mobile clinic testers [15] and pregnant women [30]) and others on specific settings (i.e. semi-private hospitals [23,24] and paediatric ART clinics [43]). Most studies obtained data retrospectively, resulting in substantial missing data. Finally, certain findings may have been prone to social desirability bias as some studies were based on self-reports only [9,22].

There are also two major limitations to the conduct of our review. First, programme experiences from resource-constrained settings may be less likely to be published (particularly if the results are not favourable), or more likely to be published in local journals that are not indexed in major databases [86]. Such potential publication bias may explain why most evidence comes from South Africa, a better-resourced country with a substantial research capacity. Second, our search strategy was restricted to publications only in English. This is unlikely to be a major limitation given our geographical scope, but may explain the paucity of studies from Francophone and Lusophone Africa. The strengths of this review are that an extensive search strategy was employed; only peer-reviewed published studies were included; conference abstracts were included; and both qualitative and quantitative studies were reviewed.

This review provides some direction for the piloting of interventions that could improve linkage to HIV and ART care and reduce attrition in the pre-ART period. In particular, future studies should examine interventions that could potentially reduce out-of-pocket transport for transport and minimize the travel to clinics for patients. The results from this review further underscore the need for task-shifting, decentralization of care, and integration of services to alleviate current health system barriers (i.e. shortage of health personnel and long waiting queues). Stigma and fear of disclosure was found to among the main psycho-social barriers to care and thus urgent interventions such as support groups and intense posttest counselling are warranted.

In conclusion, no single intervention is likely going to be sufficient to solve the high rates of attrition that are currently being reported by ART programmes in sub-Saharan Africa. Rather, a combination of interventions may be needed to respond to different contexts and support specific groups of patients who are at particularly high risk of defaulting from care.

Acknowledgements

D.G. and K.K. performed the electronic search, identified eligible studies as well as collated and analysed the data. N.F assisted in analysing and interpreting the data. D.G. wrote the first draft. All authors contributed to subsequent drafts. All authors have read and approved the final draft.

Conflicts of interest

There are no conflicts of interest.

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