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Kranzer, K; Govindasamy, D; Ford, N; Johnston, V; Lawn, SD (2012)
Quantifying and addressing losses along the continuum of care for
people living with HIV infection in sub-Saharan Africa: a systematic
review. *Journal of the International AIDS Society*, 15 (2). p. 17383.
ISSN 1758-2652 DOI: <https://doi.org/10.7448/IAS.15.2.17383>

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Research article

Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review

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Abstract

Introduction: Recent years have seen an increasing recognition of the need to improve access and retention in care for people living with HIV/AIDS. This review aims to quantify patients along the continuum of care in sub-Saharan Africa and review possible interventions.

Methods: We defined the different steps making up the care pathway and quantified losses at each step between acquisition of HIV infection and retention in care on antiretroviral therapy (ART). We conducted a systematic review of data from studies conducted in sub-Saharan Africa and published between 2000 and June 2011 for four of these steps and performed a meta-analysis when indicated; existing data syntheses were used for the remaining two steps.

Results: The World Health Organization estimates that only 39% of HIV-positive individuals are aware of their status. Among patients who know their HIV-positive status, just 57% (95% CI, 48 to 66%) completed assessment of ART eligibility. Of eight studies using an ART eligibility threshold of ≤ 200 cells/ μ L, 41% of patients (95% CI, 27% to 55%) were eligible for treatment, while of six studies using an ART eligibility threshold of ≤ 350 cells/ μ L, 57% of patients (95% CI, 50 to 63%) were eligible. Of those not yet eligible for ART, the median proportion remaining in pre-ART care was 45%. Of eligible individuals, just 66% (95% CI, 58 to 73%) started ART and the proportion remaining on therapy after three years has previously been estimated as 65%. However, recent studies highlight that this is not a simple linear pathway, as patients cycle in and out of care. Published studies of interventions have mainly focused on reducing losses at HIV testing and during ART care, whereas few have addressed linkage and retention during the pre-ART period.

Conclusions: Losses occur throughout the care pathway, especially prior to ART initiation, and for some patients this is a transient event, as they may re-engage in care at a later time. However, data regarding interventions to address this issue are scarce. Research is urgently needed to identify effective solutions so that a far greater proportion of infected individuals can benefit from long-term ART.

Keywords: HIV; linkage to care; ART; sub-Saharan Africa; retention in care; HIV testing.

Received 16 January 2012; **Revised** 7 September 2012; **Accepted** 24 October 2012; **Published** 19 November 2012

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Introduction

The success of antiretroviral therapy (ART) roll-out in sub-Saharan Africa has been remarkable. Between 2004 and the end of 2011, around 8 million people had initiated ART, leading to dramatic reductions in HIV-associated morbidity and mortality [1–3]. However, due to low HIV test uptake and losses along the pathway between HIV testing and ART treatment [4], only a minority of individuals in need of ART are estimated to ever start treatment [5]. This is further compounded by substantial additional losses that occur during long-term treatment [6,7].

The essential steps in the HIV care pathway for HIV-positive individuals 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

[8–10] where successes have resulted in improved health outcomes for the patient [11,12] and reduced costs for the healthcare system [13]. Characterization of losses along the care pathway in high-income countries [13–15] has informed the development of potential interventions [9]. 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 where healthcare systems are less well developed. It is unclear whether 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 in 2004 as treatment became affordable and major donor-funding mechanisms were established [16]. The 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 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, followed by the patient returning to receive his or her results (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.

To date, the majority of studies from sub-Saharan Africa have focused on treatment adherence and retention of patients who have started ART [6,7,17–20]. 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 from infection to treatment, quantify losses along the pathway in sub-Saharan Africa, and review

interventions to decrease attrition at different points in the pathway.

Methods

Definitions

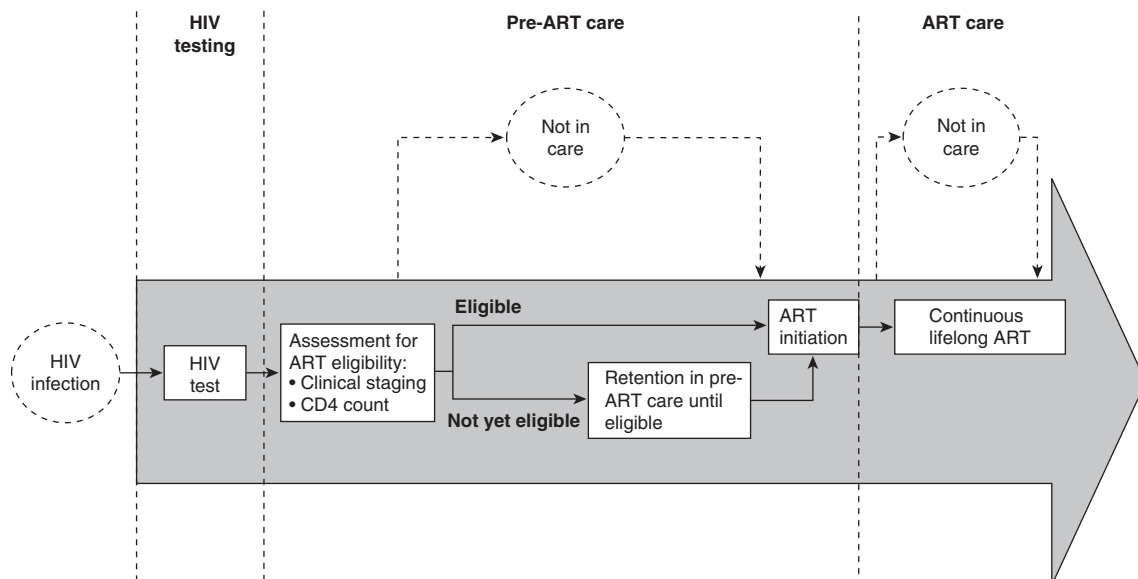
For the purpose of this review, we have divided the HIV care pathway into (1) HIV testing; (2) pre-ART care comprising assessment of ART eligibility, retention in pre-ART care prior to ART eligibility, initiation of ART; and (3) retention in ART care (Figure 1). Where available, we used synthesized data 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 syntheses. Possible interventions and operational solutions aimed to reduce losses at each stage of the pathway are subsequently reviewed and discussed.

Eligibility criteria and search strategy

We sought studies investigating retention in 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 were carried out in the private health-care sector, if they reported unsystematic observations (case reports and case series), or if they were secondary data sources (editorials and viewpoints).

Primary outcomes were the proportion of individuals completing ART assessment, retained in pre-ART care and initiating ART as defined by the authors of the study.

We searched Medline, Embase and Global Health for studies reporting retention between HIV testing and ART using a compound search strategy. Bibliographies of retrieved articles were searched for additional studies. Our search was limited to studies conducted in sub-Saharan Africa



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.

Figure 1. The care pathway for HIV positive individuals.

published between 2000 and June 2011. In addition, we 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. Articles were screened by title, then by abstract, independently, and in duplicate (GD, KK). Data was extracted in duplicate (GD, KK) using a standard data extraction form.

Data analysis

We calculated point estimates and 95% confidence intervals (CIs) for the proportion of patients linking to care at various stages of the care pathway. The variance of the raw proportions was stabilized using a Freeman-Tukey type arcsine square-root transformation, and estimates were pooled using a DerSimonian-Laird random effects model. Between study heterogeneity was assessed with the τ^2 statistic (on the transformed scale), and subgroup analyses were run 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).

Results

Out of 755 potentially eligible studies, 37 were retained for analysis (Figure 2). Study characteristics are summarized according to the different steps in the pathway (Tables 1–4).

HIV testing

The proportion of HIV-positive individuals in sub-Saharan Africa whose infection remains undiagnosed is often derived

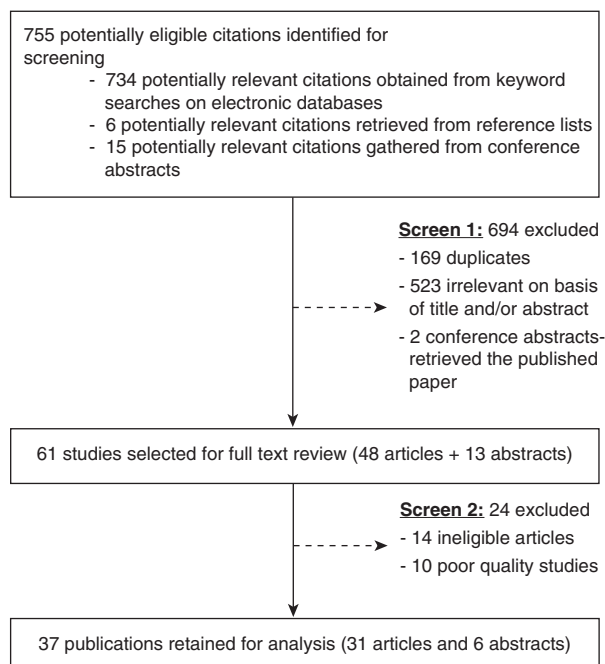


Figure 2. Study selection process.

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 overestimate [5]. This is suggested by some country-level studies. For example, the Kenya AIDS Indicator Survey linked HIV test results to perceived HIV status [60]. 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 [60]. Similarly, in a peri-urban South African community with high HIV prevalence, the prevalence of previously undiagnosed HIV was 46% despite coverage of HIV testing being high (71%) [61].

Pre-ART care

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 an initial link to care. Of the 22 published studies we identified as eligible for inclusion (Table 1), the majority were conducted in South Africa (*n* = 9). Eleven studies reported the proportions of patients enrolling in 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 [34] and among female sex workers in Rwanda [28].

The proportion of patients assessed for ART eligibility (reflecting linkage to care) ranged from 42% (95% CI, 39% to 46%) to 70% (95% CI, 68% to 72%), with an overall pooled estimate of 57% (95% CI, 48% to 66%; τ^2 0.07). In eight out of the eleven 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% to 60%) to 86% (95% CI, 77% to 94%) with a pooled proportion of 66% (95% CI, 54% to 78%; τ^2 0.14). However, only five of these studies reported the number of patients who returned for their test result, with proportions ranging from 30% (95% CI, 26% to 34%) to 88% (95% CI, 87% to 89%) and a pooled estimate of 51% (95% CI, 25% to 78%; τ^2 0.40). This pooled estimate is similar to the finding of an earlier systematic review in which a median proportion of 59% completed ART eligibility assessment [4].

Proportion of individuals eligible for ART

We next assessed the proportion 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 2) 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/ μ L, but two were excluded for reasons of non-generalizability [28,45]. The proportion found to be eligible at this CD4 count threshold ranged from 21% (95% CI, 20% to 22%) to 59% (95% CI, 59% to 60%) with a pooled proportion of 41% (95% CI, 27% to 55%; τ^2 0.15).

Table 1. Proportion of patients with newly diagnosed HIV infection who complete assessment of eligibility for antiretroviral therapy

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 [21]	Ethiopia	Public sector sites	2008	1314				47% (immediately after testing)
Assefa [21]	Ethiopia	Mobile HIV testing service for high risk individuals	2008	2035				26% (two months)
Mulissa [22]	Ethiopia	Urban, hospital	2003–08	2191				70% (no time cut-off, but 49% enrolled the same day)
Amolloh [23]	Kenya	Asembo, home-based testing service	2008–09	737				42% (two to four months)
Waxman [24]	Kenya	Eldoret, emergency department, hospital	2006	61		87% (no time cut-off)		
Gareta [25]	Malawi	Lilongwe, hospital, pregnant women	2006–08	478				55% (no time cut-off)
Taylor Smith [26]	Malawi	Thylo, district hospital, patients with clinical stage I or II	2008–09	1428			45% (at least one month follow-up)	
Micek [27]	Mozambique	Urban, HIV testing services	2004–05	7005	57% (30 days)	77% (30 days)		
Braunstein [28]	Rwanda	Kigali, female sex workers	2007–08	141				85% (no time cut off)
April [29]	SA	Cape Town, hospital, primary care clinic	2006	375		62% (six months)		
Kranzer [30]	SA	Cape Town, hospital, primary care clinic	2004–09	988		63% (six months)		
Larson [31]	SA	Johannesburg, hospital, clinic	2008–09	416		85% (12 weeks)	35% (12 weeks)	
Losina [32]	SA	Durban, semi-private hospital	2006–07	454		55% (eight weeks)	85% (eight weeks)	
Naidoo [33]	SA	Johannesburg, clinic		225			47% (one week)	
Govindasamy [34]	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 [35]	SA	Durban, semi-private hospital	2006–08	1474		69% (90 days)		
Ingle [36]	SA	Free State, public sector clinics	2004–07	44844		74% (no time cut-off)		
Luseno [37]	SA	Community-based trial		199				46% (no time cut off)
Nsigaye [38]	Tanzania	Clinic	2005–08	349				68% (no time cut-off)
Amuron [39]	Uganda	Jinja, clinic	2004–06	2483			88% (no time cut-off)	
Wanyenze [40]	Uganda	Kampala, hospital	2004–05	142				56% (six months)
Nakigozi [41]	Uganda	Rakai community cohort study		1145				69% (six months)
Wanyenze [42]	Uganda	Kampala, hospital	2004	211				48% (three months), 57% (six months)

Table 2. Proportion of individuals with new HIV diagnoses who are eligible for antiretroviral therapy

Author	Time	Country	Site	N	CD4 < 200	CD4 < 350	Stage 3	Stage 4	Eligible	Eligibility criteria
Mulissa [22]	2003–08	Ethiopia	Clinic	2191			49%	13.3%		
Mcgrath [43]	2005–06	Malawi	Hospital	730					87%	Stage 3 or 4
Micek [27]	2004–05	Mozambique	Clinic	3046					49%	CD4 < 200 or stage 4, CD4 200 to 350 or stage 3 and pregnant
Nakanjako [44]	2004	Nigeria	Emergency department	111			49%	22.0%		
Braunstein [28]	2006–07	Rwanda	FSW	192	11%	43%				
Kranzer [30]	2004–09	SA	Primary care clinic, hospital	112	34%	60%				
van Schaik [45]	2008–09	SA	Mobile clinic	65	11%	25%				
Basset [35]	2006–08	SA	Semi-private hospital	1012	53%					
Ingle [36]	2004–07	SA	Public clinics, hospitals	33182	57% (04) ^a 54% (05/6) 67% (07)					
Lessels [46]	2007	SA	Clinic	7655	41%	62%				
Losina [32]	2006–07	SA	Semi-private hospital	248	53%					
April [29]	2006	SA	Primary care clinic, hospital	375	31%		31%			
Nunu [47]	2009	Swaziland	Hospital	637					57%	Not stated
Konde-Lule [48]		Uganda	Public clinics, hospitals	203	36%	57%				
Amuron [39]	2004–06	Uganda	Clinic	4321					58%	CD4 < 200 or WHO Stage 4
Carter [49]	2003–08	Multisite	ANC, post pregnancy	6036	21%	45%	10%	1%		

^aProportions were calculated on the basis of calendar years

Table 3. Retention in care of individuals not yet eligible for antiretroviral therapy

Author	Country	Setting	Year of the study	N	Retention in pre-ART care (time cut off)	Assessment of pre-ART retention	Comment
Lessells [46]	SA	Rural Kwazulu Natal, public sector clinics	2007	4223	45% (13 months)	repeat CD4 count	
Ingle [36]	SA	Free State, public sector clinics	2004–07	11039	42% (six months)	Visits	12% died, 46% loss to follow-up
Larson [50]	SA	Johannesburg, hospital, clinic	2007–08	356	CD4 200 to 350: 6% within four months, 41% within one year CD4 350 + : 15% within nine months, 26% within one year		
Kranzer [30]	SA	Cape Town, hospital, primary care clinic	2004–09	419*	46% (no time cut-off)	Repeat CD4 count	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)
McGuire [51]	Malawi	Rural Malawi, district hospital, clinics	2004–07	5685	59% (no time cut-off)		

Six studies also reported on the proportions eligible using a CD4 count threshold of ≤ 350 cells/ μ L, with proportions ranging from 45% (95% CI, 44% to 47%) to 62% (95% CI, 61% to 63%) and a pooled estimate of 57% (95% CI, 50% to 63; τ^2 0.13). 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% to 51%) to 87% (95% CI, 84% to 89%) with a pooled proportion of 64% (95% CI, 53% to 74%; τ^2 0.13).

Pre-ART care prior to ART eligibility

We identified only five studies reporting on retention in care of individuals not yet eligible for ART; four of these were from South Africa (Table 3). The duration of pre-ART care assessed was highly variable between these studies [30,36,46,50]. No study reported the proportion retained in care on becoming eligible for ART. Retention in pre-ART care in South Africa ranged from 41% to 46% [30,36,46,50]. The remaining study from Malawi estimated retention in pre-ART care to be 59% [51]. 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 [30,51], while the other three studies assessed repeat CD4 count measurements or visits — six to twelve months after the initial eligibility assessment [36,46,50].

Initiation of ART

We identified 19 studies that reported the proportions of ART-eligible individuals who started ART (“linkage to ART”) (Table 4). 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 ($n=2$). A study reporting linkage amongst TB, co-infected patients was excluded from the meta-analysis as these patients have an unrepresentative high mortality risk [53]. In the remaining 18 studies, the proportion linking to ART ranged from 31% (95% CI, 29% to 33%) to 86% (95% CI, 83% to 89%), with an overall pooled proportion of 66% (95% CI, 58% to 73%; τ^2 0.12). An earlier review of 14 studies found the median proportion of individuals initiating ART was 68% [4]. 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 a link 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 one month; however, two studies reported median delays of between 2.4 and 6.6 months [27,35].

Eight studies assessed the contribution of mortality as a potential cause for not starting ART and reported a median mortality of 5.5% (interquartile range = 4.5% to 12%) among eligible patients waiting to start treatment [17,35,36,39,43,54,56]. In these studies, it is difficult to ascertain whether death is the cause or the result of not starting ART. Some studies traced individuals who were thought to have not started ART [39,54]; between 3% and

Table 4. Proportions of HIV-positive individuals assessed as eligible for antiretroviral therapy 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 [17]	Kenya	Nyanza, district hospital	2004–05	159	78% (no time cut-off)		3% died, 13% denied treatment
Taylor-Smith [52]	Kenya	Kibera slum, clinics	2005–08	2471	82% (one month)		
Taylor-Smith [26]	Malawi	Thyolo, district hospital, patients with WHO Stage 1/2 and CD4 <250 cells/μL	2008–09	681	64% (six months)	33 days (21–44)	
Gareta [25]	Malawi	Lilongwe, hospital, pregnant women	2006–08	222	69% (four weeks)		
Zachariah [53]	Malawi	Thyolo, district hospital, TB patients	2003–04	742	14% (no time cut-off)		
Mcgrath [43]	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 [27]	Mozambique	Urban, HIV testing services	2004–05	1506	31% (90 days)	71 days	
Kranzer [30]	SA	Cape Town, hospital, primary care clinic	2004–09	219*	67% (within six months)		
Ingle [36]	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 [36]	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
April [29]	SA	Cape Town, hospital, primary care clinic	2006	72	68% (no time cut-off)		
Bassett [54]	SA	Durban, semi-private hospital	2006	501	81% (three months)		6% died, 3% accessed a different service, 0.6% moved away, 0.6% promised to return, 7% were untraceable
Bassett [35]	SA	Durban, semi-private hospital	2006–08	538	39% (12 months)	6.6 months	17% died
Kaplan [55]	SA	Cape Town, primary care clinic, women	2002–07	2131	81% (no time cut-off)		4% died, 7% loss to follow-up
Lawn [56]	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 [57]	SA	Pretoria, hospital, children	2004	243	40% (no time cut-off)		
Geng [58]	SA	Mbarara, clinic	2009–10	697	58% (three months)		
Nunu [47]	Swaziland	Hospital	2009	363	58% (on the assigned date)		
Amuron [39]	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 [59]	Uganda	NGOs and governmental health units	2004–06	458	61% (three months)		

19% of such patients were either retained in care in the same clinical service or had accessed treatment elsewhere.

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 high in programmes in sub-Saharan Africa [62]. Systematic reviews have estimated that death accounted for around 40% of patient attrition during the first two to three years of treatment [6,7]. Key risk factors for this include a low baseline CD4 count and advanced WHO stage of disease [63]. Thus, interventions upstream in the care pathway are needed to prevent late presentation. Long-term mortality risk decreases substantially [63–66], especially once a CD4 cell count threshold of 200 cells/ μ L has been exceeded [67].

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; patients are generally less immunocompromised when commencing ART; and patient confidence in ART has grown [65]. These factors may explain why in some settings, rates of transfer between services have risen steeply [64,68]. Data on true outcomes of patients transferred from one

program to another are scarce [69,70], but if transfer of care is successful, then the patient is effectively retained in care.

A challenge to rapidly expanding ART programmes in sub-Saharan Africa is the issue of 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 reported an average retention of 65% at three years [6]. In recent years, many ART cohorts have rapidly increased in size with disproportionate increases in the number of patients compared to the number of healthcare workers. Losses to follow-up have reportedly grown over successive calendar periods, indicating a growing problem with long-term retention in care [64,65,71].

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 40% of such individuals had actually died [72]. A study from South Africa reported that 78% of such deaths occurred within the first three months after their last clinic visit [71], 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

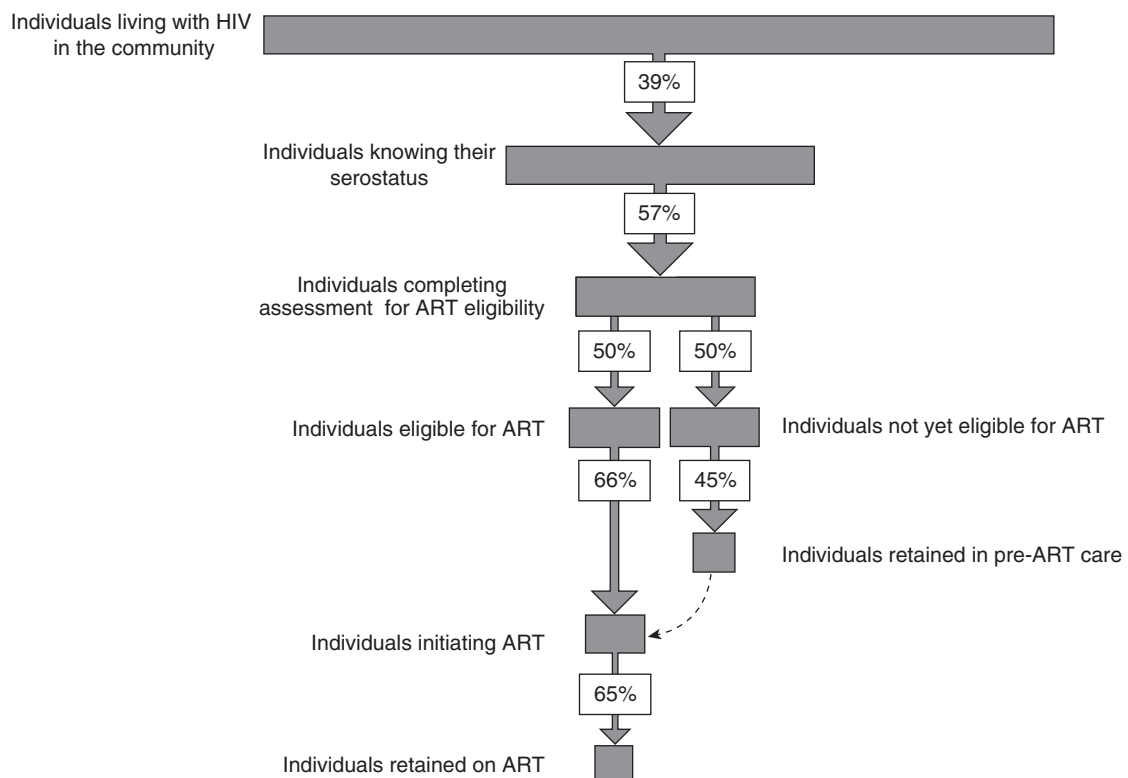


Figure 3. Cumulative losses along the HIV care pathway as reported by cross-sectional studies addressing each step in the pathway. The proportions (%) shown indicate the proportions of individuals who successfully complete each step in the pathway.

Table 5. 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	<ul style="list-style-type: none"> ● Integration of HIV testing into other healthcare services ● Testing by lay healthcare workers ● Decentralization of testing ● Self-testing 	<ul style="list-style-type: none"> ● Observational studies [75,76] ● Observational studies [77–79]
	Demand for HIV testing	<ul style="list-style-type: none"> ● Targeted testing in high risk groups ● Home-based and community-based testing, mobile services 	<ul style="list-style-type: none"> ● Feasibility study [80] ● Observational studies [81,82] ● RCT [83], observational studies [84–87,93]
		<ul style="list-style-type: none"> ● Provider-initiated testing ● Workplace testing ● Incentivized testing ● Self-testing 	<ul style="list-style-type: none"> ● Observational studies [89–91] ● RCT [87] ● RCT [93,94] ● Feasibility study [80]
	Completion of staging and linkage to pre-ART and ART care	<ul style="list-style-type: none"> ● Point of Care CD4 count testing ● Decentralization ● Integration into existing services/primary healthcare ● Support tools (e.g. cell phone messages, patient held appointment cards) 	<ul style="list-style-type: none"> ● Observational studies [95,96] ● Observational study [38] ● Observational study [38]
Pre-ART care		<ul style="list-style-type: none"> ● Efficient referral service ● Transport allowance ● Adherence counselling ● Regular visits (e.g. Cotrimoxazole prophylaxis) 	<ul style="list-style-type: none"> ● Observational study [97]
	Retention in pre-ART care prior to ART eligibility	<ul style="list-style-type: none"> ● Decentralization ● Integration into existing services/primary healthcare ● Task shifting ● Earlier initiation ● Home-delivered ART ● Community ART ● Targeted adherence counselling ● Drugs with less toxicity, side effects and easier schedule ● Task shifting ● Decentralization 	<ul style="list-style-type: none"> ● RCT [98] ● Observational study [99,100] ● Observational studies [101,102] ● Some evidence from resource rich settings[103] ● RCT[104], observational studies [102,105–109] ● Observational study [77,106,108–113]

Table 5 (Continued)

Step	Targeting	Intervention/operational solution	Evidence
ART care	Increase retention	<ul style="list-style-type: none"> ● Integration into existing services/primary healthcare ● Support tools (cell phones, lay community adherence counsellors) ● Continuous drug supply ● Transport re-imburement ● Early initiation ● Improved referral systems ● Incentives such as nutritional support ● Health information systems to allow patients to be tracked between services ● 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 	<ul style="list-style-type: none"> ● Feasibility study [114], RCT for PMTCT [115] ● RCT [116], observational studies [117] ● Observational studies [118,119] ● Qualitative studies [118,120,121] ● Observational study [122]
	Increase re-initiation for treatment interrupters		<ul style="list-style-type: none"> ● Observational studies [123,124]

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 nine studies from sub-Saharan Africa and found that an average of 12% of individuals on ART had previously interrupted but subsequently restarted treatment [73].

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 [4]. 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 3 might erroneously lead to the conclusion that of all HIV-positive individuals in the community, only 7% ($0.39 \times 0.57 \times 0.50 \times 0.66$) would start ART and 5% ($0.039 \times 0.57 \times 0.50 \times 0.45$) would be retained in pre-ART care for some duration.

The assertion that these are likely to be underestimates of the true proportions receiving care is supported by detailed data from a high HIV prevalence community in South Africa. In a population-based sero-prevalence survey, 54% of all HIV-positive individuals knew their positive HIV sero-status [61]. A study of this community from the same period showed that 63% of HIV-positive individuals were assessed for ART eligibility within six months of diagnosis, 26% were eligible for ART and 66% started ART within six months of diagnosis [30]. 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% ($0.54 \times 0.63 \times 0.26 \times 0.66$), whereas in reality a population-based survey reported a coverage of 33.5%, which is more than five-fold higher [61]. This illustrates the complexities involved in studying the HIV care pathway and the need for better means of assessment.

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 [74], so instead, we should focus on strategies to increase HIV diagnosis and engagement of patients in pre-ART care and aim to reduce losses to follow-up throughout the pathway.

Interventions either aim to increase the efficiency and capacity of services, or accessibility and acceptability of these services (Table 5). Interventions to increase HIV testing include task-shifting (testing through lay healthcare workers) [77–79] and provider-initiated testing [89–91] as well as mobile, community, home-based and workplace services

Table 6. 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

[83–87,92] which bring the service nearer to the patient and thus increase accessibility, which might in turn increase acceptability. Other interventions aimed to increase acceptability of testing are self-testing [80] and incentivized testing [93,94]. More recently, community-based strategies for HIV testing and ART delivery have been developed [84,88,99] as a way to further expand access to care. By virtue of being placed in the community, these strategies are decentralized and use task-shifting to engage lesser trained health staff, and thus might be more cost-effective [125].

Only four studies have assessed interventions aimed at reducing losses in the pre-ART period. These have examined point-of-care CD4 count testing [95,96], more efficient referral systems [38], transport vouchers [38] and regular visits to refill trimethoprim-sulphamethoxazole prophylaxis [97]. In contrast, many studies have reported on interventions to reduce loss to follow-up of patients on ART [126]. Some of these interventions are structural such as task-shifting [104–108], decentralization [77,106,108–111], integration [114,115] and continuous drug supply [118,119], whereas others are aimed at the individual such as adherence counselling [101,102] and transport reimbursement [118,120,121].

Few interventions have been assessed for their efficacy and cost-effectiveness in randomized controlled trials [83,92,94,104,116], and most observational studies have assessed feasibility rather than effectiveness [80,114,123]. Evidence for a positive effect of, for example, transport vouchers and secured drug supplies comes mainly from risk factor analysis and semi-qualitative studies [118–121]. 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 [101,102], but the effect

of counselling on retention in pre-ART care or on linkage to ART care has not yet been formally assessed.

Integration of care has mainly concentrated on tuberculosis and PMTCT programs [115,127] or the beneficial effects derived by other health services through the integration of HIV care [128]. 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 [129]. 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 [130]. As HIV is a chronic disease, integration is important not only to improve retention, but also to provide comprehensive care (Table 6). This has been conceptualized in the WHO's Integrated Management of Adolescent and Adult Illness programme [131].

Conclusions

Substantial losses occur at every stage of the HIV care pathway for HIV-positive individuals in sub-Saharan Africa. Assessment of these losses is complex as is engagement in care; loss to care and 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 regards to the care pathway prior to ART initiation. Research is urgently needed to identify effective solutions so that a far greater proportion of HIV-positive individuals can reap the benefits of ART. Such research should take into account the important gender differences that are becoming increasingly apparent with respect to accessing testing [132] and treatment and care [133].

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 [134], 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, “test and treat” will become a more viable strategy.

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Competing interests

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.

Acknowledgements

KK, VJ, SDL are funded by the Wellcome Trust, London, UK. The funding sources played no role in the decision to publish these data.

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