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Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature

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Abstract [234 words]

Objective. We aimed at summarizing the scientific knowledge on retention in HIV care before antiretroviral therapy (ART) eligibility in sub-Saharan Africa.

Design. We conducted a systematic literature review (2002 to 2014). We searched in Medline/Pubmed, Scopus and Web of Science as well as conferences proceedings. We included all original research studies published in peer-reviewed journals which used quantitative indicators of retention in care for people not yet eligible to ART.

Participants. People not yet eligible for ART.

Primary and secondary outcomes. Rate of retention in HIV care among people not-yet-eligible for ART and associated factors.

Results. Ten papers and two abstracts were included. Most of the studies took place in Southern and Eastern Africa between 2004 and 2011 and reported retention rates in pre-ART care up to the second CD4 measurement. Definition of pre-ART care retention differed substantially across studies. Retention rates ranged between 23 and 88% based on series ranging from 112 to 10,314 individuals; retention was higher in women, individuals aged >25 years, those with low CD4 count, high body mass index or co-infected with tuberculosis, and in settings with free cotrimoxazole use.

Conclusions. Retention in pre-ART care in sub-Saharan Africa has been insufficiently described so far leaving major research gaps, especially regarding long-term retention rates and socio-demographic, economic, epidemiologic, programmatic and logistic determinants. The prospective follow-up of newly diagnosed individuals is required to better evaluate attrition among not-yet ART-eligible HIV-infected people.

Key words: HIV; Continuity of Patient Care; Adults; Treatment eligibility; Africa South of Sahara; Review.

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Article summary

- We aimed at summarizing the scientific knowledge on retention in pre-ART care for adults not-yet eligible for ART in sub-Saharan Africa.
- We have found that retention in HIV care before ART eligibility has been insufficiently described so far in sub-Saharan Africa, leaving major research gaps that we have discussed.
- We suggest the need for prospective follow-up of newly HIV diagnosed individuals to better understand barriers to retention in care before ART eligibility and to evaluate interventions minimizing attrition during this specific period.
- A strength of this study is that we have searched three different and large databases and enlarged our search to HIV conferences abstracts.
- A limitation of this study is that although we aimed to conduct an exhaustive literature review, we cannot exclude that we missed some that did not correspond to our search equation.

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Manuscript [2995 words]

Introduction

In 2012, it was estimated that 22.1 million of adults were living with HIV in sub-Saharan Africa of whom 1.4 million were newly infected [1]. To prevent HIV transmission and help those who live with HIV to access care and treatment in due time, the consensus today is that individuals should be diagnosed as early as possible in the course of HIV infection, that is to say before eligibility criteria for antiretroviral therapy (ART) initiation are met. Once an individual is diagnosed HIV-positive, there are several steps up to ART initiation [2-4]: i/ from HIV diagnosis to linkage to HIV care, ii/ from linkage to HIV care to ART eligibility, iii/ from ART eligibility to ART initiation. Continuum in HIV care through these different steps is critical for individuals to receive adequate clinical and biological monitoring and to initiate ART immediately upon becoming eligible in order to minimize early morbidity and mortality. It has indeed been shown that people who engaged in HIV care prior to eligibility were more likely to initiate and remain on ART than those entering in care already eligible [5, 6], and that the risk of mortality was reduced if ART was initiated early enough in the course of HIV infection [7]. Finally, being more than six months in pre-ART care was significantly associated with reduced rates of mortality and loss-to-follow-up after starting ART [8].

In sub-Saharan Africa, many people are lost to follow-up between HIV diagnosis and ART initiation and these individuals are thus at risk of delayed ART initiation [9]. Although the 2013 World Health Organization (WHO) recommendations for initiating ART reduce the length of time before reaching ART eligibility [10], most of the African countries have still an ART eligibility criteria based on a CD4 <350 cells/µL threshold, and it will probably take time for these countries to expand their ART eligibility criteria and translate this recommendation into practice. In the evolving context where many interventions are developed, evaluated and implemented with the aim of increasing the uptake of HIV testing among people early in the course of HIV infection [11], retention in pre-ART care of individuals not-yet eligible for ART is a key issue that needs to be better understood.

Three literature reviews have been conducted on HIV care prior to ART initiation in the recent years [2-4], but they mostly focused on linkage to care and provided very little information on retention in HIV care before ART eligibility. We thus aimed at summarizing the scientific knowledge on retention in pre-ART care (definition, rates and barriers) specifically among adults who are not yet eligible for ART in sub-Saharan Africa.

Methods

Data source and search strategy

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We conducted a systematic literature review on retention in HIV care in sub-Saharan Africa searching Medline/Pubmed, Scopus (which contains Embase references) and Web of Science until January 21st, 2014. This literature review was conducted using a research equation combining these following free text words: HIV, retention, and a list of all the African countries (except Maghreb) (Figure 1[1]). In addition, we also screened the abstracts of major HIV conferences (CROI, IAS and ICASA) that took place between 2011 and 2013.

Eligibility criteria and study selection

We included all original research studies published in peer-reviewed journals between January 1, 2002 and January 21st, 2014 and which used quantitative indicators of retention for people not yet eligible to ART. We first excluded papers from title and abstract screening, if i/ the major subject was not HIV, ii/ papers did not focus on linkage or retention in HIV care, iii/ papers were not original studies or were modelling studies or methodological papers without original data, iv/ papers were focused on a specific population such as children, adolescents, men who have sex with men, sex workers and migrants, v/ studies took place outside sub-Saharan Africa, vi/ reports were based only on qualitative indicators, vii/ papers were focused on post-ART retention, viii/ papers focused only on linkage to HIV or ART initiation. We did not specify any language restriction. After reading full-text papers, we secondarily excluded papers that did not report explicitly on retention in pre-ART care for people not-yet eligible to ART or if the definition of retention was not specified. For conferences proceedings, we first selected the tracks and sessions where the topic corresponded to our literature review. Selection was then carried out after systematic abstract screening. Authors of the papers and abstracts included were systematically contacted in case of missing information.

Parameters of interest

For each study included, we report definition and rate of retention in pre-ART care among people not-yet-eligible for ART and we present cumulative incidence rates of retention at different time points. These rates are displayed in a bubble graph taking into account population size for each study. We distinguish between retention documented between the first and the second CD4 measurement or after the second measurement, and describe how deaths and transfers were considered for estimating the retention rate. We also indicate the follow-up duration considered when measuring the retention rate. Finally, we present factors associated with retention in pre-ART care when they were reported in multivariable analysis. These factors did not necessarily focus only on patients not yet eligible for ART as most papers considered global retention in pre-ART care; when this was the case, we distinguished the size of the overall population in pre-ART care and the size of the not-yet-ART-eligible population. We did not report on associations when studies did not distinguish factors of retention in pre-ART care and post ART initiation.

[1] For the editor : This figure may alternatively be presented as an Appendix

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Results

Paper selection

In total, 635 published references were identified through the search equation, of which 144 were duplicates and 472 others were excluded based on title and abstract review (Figure 2). Of the 18 remaining references, we left out eight papers after reading the full-text. We thus included ten published studies in this review [12-21]. In addition, we also identified two eligible studies from the abstract search [22, 23].

Studies characteristics

Table 1 summarizes the characteristics of the 12 studies selected. One of them involved three countries, the 11 others were performed in a single country. The majority of them took place in Southern and Eastern Africa: South Africa for four reports [13, 14, 18, 19], Kenya for three [12, 15, 17], Uganda for two [12, 20], and one each in Malawi [12], Mozambique [21], and Zambia [23]; only two studies were conducted in West Africa, namely Nigeria [22] and Guinea-Bissau [16]. All the studies were conducted between 2004 and 2012. Six of them were conducted in urban or peri-urban settings [13, 14, 16-18, 22], two in rural settings [15, 19] and four in both contexts [12, 20, 21, 23]. Populations included were all individuals aged more than 15 years old in four reports [12, 15, 21, 23], more than 16 years old in two [16, 19] or more than 18 years old in four [13, 14, 18, 20, 22]; one study focused on pregnant women older than 18 years old [13] and we did not have the information for the last one [17]. ART eligibility criteria varied according to countries, and were based either on both CD4 cell count and WHO staging [12, 15-17, 21, 23] or only on CD4 cell count [13, 14, 18-20, 22].

Retention in pre-ART care

Table 2 and Figure 3 summarize the study findings.

Definition of retention in pre-ART care

Criteria used for the definition of retention in pre-ART care among individuals not-yet eligible for ART varied across the 12 studies and depended mostly on programmatic factors. The majority of studies reported retention rates in pre-ART care between the first and the second CD4 measurement [13-16, 18, 19], and only one study explicitly reported retention rate after the second CD4 measurement [15]. Other papers reported retention rates from enrolment of patients in the HIV program to the end of the studies regardless of the number of CD4 measurements [12, 20, 22, 23]. Almost all the studies did exclude death and/or transfers for studying retention in pre-ART care. One study used a tracking method ascertaining the vital status of a subsample of patients lost to follow-up for correcting the estimation of retention in pre-ART care [20].

Rates of retention in pre-ART care for patients not-yet eligible for ART

The lowest crude rate of retention in pre-ART care was observed in the study focused on pregnant women (23%) [13], followed by the study conducted in West Africa (27%) [16]. Three other studies reported rates of retention in pre-ART care lower than 50% [18, 19, 21]. The

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highest crude rates of retention in pre-ART care were observed in Kenya (82%) [15] and in Uganda (88%) [20].

Factors associated with retention in pre-ART care

Retention in pre-ART care was mostly associated with individual factors which varied according to the setting. Factors which were most consistently found associated with a higher retention in pre-ART care included age above 25/30 years old compared to the younger ones [12, 14, 16-19, 21, 23] and female gender [12, 14, 19]. One study also showed that non-pregnant women were more likely to be retained compared to men and pregnant women [21]. Also, in Uganda, high income was significantly associated with better retention in pre-ART care [20]. Religion and nationality were investigated but not reported to be associated with retention in pre-ART care.

Distance to clinic was studied in two settings and showed conflicting results: in Kenya, people who lived ≤5 kilometers (versus >5 kilometers) away from the clinic were more likely to be retained in pre-ART care [15] while in Zambia, people who lived ≤20 kilometers (versus >20 kilometers) from the clinic were more likely to be lost-to-follow-up [23]. Biological and clinical factors were also associated with a higher retention in pre-ART care, including low CD4 cell count [12, 19], high body mass index [12, 17], heavier weight [20, 21], and anemia [16]. Additionally, retention in pre-ART care was higher in patient co-infected with tuberculosis [12, 14].

Lastly, two studies showed that the introduction of free cotrimoxazole increased retention in pre-ART care in Kenya [17] and Nigeria [22]. In Nigeria, in addition to the provision of free cotrimoxazole, the intervention package was also composed of synchronized pharmacy and laboratory appointments, task-shifting to nurse and data-clerks, same-day CD4 monitoring and receipt of results and integrated clinics [22].

Discussion

Although many HIV-infected adults are deemed to be lost to follow-up before reaching ART eligibility, little research has been published on retention in pre-ART among individuals who were not eligible for ART; indeed, we found only 12 studies to include in this review over a 12-year period. Definitions of retention in pre-ART care varied across settings and healthcare systems, thus making the comparison between studies challenging. Nevertheless, reported rates of retention in pre-ART care were consistently low; this was especially the case among pregnant women [13] and in West Africa (Guinea-Bissau) [16]. Only three studies reported a retention rate >75% [15, 17, 20].

Clouse et al [13] observed that retention in pre-ART care was much higher during pregnancy compared to the post-delivery period, and especially in women not-yet eligible for ART, concluding that "among HIV-positive pregnant women, the challenge is to ensure that HIV care extends beyond the period of pregnancy and continues for the lifetime of the mothers" [13]. High loss-to-follow-up rates within prevention of mother-to-child-transmission of HIV (PMTCT)

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programs have been consistently reported, regardless of the WHO recommendation (Option A or B) as shown in a meta-analysis [24] and also under the more recent Option B+ as found in Malawi [25].

As noted by several authors [13, 14, 18, 21], misclassification of care transfers, incorrectly considered as failures to continue care, may have led to underestimating the rates of retention in HIV care. This may be particularly the case in the study conducted in Guinea-Bissau, where many people worked outside the city of Bissau during the crop season [16]. Indeed, patients not retained in the study clinic may have continued HIV care elsewhere without informing their doctor or nurse. Only one study tried to account for this concern, using a tracking method to establish the updated status of a random sample of patients not retained in the initial study clinic setting [20]. Once the vital status of people who were firstly considered as lost-to-follow-up was verified, the authors estimated a corrected rate of retention in pre-ART care of 90%, much higher than the uncorrected estimate of 70%.

This literature review confirms that retention in pre-ART care for people not-yet eligible for ART is lower in younger individuals [12, 14, 16-19, 21, 23] and in men [12, 14, 19], as it has been already reported in previous literature reviews exploring retention in HIV care overall [3, 26]. Some papers included in our review also suggest that some biological and clinical factors are associated with retention in pre-ART care. Indeed, it has been shown that patients who are co-infected with tuberculosis [12, 14], those who have anemia [16] or those with low CD4 count [12, 19] are more likely to be retained in pre-ART care than patients without these characteristics. These results suggest that it is important for programs to focus attention during pre-ART care on younger individuals, men in general, and also on individuals with less advanced HIV disease who may feel healthier. While tuberculosis co-infection [27] and anemia [28] are HIV-related diseases, the association between these complications and retention in pre-ART care is only supported by limited evidence so far and needs to be further explored.

This literature review highlights several gaps in knowledge on retention in pre-ART care among individuals not yet eligible for ART. First, 10 of the 12 studies identified were conducted in Eastern and Southern Africa; reports from West Africa where healthcare systems have been described as less efficient, are lacking. Second, three of these studies reported that, among patients with a second CD4 measurement, about 70% of individuals were still not ART-eligible at that time [14, 19, 21]. However, only one paper focused on retention in pre-ART care beyond the second CD4 measurement [15] and three others reported retention regardless of the number of CD4 measurements [12, 20, 22]. As the consensus is that individuals should be diagnosed as early as possible in the course of HIV infection before becoming eligible for ART [11], and bearing in mind that the CD4 threshold for ART initiation has been recently enlarged [10], the period between HIV diagnosis and ART initiation is a critical one for optimizing the care plan. Longer-term retention in pre-ART care, i.e. up to ART eligibility should thus be further documented. Thirdly, further methods such as tracking by peer educators and use of mobile

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technologies would contribute to better retention and its correct estimate, accounting for people who are retained in care in the overall health system, but outside a given study clinic. Lastly, the 12 studies included showed that retention in pre-ART care was associated with some socio-demographic and clinical individual factors. However, the role of programmatic and logistic factors (such as time/distance to clinic, waiting time in clinic, costs for transportation or looking after the children) was very rarely studied, as well as perceptions on HIV care at individual and community levels. Indeed, as discussed by Boyles et al [8], reasons for low retention in pre-ART care may include the lack of availability of comprehensive HIV care services and the perception that ART is only necessary in individuals who become sick, suggesting that these factors should be further explored as potential barriers to pre-ART care.

The results of our review highlight the urgent need to continue designing and evaluating interventions aimed at improving retention in HIV care, especially for people not-yet eligible for ART. To date, several interventions have targeted the improvement of ART adherence, e.g. reminder services (such as mobile phones, text messaging and diary cards) [29, 30] and treatment supporters [30]. These interventions should now be adapted for improving retention in pre-ART care too. Some interventions such as CD4 point-of-care [31] and involvement of community health care workers and peers counsellors [32] have already been shown to improve retention in pre-ART care but are insufficiently used. A combination of different interventions [32, 33], adapted to the setting will most often be necessary in helping the majority of people to remain in care up to ART initiation.

A limitation of this review is that although we aimed to conduct an exhaustive literature review, we cannot exclude that we missed some that did not correspond to our search equation. However, we have searched three different and large databases and enlarged our search to HIV conferences abstracts.

In conclusion, this literature reviews shows that, as more and more subjects are offered HIV testing earlier in the course of HIV infection and as ART eligibility criteria are enlarged over time, rates of retention in pre-ART care remain insufficient. Large-scale community randomized trials are currently evaluating the effectiveness of universal test and treat interventions, where ART initiation is initiated immediately after HIV testing, regardless of immunological or clinical criteria [34, 35]. Such an approach would a *priori* solve the issue of pre-ART care and a recent report has shown good feasibility and acceptability in rural South Africa [36]. However, even if test and treat strategies are shown to be effective in reducing HIV incidence at population levels, the timeframe until their large-scale implementation is unclear. Thus in the medium-term, pre-ART care does remain a challenge for health care systems and societies and deserves further consideration in sub-Saharan Africa. Longitudinal follow-up of newly HIV-diagnosed individuals tested under various circumstances would contribute to better characterize and understand attrition for those not-yet ART eligible in order to better guide local HIV care

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programs. Finally, innovative support interventions, home or clinic-based, will need to be evaluated on their capacity to retain this population in comprehensive HIV care services up to ART initiation and thus prepare them better to life-long ART and case management.

2995 words, 2 tables and 3 figures

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Contributorship statement

Conceived and designed the review: MP, JOG. Analyzed the data: MP. Wrote the paper: MP, RDS, JOG, FD.

Competing interests

The authors have no competing interest to declare.

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Data sharing

No additional data available.

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Table 1. Characteristics of the 12 sub-Saharan Africa studies included in the review of retention in pre-ART care among patients not-yet eligible for antiretroviral therapy (ART)

Country *(Reference)*	Year of the study	Urban / Rural	ART eligibility criteria	Population	Overall population size in pre-ART care	Population size of not-yet ART-eligible
PAPERS						
Kenya, Malawi, Uganda [12]	2004-2011	Rural and urban	Until January 2007: CD4 <200 or WHO stage IV Since January 2007: CD4 <200 or WHO stage III/IV Since March 2010: CD4 <350 or WHO stage III/IV	≥15 years old	N = 55,789	N = 10,314
South Africa [13]	2010-2011	Urban	CD4 ≤350	Pregnant women ≥18 years old	N = 271	N = 112
South Africa [14]	2010-2011	Urban	CD4 ≤350	Non pregnant adult ≥18 years old	N = 842	N = 155
Kenya [15]	2008-2010	Rural	CD4 <200 OR WHO stage III/IV OR no CD4 count and WHO staging at baseline	≥15 years old and with HIV diagnosis <3 months before registration in care	N = 530	N = 530
Guinea-Bissau [16]	2005-2012	Urban	Undefined	≥16 years old	N = 484	N = 484
Kenya [17]	2005-2007	Urban	CD4 <250 or WHO stage III/IV	Not clear	N = 1,024	N = 1,024
South Africa [18]	2004-2009	Peri-urban	CD4 <200	≥18 years old	N = 419	N = 419
South Africa [19]	2007-2008	Rural	CD4 <200	≥16 years old	N = 4,223	N = 4,223
Mozambique [21]	2005-2009	Rural and urban	WHO stage IV OR WHO stage III and CD4 <350 OR CD4 <200	≥15 years old	N = 17,598	N = 12,992
Uganda [20]	2008-2011	Semirural	CD4 <350	≥18 years old	N = 6,473	N = 6,473

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		and urban				
CONFERENCES ABSTRACTS						
Nigeria [22]	2009-2012	Urban	CD4 <350	≥18 years old	N = 414	N = 191
Zambia [23]	2009-2010	Rural and urban	CD4 <250 OR WHO stage III/IV	≥15 years old	N = 145	N = 145

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Table 2. Retention in pre-ART care among patients who are not-yet eligible for antiretroviral therapy (ART). Twelve studies in sub-Saharan Africa.

Country *(reference)*	Period when retention was studied	Definition of retention	Retention time point	Rate of retention	Consideration of deaths and transfers for calculating the rate	Factors associated with retention in pre-ART care	Factors not associated with LTFU in pre-ART care
PAPERS							
Kenya, Malawi, Uganda [12]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	Having missed an appointment for more than 6 months	Median: 18.4 months (IQR*=8·5-32·2)	68·4%	Deaths excluded Transfers excluded when reported	Being old, female gender, BMI >18.5, low CD4 cell count, being diagnosed with TB, entry in VCT or PMTCT vs in or outpatient services or medical referral, not eligible for ART at enrollment	
South Africa [13]	Between the 1st and the 2nd CD4 measurements	Receiving a repeat CD4 count after delivery	12 months	23·2%	Transfers excluded when reported No deaths reported		
South Africa [14]	Between the 1st and the 2nd CD4 measurements	Receiving a second CD4 test within one year after the first CD4 staging	12 months	57·4%	Transfers excluded when reported Deaths not excluded	≥30 years old, female gender, receiving a TB treatment	Nationality, being employed, CD4 cell count
Kenya [15]	Between the 1st and the 2nd CD4 measurements	Not being more than 60 days late for the scheduled appointment	Undefined	81·9%	Deaths excluded Transfers excluded when reported	Living ≤5km from the main road, Not being single	Gender, age, entry point in care, religion, education level, season, population density, WHO staging, BMI
	After the 2nd CD4 measurement	Not being more than 60 days late for the scheduled	Undefined	63·2%	Deaths excluded Transfers excluded when reported	Low education level, living ≤5km from the main road, wet season	Gender, age, marital status, entry point, religion, population

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		appointment after the second visit					density, WHO staging, BMI, CD4, Hb
Guinea-Bissau [16]	Between the 1st and the 2nd CD4 measurements	Being less than one month late for the scheduled appointment	Median: 147 days (IQR*=7-653)	27·2%	Deaths excluded Transfers excluded when reported	>30 years old, having anemia, attending school, being infected by HIV-1 (vs HIV-2)	Sex, BMI, marital status, religion
Kenya [17]	Undefined	Returning to clinic less than 30 days after the next scheduled pharmacy or clinic appointment	12 months	75·5%	Transferred excluded when reported Deaths not systematically taken into account	Being older, high BMI, enrolled after free cotrimoxazole provision	Sex, TB status, baseline CD4 count
South Africa [18]	Between the 1st and the 2nd CD4 measurements	Having a repeat CD4 count before 2009	Undefined	46·3%	Undefined	≥30 years old	Sex, year of HIV test
South Africa [19]	Between the 1st and the 2nd CD4 measurements	Repeating CD4 count within 13 months of the initial test	13 months	44·9%	No exclusion of deaths and transfers	Female gender, >25 years old, ≤350 CD4 cells/µL, not out-migrant, not full-time employed, not living in a household size >10	
Mozambique [21]	Undefined	Having less 12 months elapsed since the last documented clinic visit	12 months	37·6%	Transfers and deaths excluded	Non-pregnant female, >25 years old, having at least finished primary school, weight >56kg, no WHO stage I	Marital status, number of children, socio-economic status, CD4 count,
Uganda [20]	From enrolment in the HIV program to end of the study	Having seen an HIV provider in the 6 months before the interview	30 months	88·2%	Using of a weighing method for correcting the rate, taking into account	High income, employment, high weight, urban setting	Age, sex, CD4 level, education level, marital status, calendar date at

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	regardless of the number of CD4 measurements				all outcomes (transfers, deaths) after tracking		enrollment
CONFERENCE ABSTRACTS							
Nigeria [22]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No clinic appointment missed for three consecutive times	Undefined	52·8%	No exclusion	Intervention package: provision of free cotrimoxazole prophylaxis, harmonized pharmacy and laboratory appointments, task-shifting to nurses and data-clerks, same-day CD4 monitoring and receipt of results, integrated clinic services	
Zambia [23]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No fail to return for an appointment on two and more occasion	12 months	51%	No détail provided	≥30 years old, >20 km from the hospital	Gender, marital status, education level, monthly outcome, partner's HIV status, WHO clinical stage, CD4 cell count

**IQR: Interquartile Range*

BMI: body mass index, Hb: hemoglobin, PMTCT: prevention of mother-to-child transmission of HIV, TB: tuberculosis, VCT: voluntary counseling and testing

LTFU: Loss to Follow Up.

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Medline/Pubmed

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Scopus

TITLE-ABS-KEY*(HIV) AND* ***TITLE-ABS-KEY****(retention)* ***AND TITLE-ABS-KEY****({sub-Saharan Africa} OR {Burundi} OR {Djibouti} OR {Eritrea} OR {Ethiopia} OR {Kenya} OR {Rwanda} OR {Somalia} OR {Sudan} OR {Tanzania} OR {Uganda} OR {Cameroon} OR {Central African Republic} OR {Chad} OR {Congo} OR {Democratic Republic of Congo} OR {Equatorial Guinea} OR {Gabon} OR {Angola} OR {Botswana} OR {Lesotho} OR {Malawi} OR {Mozambique} OR {Namibia} OR {South Africa} OR {Swaziland} OR {Zambia} OR {Zimbabwe} OR {Benin} OR {Burkina Faso} OR {Cape Verde} OR {Cote d'Ivoire} OR {Gambia} OR {Ghana} OR {Guinea} OR {Guinea-bissau} OR {Liberia} OR {Mali} OR {Mauritania} OR {Niger} OR {Nigeria} OR {Senegal} OR {Sierra Leone} OR {Togo}) AND PUBYEAR > 2002*

Web of Sciences

TOPIC: *(hiv AND retention AND ("sub-Saharan Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "Sudan" OR "Tanzania" OR "Uganda" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR "Benin" OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo")) AND* **YEAR PUBLISHED:** *(2002-2014)*

Figure 1. Search strategy for the systematic literature review on retention in HIV care in sub-Saharan Africa. January 2014.

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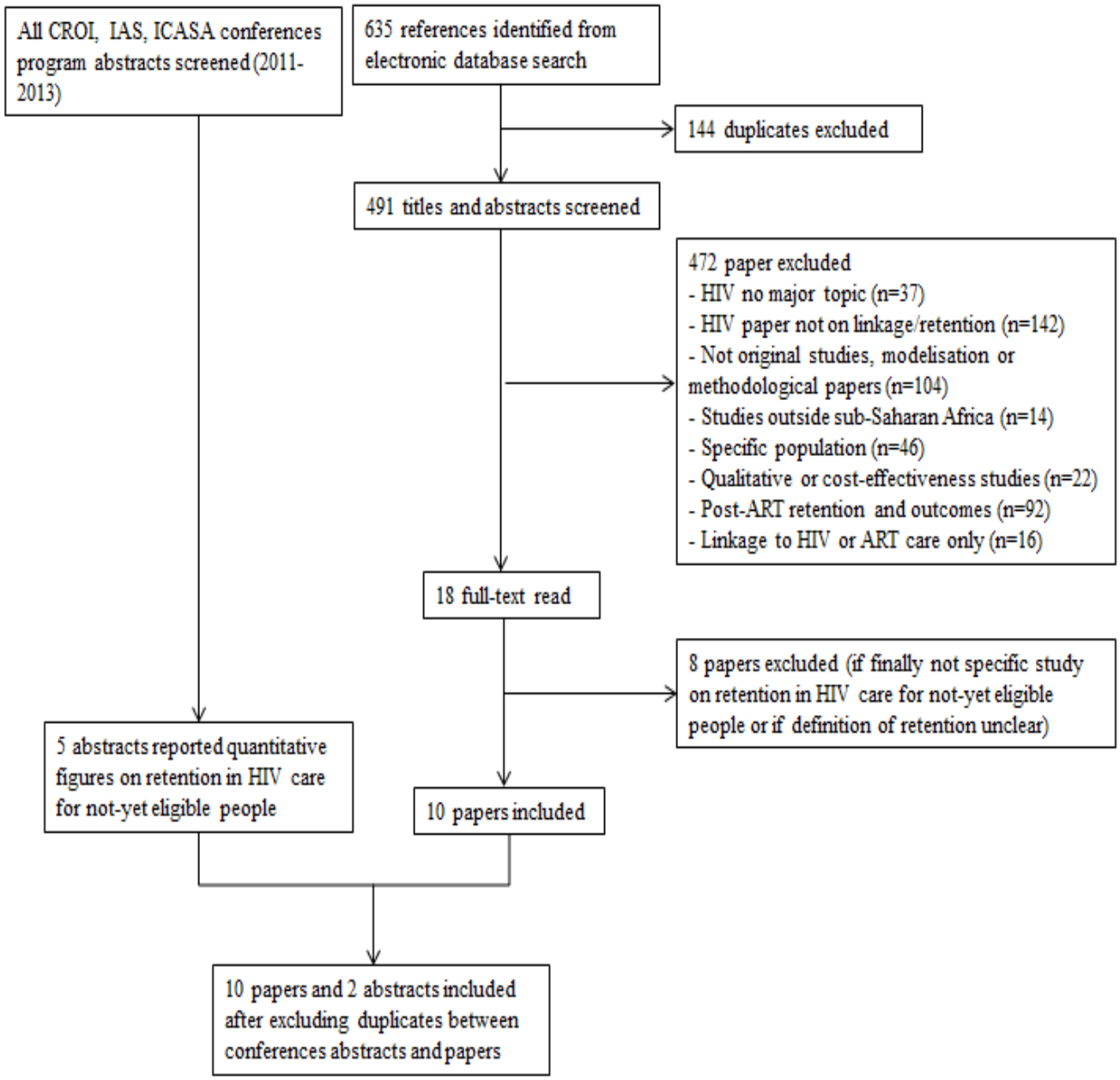

Figure 2. Flow chart of literature search on retention in HIV care among individuals not yet eligible for antiretroviral therapy (ART) in sub-Saharan Africa. January 2014.

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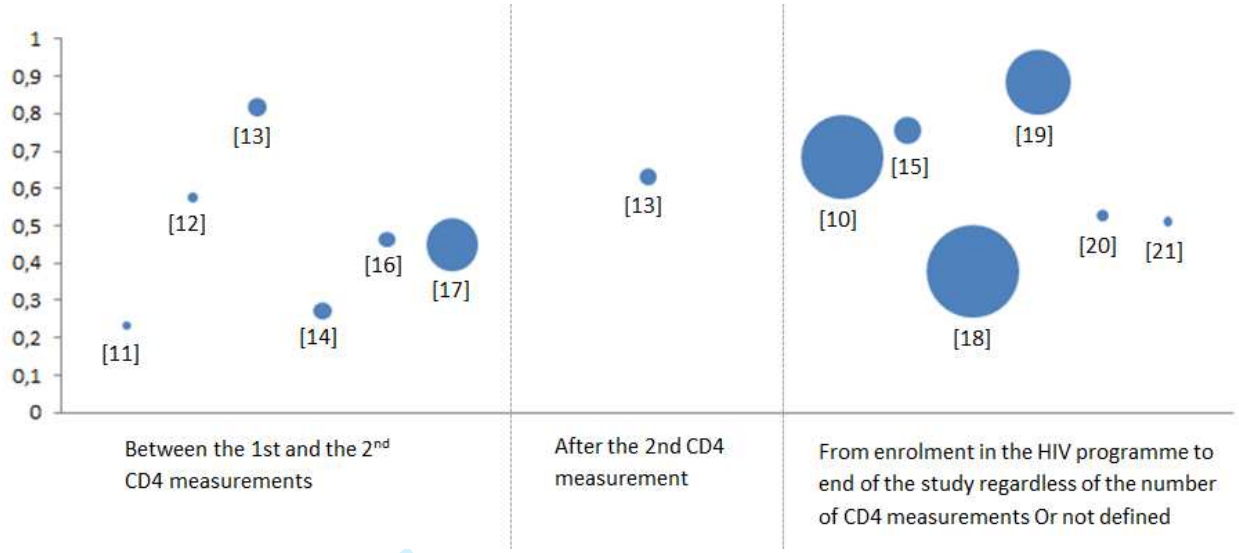

Figure 3. Rates of retention in pre-ART care among patients who are not yet eligible for antiretroviral therapy (ART). Twelve studies in sub-Saharan Africa. Bubble size proportional to population size.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not concerned
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p.5, Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not concerned
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not concerned

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not concerned
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not concerned
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.6. Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p.6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not concerned
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p.6, p.7. Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not concerned
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not concerned
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not concerned
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p.7, p.8, p.9.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.9.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.9, p.10.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.11 (see Acknowledgments)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature

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Primary Subject Heading:	HIV/AIDS
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Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature

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Abstract [231 words]

Objective. We aimed at summarizing rates and factors associated with retention in HIV care prior to antiretroviral treatment (ART) eligibility in sub-Saharan Africa.

Design. We conducted a systematic literature review (2002 to 2014). We searched Medline/Pubmed, Scopus and Web of Science as well as conferences proceedings. We included all original research studies published in peer-reviewed journals, which used quantitative indicators of retention in care prior to ART eligibility.

Participants. People not yet eligible for ART.

Primary and secondary outcomes. Rate of retention in HIV care prior to ART eligibility and associated factors.

Results. Ten papers and two abstracts were included. Most studies were conducted in Southern and Eastern Africa between 2004 and 2011 and reported retention rates in pre-ART care up to the second CD4 measurement. Definition of pre-ART care retention differed substantially across studies. Retention rates ranged between 23 and 88% based on series ranging from 112 to 10,314 individuals; retention was higher in women, individuals aged >25 years, those with low CD4 count, high body mass index or co-infected with tuberculosis, and in settings with free cotrimoxazole use.

Conclusions. Retention in pre-ART care in sub-Saharan Africa has been insufficiently described so far leaving major research gaps, especially regarding long-term retention rates and socio-demographic, economic, clinical and programmatic logistic determinants. The prospective follow-up of newly diagnosed individuals is required to better evaluate attrition prior to ART eligibility among HIV-infected people.

Key words: HIV; Continuity of Patient Care; Adults; Treatment eligibility; Africa South of Sahara; Review.

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Article summary

- This literature review is one of the first summarizing the scientific knowledge on retention in care (including definitions, rates and factors associated) prior to ART eligibility among adults in sub-Saharan Africa.
- It is based on a systematic screening of the published literature in three large databases as well as of HIV conferences proceedings.
- Few studies were included according to our inclusion criteria. Although we aimed to conduct an exhaustive review of the published literature, we cannot exclude that we missed some that did not correspond to our search equation.
- Also considering that the definitions of retention in HIV care prior to ART eligibility varied substantially, we decided not to conduct a meta-analysis.

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Manuscript [3162 words]

Introduction

In 2012, it was estimated that 22.1 million of adults were living with HIV in sub-Saharan Africa of whom 1.4 million were newly infected [1]. To prevent HIV transmission and help those who live with HIV access care and treatment in due time, the consensus today is that individuals should be diagnosed as early as possible in the course of HIV infection, that is to say before eligibility criteria for antiretroviral therapy (ART) initiation are met. Once an individual is diagnosed HIV-positive, there are several steps up to ART initiation, known as the HIV cascade [2-4]: i/ from HIV diagnosis to linkage to HIV care, ii/ from linkage to HIV care to ART eligibility, iii/ from ART eligibility to ART initiation. Continuum in HIV care through these different steps is critical for individuals to receive adequate clinical and biological monitoring and to initiate ART immediately upon becoming eligible in order to minimize early morbidity and mortality. It has indeed been shown that people who engaged in HIV care prior to eligibility were more likely to initiate and remain on ART than those entering in care when already eligible [5, 6], and that the risk of mortality was reduced if ART was initiated early enough in the course of HIV infection [7]. Finally, being in pre-ART care for more than six months was significantly associated with reduced rates of mortality and loss-to-follow-up after starting ART [8].

In sub-Saharan Africa, many people are lost to follow-up between HIV diagnosis and ART initiation and these individuals are thus at risk of delayed ART initiation [9]. Although the 2013 World Health Organization (WHO) recommendations for initiating ART reduce the length of time before reaching ART eligibility [10], ART eligibility criteria in most of African countries are based on a CD4 <350 cells/µL threshold, and it will probably take time for these countries to expand their ART eligibility criteria and translate the WHO recommendation into practice. In the evolving context where many interventions are developed, evaluated and implemented with the aim of increasing the uptake of HIV testing among people early in the course of HIV infection [11], retention in care prior to ART eligibility is a key issue that needs to be better understood.

Three literature reviews have been conducted on HIV care prior to ART initiation in the recent years [2-4], but they mostly focused on linkage to care and provided very little information on retention in HIV care prior to ART eligibility as well as on risk factors for retention. In this paper, we have thus focused on this second step of the HIV cascade. We specifically aimed at summarizing the scientific knowledge on retention in care prior to ART eligibility (definition, rates and risk factors) among adults in sub-Saharan Africa.

Methods

Data source and search strategy

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We conducted a systematic literature review on retention in HIV care in sub-Saharan Africa searching Medline/Pubmed, Scopus (which contains Embase references) and Web of Science until January 21st, 2014. This review of published literature was conducted using a research equation combining these following free text words: HIV, retention, and a list of all the African countries (except Maghreb) (Figure 1[1]). In addition, we also screened the abstracts of three major HIV conferences (CROI, IAS and ICASA) that took place between 2011 and 2013.

Eligibility criteria and study selection

We included all original research studies published in peer-reviewed journals between January 1, 2002 and January 21st, 2014 and that used quantitative indicators of retention in HIV care prior to ART eligibility. We first excluded papers from title and abstract screening, if i/ the major subject was not HIV, ii/ papers did not focus on linkage or retention in HIV care, iii/ papers were not original studies or were modelling studies or methodological papers without original data, iv/ papers were focused on a specific population such as children, adolescents, men who have sex with men, sex workers and migrants, v/ studies took place outside sub-Saharan Africa, vi/ reports were based only on qualitative indicators, vii/ papers were focused on post-ART retention, viii/ papers focused only on linkage to HIV or ART initiation. We did not specify any language restriction. After reading full-text papers, we secondarily excluded papers that did not report explicitly on retention in care prior to ART eligibility or if the definition of retention was not specified. For conferences proceedings, we first selected the tracks and sessions where the topic corresponded to our literature review. Selection was then carried out after systematic abstract screening. Authors of the papers and abstracts included were systematically contacted in case of missing information.

Parameters of interest

For each study included, we report definition and rate of retention in care prior to ART eligibility and we present cumulative incidence rates of retention at different time points. These rates are displayed in a bubble graph taking into account population size for each study. We distinguish between retention documented between the first and the second CD4 measurement or after the second measurement, and describe how deaths and transfers were considered for estimating the retention rate. We also indicate the follow-up duration considered when measuring the retention rate. Finally, we present factors associated with retention in pre-ART care when they were reported in multivariable analysis. These factors did not necessarily focus only on retention in care prior to ART eligibility as most papers considered global retention in pre-ART care, between HIV diagnosis to ART initiation; when this was the case, we distinguished between the size of the overall population in pre-ART care and the size of the population not yet ART-eligible. We did not report on associations when studies did not distinguish between factors associated with retention in pre-ART care and post ART initiation.

[1] For the editor : This figure may alternatively be presented as an Appendix

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Results

Paper selection

In total, 635 published references were identified through the search equation, of which 144 were duplicates and 472 others were excluded based on title and abstract review (Figure 2). Of the 18 remaining references, we left out eight papers after reading the full-text. In addition, we also identified five studies from the conference proceedings search; three of them were excluded because duplicated with included papers. We thus included ten published studies and [12-21] two abstracts [22, 23] in this review.

Studies characteristics

Table 1 summarizes the characteristics of the 12 studies selected. One of them was conducted in three different countries; the 11 others were conducted in a single country. The majority of them took place in Southern and Eastern Africa: South Africa for four reports [13, 14, 18, 19], Kenya for three [12, 15, 17], Uganda for two [12, 20], and one each in Malawi [12], Mozambique [21], and Zambia [23]; only two studies were conducted in West Africa, namely Nigeria [22] and Guinea-Bissau [16]. All the studies were conducted between 2004 and 2012. Six of them were conducted in urban or peri-urban settings [13, 14, 16-18, 22], two in rural settings [15, 19] and four in both contexts [12, 20, 21, 23]. Populations included were all individuals aged more than 15 years old in four reports [12, 15, 21, 23], more than 16 years old in two [16, 19] or more than 18 years old in four [13, 14, 18, 20, 22]; one study focused on pregnant women older than 18 years old [13] and we did not have the information for the last one [17]. ART eligibility criteria varied according to countries, and were based either on both CD4 cell count and WHO staging [12, 15-17, 21, 23] or only on CD4 cell count [13, 14, 18-20, 22]. All these studies used data collected in cohorts from either clinics with NGO support or public HIV programmes.

Retention in pre-ART care

Table 2 and Figure 3 summarize the study findings.

Definition of retention in pre-ART care

Criteria used for the definition of retention in HIV care prior to ART eligibility varied across the 12 studies and depended mostly on programmatic factors. The majority of studies reported retention rates in pre-ART care between the first and the second CD4 measurement [13-16, 18, 19], and only one study explicitly reported a retention rate after the second CD4 measurement [15]. Other papers reported retention rates from enrolment of patients in the HIV program to the end of the study regardless of the number of CD4 measurements [12, 20, 22, 23]. Almost all the studies did exclude death and/or transfers for studying retention in pre-ART care. One study used a tracking method ascertaining the vital status of a subsample of patients lost to follow-up for correcting the estimation of retention in pre-ART care [20].

Rates of retention in HIV care prior to ART eligibility

The lowest crude rate of retention in pre-ART care was observed in the study focused on pregnant women (23%) [13], followed by the study conducted in West Africa (27%) [16]. Three

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other studies reported rates of retention in pre-ART care lower than 50% [18, 19, 21]. The highest crude rates of retention in pre-ART care were observed in Kenya (82%) [15] and in Uganda (88%) [20].

Factors associated with retention in pre-ART care

Retention in pre-ART care was mostly associated with individual factors, which varied according to settings. Factors that were most consistently found associated with a higher retention in pre-ART care included age above 25/30 years old compared to the younger ones [12, 14, 16-19, 21, 23] and female gender [12, 14, 19]. One study also showed that non-pregnant women were more likely to be retained compared to men and pregnant women [21]. Also, in Uganda, high income was significantly associated with better retention in pre-ART care [20]. Religion and nationality were investigated but not reported to be associated with retention in pre-ART care.

Distance to clinic was studied in two settings and showed conflicting results: in Kenya, people who lived ≤5 kilometers (versus >5 kilometers) away from the clinic were more likely to be retained in pre-ART care [15] while in Zambia, people who lived ≤20 kilometers (versus >20 kilometers) from the clinic were more likely to be lost-to-follow-up [23]. Biological and clinical factors were also associated with a higher retention in pre-ART care, including low CD4 cell count [12, 19], high body mass index [12, 17], heavier weight [20, 21], and anemia [16]. Additionally, retention in pre-ART care was higher in patients co-infected with tuberculosis [12, 14].

Lastly, two studies showed that the introduction of free cotrimoxazole increased retention in pre-ART care in Kenya [17] and Nigeria [22]. In Nigeria, in addition to the provision of free cotrimoxazole, the intervention package was also composed of synchronized pharmacy and laboratory appointments, task-shifting to nurse and data-clerks, same-day CD4 monitoring and receipt of results and integrated clinics [22].

Discussion

Although many HIV-infected adults are deemed to be lost to follow-up before reaching ART eligibility, little research has been published on retention in HIV care prior to ART eligibility; indeed, only 12 studies were included in this review over a 12-year period. Definitions of retention in pre-ART care varied across settings and healthcare systems, thus making the comparison between studies challenging. Nevertheless, reported rates of retention in pre-ART care were consistently low; this was especially the case among pregnant women [13] and in West Africa (Guinea-Bissau) [16]. Only three studies reported a retention rate >75% [15, 17, 20].

Clouse et al [13] observed that retention in pre-ART care was much higher during pregnancy compared to the post-delivery period, and especially in women not-yet eligible for ART, concluding that “among HIV-positive pregnant women, the challenge is to ensure that HIV care extends beyond the period of pregnancy and continues for the lifetime of the mothers” [13]. High

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loss-to-follow-up rates within prevention of mother-to-child-transmission of HIV (PMTCT) programs have been consistently reported, regardless of the WHO recommendation (Option A or B) as shown in a meta-analysis [24] and also under the more recent Option B+ as found in Malawi [25].

As noted by several authors [13, 14, 18, 21], misclassification of care transfers, incorrectly considered as failures to continue care, may have led to underestimate the rates of retention in HIV care. This may be particularly the case in the study conducted in Guinea-Bissau, where many people worked outside the city of Bissau during the crop season [16]. Indeed, patients not retained in the study clinic may have continued HIV care elsewhere without informing their doctor or nurse. Only one study tried to account for this concern, using a tracking method to establish the updated status of a random sample of patients not retained in the initial study clinic setting [20]. Once the vital status of people who were firstly considered as lost-to-follow-up was verified, the authors estimated a corrected rate of retention in pre-ART care of 90%, much higher than the uncorrected estimate of 70%.

This literature review confirms that retention in HIV care prior to ART eligibility is lower in younger individuals [12, 14, 16-19, 21, 23] and in men [12, 14, 19], as it has been already reported in previous literature reviews exploring retention in HIV care overall [3, 26]. Some papers included in our review also suggest that biological and clinical factors are associated with retention in pre-ART care. Indeed, it was shown that patients who are co-infected with tuberculosis [12, 14], those who have anemia [16] or those with low CD4 count [12, 19] are more likely to be retained in pre-ART care than patients without these characteristics. These results suggest that it is important for programs to focus attention during pre-ART care on younger individuals, men in general, and also on individuals with less advanced HIV disease, who may feel healthier. While tuberculosis co-infection [27] and anemia [28] are HIV-related diseases, the association between these complications and retention in pre-ART care is only supported by limited evidence so far and needs to be further explored.

This literature review highlights several gaps in knowledge on retention in care prior to ART eligibility. First, 10 of the 12 studies identified were conducted in Eastern and Southern Africa; reports from West Africa where healthcare systems have been described as less efficient, are lacking. Second, three of these studies reported that, among patients with a second CD4 measurement, about 70% of individuals were still not ART-eligible at that time [14, 19, 21]. However, only one paper focused on retention in pre-ART care beyond the second CD4 measurement [15] and three others reported retention regardless of the number of CD4 measurements [12, 20, 22]. As the consensus is that individuals should be diagnosed as early as possible in the course of HIV infection before becoming eligible for ART [11], and bearing in mind that the CD4 threshold for ART initiation has been recently enlarged [10], the period between HIV diagnosis and ART initiation is a critical one for optimizing the care plan. Longer-term retention in pre-ART care, i.e. up to ART eligibility should thus be further documented.

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Thirdly, further methods such as tracking by peer educators and use of mobile technologies could contribute to better retention and more correct estimations of retention [20], accounting for people who are retained in care in the overall health system, but outside a given study clinic. Lastly, the 12 studies included in our review showed that retention in pre-ART care was associated with socio-demographic and clinical individual factors. However, the role of programmatic and logistic factors (such as time/distance to clinic, waiting time in clinic, costs for transportation or looking after the children) was very rarely studied, as well as perceptions on HIV care at individual and community levels. And yet, as discussed by Boyles et al [8], reasons for low retention in pre-ART care may include the lack of availability of comprehensive HIV care services and the perception that ART is only necessary in individuals who become sick, suggesting that these factors should be further explored as potential barriers to pre-ART care.

The results of our review highlight the urgent need to continue designing and evaluating interventions aimed at improving retention in HIV care, especially for people not-yet eligible for ART. To date, several interventions have targeted the improvement of ART adherence, e.g. reminder services (such as mobile phones, text messaging and diary cards) [29, 30] and treatment supporters [30]. These interventions should now be adapted for improving retention in pre-ART care too. Some interventions such as CD4 point-of-care [31] and involvement of community health care workers and peers counsellors [32] have already been shown to improve retention in pre-ART care but are insufficiently used. A combination of different interventions [32, 33], adapted to the setting will most often be necessary in helping the majority of people to remain in care up to ART initiation.

A limitation of this review is that we only found a few number of published studies exploring retention in HIV care prior to ART eligibility. Although we aimed to conduct an exhaustive review of published literature, we cannot exclude that we missed some that did not correspond to our search equation; however, we have searched three different and large databases and enlarged our search to HIV conferences abstracts. Another limitation was that definition of retention in HIV care prior to ART eligibility substantially varied across the studies reviewed, making it challenging to compile and compare the retention rates reported in the various studies. Considering the small number of studies included and the non-standardized definitions of retention in HIV care prior to ART eligibility, we could not conduct a meta-analysis. Finally, the generalizability of these findings need to be done with caution; indeed, it is possible that only HIV programmes with better resources have analysed and published their data.

In conclusion, this literature reviews shows that, as more and more subjects are offered HIV testing earlier in the course of HIV infection and as ART eligibility criteria are enlarged over time, rates of retention in pre-ART care remain insufficient. Large-scale community randomized trials are currently evaluating the effectiveness of universal test and treat interventions, where ART initiation is initiated immediately after HIV testing, regardless of immunological or clinical

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criteria [34, 35]. Such an approach would a *priori* solve the issue of pre-ART care and a recent report has shown good feasibility and acceptability in rural South Africa [36]. However, even if test and treat strategies are shown to be effective in reducing HIV incidence at population levels, the timeframe until their large-scale implementation is unclear. Thus in the medium-term, pre-ART care does remain a challenge for health care systems and societies and deserves further consideration in sub-Saharan Africa. Longitudinal follow-up of newly HIV-diagnosed individuals tested under various circumstances would contribute to better characterize and understand attrition for those not yet eligible to ART in order to better guide local HIV care programs. Finally, innovative support interventions, home or clinic-based, will need to be evaluated on their capacity to retain this population in comprehensive HIV care services up to ART initiation and thus prepare them better to life-long ART and case management.

3162 words, 2 tables and 3 figures

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Contributorship statement

Conceived and designed the review: MP, JOG, RDS. Analyzed the data: MP. Wrote the paper: MP, RDS, JOG, FD.

Competing interests

The authors have no competing interest to declare.

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Data sharing

No additional data available.

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Table 1. Characteristics of the 12 sub-Saharan Africa studies included in the review of retention in HIV care prior to antiretroviral therapy (ART) eligibility

Country *(Reference)*	Year of the study	Urban / Rural	Programmatic context	ART eligibility criteria	Population	Overall population size in pre-ART care	Population size prior to ART eligibility
PAPERS							
Kenya, Malawi, Uganda [12]	2004-2011	Rural and urban	HIV programmes supported by a NGO	Until January 2007: CD4 <200 or WHO stage IV Since January 2007: CD4 <200 or WHO stage III/IV Since March 2010: CD4 <350 or WHO stage III/IV	≥15 years old	N = 55,789	N = 10,314
South Africa [13]	2010-2011	Urban	Clinic operated by a NGO	CD4 ≤350	Pregnant women ≥18 years old	N = 271	N = 112
South Africa [14]	2010-2011	Urban	Clinic operated by a NGO	CD4 ≤350	Non pregnant adult ≥18 years old	N = 842	N = 155
Kenya [15]	2008-2010	Rural	Public health care institution	CD4 <200 OR WHO stage III/IV OR no CD4 count and WHO staging at baseline	≥15 years old and with HIV diagnosis <3 months before registration in care	N = 530	N = 530
Guinea-Bissau [16]	2005-2012	Urban	National hospital	Undefined	≥16 years old	N = 484	N = 484
Kenya [17]	2005-2007	Urban	Clinic supported by a NGO	CD4 <250 or WHO stage III/IV	Not clear	N = 1,024	N = 1,024
South Africa [18]	2004-2009	Peri-urban	Public clinic	CD4 <200	≥18 years old	N = 419	N = 419
South Africa [19]	2007-2008	Rural	Public HIV programme	CD4 <200	≥16 years old	N = 4,223	N = 4,223
Mozambique [21]	2005-2009	Rural and urban	National ART programme	WHO stage IV OR WHO stage III and CD4 <350 OR CD4 <200	≥15 years old	N = 17,598	N = 12,992

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Uganda [20]	2008-2011	Semirural and urban	Public HIV programme	CD4 <350	≥18 years old	N = 6,473	N = 6,473
CONFERENCES ABSTRACTS							
Nigeria [22]	2009-2012	Urban	Unknown	CD4 <350	≥18 years old	N = 414	N = 191
Zambia [23]	2009-2010	Rural and urban	District hospital	CD4 <250 OR WHO stage III/IV	≥15 years old	N = 145	N = 145

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Table 2. Retention in pre-ART care among patients who are not-yet eligible for antiretroviral therapy (ART). Twelve studies in sub-Saharan Africa.

Country *(reference)*	Period when retention was studied	Definition of retention	Retention time point	Rate of retention	Consideration of deaths and transfers for calculating the rate	Factors associated with retention in pre-ART care	Factors investigated but not associated with retention in pre-ART care
PAPERS							
Kenya, Malawi, Uganda [12]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	Having missed an appointment for more than 6 months	Median: 18.4 months (IQR*=8·5-32·2)	68·4%	Deaths excluded Transfers excluded when reported	Being old, female gender, BMI >18.5, low CD4 cell count, being diagnosed with TB, entry in VCT or PMTCT vs in or outpatient services or medical referral, not eligible for ART at enrollment	
South Africa [13]	Between the 1st and the 2nd CD4 measurements	Receiving a repeat CD4 count after delivery	12 months	23·2%	Transfers excluded when reported No deaths reported		
South Africa [14]	Between the 1st and the 2nd CD4 measurements	Receiving a second CD4 test within one year after the first CD4 staging	12 months	57·4%	Transfers excluded when reported Deaths not excluded	≥30 years old, female gender, receiving a TB treatment	Nationality, being employed, CD4 cell count
Kenya [15]	Between the 1st and the 2nd CD4 measurements	Not being more than 60 days late for the scheduled appointment	Undefined	81·9%	Deaths excluded Transfers excluded when reported	Living ≤5km from the main road, Not being single	Gender, age, entry point in care, religion, education level, season, population density, WHO staging, BMI
	After the 2nd CD4 measurement	Not being more than 60 days late for the scheduled	Undefined	63·2%	Deaths excluded Transfers excluded when reported	Low education level, living ≤5km from the main road, wet season	Gender, age, marital status, entry point, religion, population

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		appointment after the second visit					density, WHO staging, BMI, CD4, Hb
Guinea-Bissau [16]	Between the 1st and the 2nd CD4 measurements	Being less than one month late for the scheduled appointment	Median: 147 days (IQR*=7-653)	27·2%	Deaths excluded Transfers excluded when reported	>30 years old, having anemia, attending school, being infected by HIV-1 (vs HIV-2)	Sex, BMI, marital status, religion
Kenya [17]	Undefined	Returning to clinic less than 30 days after the next scheduled pharmacy or clinic appointment	12 months	75·5%	Transferred excluded when reported Deaths not systematically taken into account	Being older, high BMI, enrolled after free cotrimoxazole provision	Sex, TB status, baseline CD4 count
South Africa [18]	Between the 1st and the 2nd CD4 measurements	Having a repeat CD4 count before 2009	Undefined	46·3%	Undefined	≥30 years old	Sex, year of HIV test
South Africa [19]	Between the 1st and the 2nd CD4 measurements	Repeating CD4 count within 13 months of the initial test	13 months	44·9%	No exclusion of deaths and transfers	Female gender, >25 years old, ≤350 CD4 cells/µL, not out-migrant, not full-time employed, not living in a household size >10	
Mozambique [21]	Undefined	Having less 12 months elapsed since the last documented clinic visit	12 months	37·6%	Transfers and deaths excluded	Non-pregnant female, >25 years old, having at least finished primary school, weight >56kg, no WHO stage I	Marital status, number of children, socio-economic status, CD4 count,
Uganda [20]	From enrolment in the HIV program to end of the study	Having seen an HIV provider in the 6 months before the interview	30 months	88·2%	Using of a weighing method for correcting the rate, taking into account	High income, employment, high weight, urban setting	Age, sex, CD4 level, education level, marital status, calendar date at

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	regardless of the number of CD4 measurements				all outcomes (transfers, deaths) after tracking		enrollment
CONFERENCE ABSTRACTS							
Nigeria [22]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No clinic appointment missed for three consecutive times	Undefined	52·8%	No exclusion	Intervention package: provision of free cotrimoxazole prophylaxis, harmonized pharmacy and laboratory appointments, task-shifting to nurses and data-clerks, same-day CD4 monitoring and receipt of results, integrated clinic services	
Zambia [23]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No fail to return for an appointment on two and more occasion	12 months	51%	No détail provided	≥30 years old, >20 km from the hospital	Gender, marital status, education level, monthly outcome, partner's HIV status, WHO clinical stage, CD4 cell count

**IQR: Interquartile Range*

BMI: body mass index, Hb: hemoglobin, PMTCT: prevention of mother-to-child transmission of HIV, TB: tuberculosis, VCT: voluntary counseling and testing

LTFU: Loss to Follow Up.

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Figure 1. Search strategy for the systematic literature review on retention in HIV care in sub-Saharan Africa. January 2014.

Figure 2. Flow chart of literature search on retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. January 2014.

Figure 3. Rates of retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. Twelve studies in sub-Saharan Africa. Bubble size proportional to population size.

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Medline/Pubmed

((hiv AND retention AND ("Sub-Saharan Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "Sudan" OR "Tanzania" OR "Uganda" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR "Benin" OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea Bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo")) AND ("2002"[PDAT] : "2014"[PDAT]))

Scopus

TITLE-ABS-KEY*(HIV) AND* ***TITLE-ABS-KEY****(retention)* ***AND TITLE-ABS-KEY****({sub-Saharan Africa} OR {Burundi} OR {Djibouti} OR {Eritrea} OR {Ethiopia} OR {Kenya} OR {Rwanda} OR {Somalia} OR {Sudan} OR {Tanzania} OR {Uganda} OR {Cameroon} OR {Central African Republic} OR {Chad} OR {Congo} OR {Democratic Republic of Congo} OR {Equatorial Guinea} OR {Gabon} OR {Angola} OR {Botswana} OR {Lesotho} OR {Malawi} OR {Mozambique} OR {Namibia} OR {South Africa} OR {Swaziland} OR {Zambia} OR {Zimbabwe} OR {Benin} OR {Burkina Faso} OR {Cape Verde} OR {Cote d'Ivoire} OR {Gambia} OR {Ghana} OR {Guinea} OR {Guinea-bissau} OR {Liberia} OR {Mali} OR {Mauritania} OR {Niger} OR {Nigeria} OR {Senegal} OR {Sierra Leone} OR {Togo}) AND PUBYEAR > 2002*

Web of Sciences

TOPIC: *(hiv AND retention AND ("sub-Saharan Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "Sudan" OR "Tanzania" OR "Uganda" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR "Benin" OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo")) AND* **YEAR PUBLISHED:** *(2002-2014)*

Figure 1. Search strategy for the systematic literature review on retention in HIV care in sub-Saharan Africa. January 2014.
210x297mm (200 x 200 DPI)

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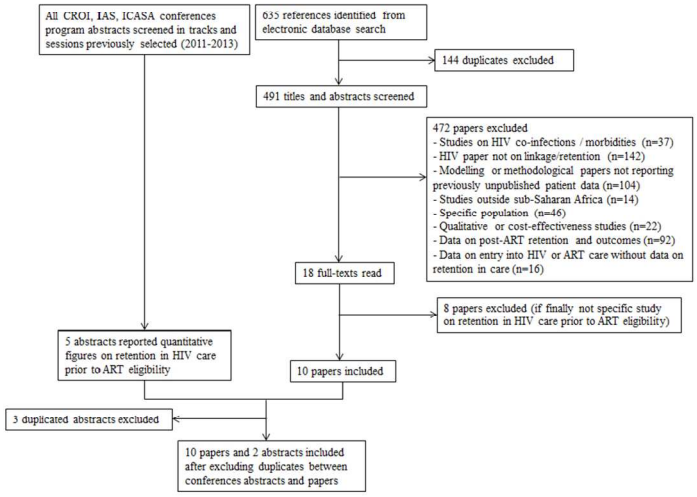

Figure 2. Flow chart of literature search on retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. January 2014.
297x210mm (105 x 105 DPI)

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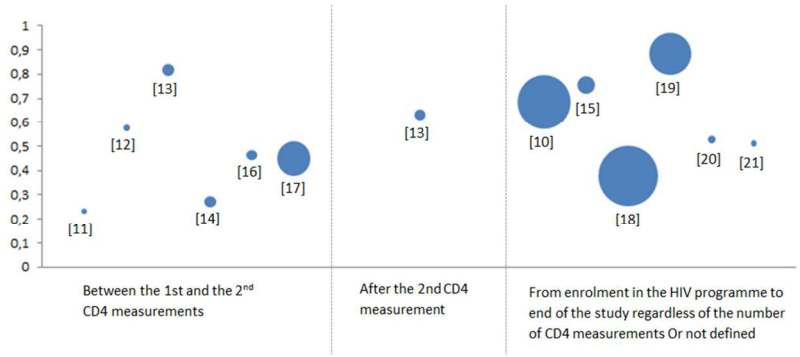

Figure 3. Rates of retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. Twelve studies in sub-Saharan Africa. Bubble size proportional to population size.
297x210mm (96 x 96 DPI)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not concerned
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p.5, Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not concerned
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not concerned

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not concerned
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not concerned
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.6. Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p.6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not concerned
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p.6, p.7. Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not concerned
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not concerned
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not concerned
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p.7, p.8, p.9.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.9.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.9, p.10.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.11 (see Acknowledgments)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, PRIMARY CARE, PUBLIC HEALTH

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Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature

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Abstract [240 words]

Objective. We aimed at summarizing rates and factors associated with retention in HIV care prior to antiretroviral treatment (ART) eligibility in sub-Saharan Africa.

Design. We conducted a systematic literature review (2002 to 2014). We searched Medline/Pubmed, Scopus and Web of Science as well as conferences proceedings. We included all original research studies published in peer-reviewed journals, which used quantitative indicators of retention in care prior to ART eligibility.

Participants. People not yet eligible for ART.

Primary and secondary outcomes. Rate of retention in HIV care prior to ART eligibility and associated factors.

Results. Ten papers and two abstracts were included. Most studies were conducted in Southern and Eastern Africa between 2004 and 2011 and reported retention rates in pre-ART care up to the second CD4 measurement. Definition of retention in HIV care prior to ART eligibility differed substantially across studies. Retention rates ranged between 23 and 88% based on series ranging from 112 to 10,314 individuals; retention was higher in women, individuals aged >25 years, those with low CD4 count, high body mass index or co-infected with tuberculosis, and in settings with free cotrimoxazole use.

Conclusions. Retention in HIV care prior to ART eligibility in sub-Saharan Africa has been insufficiently described so far leaving major research gaps, especially regarding long-term retention rates and socio-demographic, economic, clinical and programmatic logistic determinants. The prospective follow-up of newly diagnosed individuals is required to better evaluate attrition prior to ART eligibility among HIV-infected people.

Key words: HIV; Continuity of Patient Care; Adults; Treatment eligibility; Africa South of Sahara; Review.

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Article summary

- This literature review is one of the first summarizing the scientific knowledge on retention in care (including definitions, rates and factors associated) prior to ART eligibility among adults in sub-Saharan Africa.
- It is based on a systematic screening of the published literature in three large databases as well as of HIV conferences proceedings.
- Few studies were included according to our inclusion criteria. Although we aimed to conduct an exhaustive review of the published literature, we cannot exclude that we missed some that did not correspond to our search equation.
- Also considering that the definitions of retention in HIV care prior to ART eligibility varied substantially, we decided not to conduct a meta-analysis.

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Manuscript [3272 words]

Introduction

In 2012, it was estimated that 22.1 million of adults were living with HIV in sub-Saharan Africa of whom 1.4 million were newly infected [1]. To prevent HIV transmission and help those who live with HIV access care and treatment in due time, the consensus today is that individuals should be diagnosed as early as possible in the course of HIV infection, that is to say before eligibility criteria for antiretroviral therapy (ART) initiation are met. Once an individual is diagnosed HIV-positive, there are several steps up to ART initiation, known as the HIV cascade [2-4]: i/ from HIV diagnosis to linkage to HIV care, ii/ from linkage to HIV care to ART eligibility, iii/ from ART eligibility to ART initiation. Continuum in HIV care through these different steps is critical for individuals to receive adequate clinical and biological monitoring and to initiate ART immediately upon becoming eligible in order to minimize early morbidity and mortality. It has indeed been shown that people who engaged in HIV care prior to eligibility were more likely to initiate and remain on ART than those entering in care when already eligible [5, 6], and that the risk of mortality was reduced if ART was initiated early enough in the course of HIV infection [7]. Finally, being in pre-ART care for more than six months was significantly associated with reduced rates of mortality and loss-to-follow-up after starting ART [8].

In sub-Saharan Africa, many people are lost to follow-up between HIV diagnosis and ART initiation and these individuals are thus at risk of delayed ART initiation [9]. Although the 2013 World Health Organization (WHO) recommendations for initiating ART reduce the length of time before reaching ART eligibility [10], ART eligibility criteria in most of African countries are based on a CD4 <350 cells/µL threshold, and it will probably take time for these countries to expand their ART eligibility criteria and translate the WHO recommendation into practice. In the evolving context where many interventions are developed, evaluated and implemented with the aim of increasing the uptake of HIV testing among people early in the course of HIV infection [11], retention in care prior to ART eligibility is a key issue that needs to be better understood.

Three literature reviews have been conducted on HIV care prior to ART initiation in the recent years [2-4], but they mostly focused on linkage to care and provided very little information on retention in HIV care prior to ART eligibility as well as on risk factors for retention. In this paper, we have thus focused on this second step of the HIV cascade. We specifically aimed at summarizing the scientific knowledge on retention in care prior to ART eligibility (definition, rates and risk factors) among adults in sub-Saharan Africa.

Methods

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Data source and search strategy

We conducted a systematic literature review on retention in HIV care prior to ART eligibility in sub-Saharan Africa searching Medline/Pubmed, Scopus (which contains Embase references) and Web of Science until January 21st, 2014. This review of published literature was conducted using a research equation combining these following free text words: HIV, retention, and a list of all the African countries (except Maghreb) (Figure 1[1]). In addition, we also screened the abstracts of three major HIV conferences (CROI, IAS and ICASA) that took place between 2011 and 2013.

Eligibility criteria and study selection

We included all original research studies published in peer-reviewed journals between January 1, 2002 and January 21st, 2014 and that used quantitative indicators of retention in HIV care prior to ART eligibility. We first excluded papers from title and abstract screening, if i/ the major subject was not HIV, ii/ papers did not focus on linkage or retention in HIV care, iii/ papers were not original studies or were modelling studies or methodological papers without original data, iv/ papers were focused on a specific population such as children, adolescents, men who have sex with men, sex workers and migrants, v/ studies took place outside sub-Saharan Africa, vi/ reports were based only on qualitative indicators, vii/ papers were focused on post-ART retention, viii/ papers focused only on linkage to HIV or ART initiation. We did not specify any language restriction. After reading full-text papers, we secondarily excluded papers that did not report explicitly on retention in care prior to ART eligibility or if the definition of retention was not specified. We did not apply any specific quality criteria to the assessment beyond the strict reference selection criteria. For conferences proceedings, we first selected the tracks and sessions where the topic corresponded to our literature review. Selection was then carried out after systematic abstract screening. Authors of the papers and abstracts included were systematically contacted in case of missing information. The choice of inclusion criteria and the selection of references involved all the members of the research team. Only one researcher then reviewed the paper contents and abstracted the data.

Parameters of interest

For each study included, we report definition and rate of retention in care prior to ART eligibility and we present cumulative incidence rates of retention at different time points. These rates are displayed in a bubble graph taking into account population size for each study. We distinguish between retention documented between the first and the second CD4 measurement or after the second measurement, and describe how deaths and transfers were considered for estimating the retention rate. We also indicate the follow-up duration considered when measuring the retention rate. Finally, we present factors associated with retention in pre-ART care when they were reported in multivariable analysis. These factors did not necessarily focus only on retention in care prior to ART eligibility as most papers considered global retention in pre-ART care,

[1] For the editor : This figure may alternatively be presented as an Appendix

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between HIV diagnosis to ART initiation; when this was the case, we distinguished between the size of the overall population in pre-ART care and the size of the population not yet ART-eligible. We did not report on associations when studies did not distinguish between factors associated with retention in pre-ART care and post ART initiation.

Results

Paper selection

In total, 635 published references were identified through the search equation, of which 144 were duplicates and 472 others were excluded based on title and abstract review (Figure 2). Of the 18 remaining references, we left out eight papers after reading the full-text. In addition, we also identified five studies from the conference proceedings search; three of them were excluded because duplicated with included papers. We thus included ten published studies and [12-21] two abstracts [22, 23] in this review.

Studies characteristics

Table 1 summarizes the characteristics of the 12 studies selected. One of them was conducted in three different countries; the 11 others were conducted in a single country. The majority of them took place in Southern and Eastern Africa: South Africa for four reports [13, 14, 18, 19], Kenya for three [12, 15, 17], Uganda for two [12, 20], and one each in Malawi [12], Mozambique [21], and Zambia [23]; only two studies were conducted in West Africa, namely Nigeria [22] and Guinea-Bissau [16]. All the studies were conducted between 2004 and 2012. Six of them were conducted in urban or peri-urban settings [13, 14, 16-18, 22], two in rural settings [15, 19] and four in both contexts [12, 20, 21, 23]. Populations included were all individuals aged more than 15 years old in four reports [12, 15, 21, 23], more than 16 years old in two [16, 19] or more than 18 years old in four [13, 14, 18, 20, 22]; one study focused on pregnant women older than 18 years old [13] and we did not have the information for the last one [17]. ART eligibility criteria varied according to countries, and were based either on both CD4 cell count and WHO staging [12, 15-17, 21, 23] or only on CD4 cell count [13, 14, 18-20, 22]. All these studies used data collected in cohorts from either clinics with NGO support or public HIV programmes.

Retention in HIV care prior to ART eligibility

Table 2 and Figure 3 summarize the study findings.

Definition of retention in HIV care prior to ART eligibility

Criteria used for the definition of retention in HIV care prior to ART eligibility varied across the 12 studies and depended mostly on programmatic factors. The majority of studies reported retention rates between the first and the second CD4 measurement [13-16, 18, 19], and only one study explicitly reported a retention rate after the second CD4 measurement [15]. Other papers reported retention rates in HIV care prior to ART eligibility from enrolment of patients in the

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HIV program to the end of the study regardless of the number of CD4 measurements [12, 20, 22, 23]. Almost all the studies did exclude death and/or transfers for studying retention in HIV care. One study used a tracking method ascertaining the vital status of a subsample of patients lost to follow-up for correcting the estimation of retention in HIV care prior to ART eligibility [20].

Rates of retention in HIV care prior to ART eligibility

The lowest crude rate of retention in HIV care prior to ART eligibility was observed in the study focused on pregnant women (23%) [13], followed by the study conducted in West Africa (27%) [16]; three other studies reported rates of retention lower than 50% [18, 19, 21]. The highest crude rates of retention in HIV care prior to ART eligibility were observed in Kenya (82%) [15] and in Uganda (88%) [20].

Factors associated with retention in pre-ART care

Retention in pre-ART care was mostly associated with individual factors, which varied according to settings. Factors that were most consistently found associated with a higher retention in pre-ART care included age above 25/30 years old compared to the younger ones [12, 14, 16-19, 21, 23] and female gender [12, 14, 19]. One study also showed that non-pregnant women were more likely to be retained compared to men and pregnant women [21]. Also, in Uganda, high income was significantly associated with better retention in pre-ART care [20]. Religion and nationality were investigated but not reported to be associated with retention in pre-ART care.

Distance to clinic was studied in two settings and showed conflicting results: in Kenya, people who lived ≤5 kilometers (versus >5 kilometers) away from the clinic were more likely to be retained in pre-ART care [15] while in Zambia, people who lived ≤20 kilometers (versus >20 kilometers) from the clinic were more likely to be lost-to-follow-up [23]. Biological and clinical factors were also associated with a higher retention in pre-ART care, including low CD4 cell count [12, 19], high body mass index [12, 17], heavier weight [20, 21], and anemia [16]. Additionally, retention in pre-ART care was higher in patients co-infected with tuberculosis [12, 14].

Lastly, two studies showed that the introduction of free cotrimoxazole increased retention in pre-ART care in Kenya [17] and Nigeria [22]. In Nigeria, in addition to the provision of free cotrimoxazole, the intervention package was also composed of synchronized pharmacy and laboratory appointments, task-shifting to nurse and data-clerks, same-day CD4 monitoring and receipt of results and integrated clinics [22].

Discussion

Although many HIV-infected adults are deemed to be lost to follow-up before reaching ART eligibility, little research has been published on retention in HIV care prior to ART eligibility; indeed, only 12 studies were included in this review over a 12-year period. Definitions of

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retention in HIV care prior to ART eligibility varied across settings and healthcare systems, thus making the comparison between studies challenging. Nevertheless, reported rates of retention in HIV care prior to ART eligibility were consistently low; this was especially the case among pregnant women [13] and in West Africa (Guinea-Bissau) [16]. Only three studies reported a retention rate >75% [15, 17, 20].

Clouse et al [13] observed that retention in pre-ART care was much higher during pregnancy compared to the post-delivery period, and especially in women not-yet eligible for ART, concluding that "among HIV-positive pregnant women, the challenge is to ensure that HIV care extends beyond the period of pregnancy and continues for the lifetime of the mothers" [13]. High loss-to-follow-up rates within prevention of mother-to-child-transmission of HIV (PMTCT) programs have been consistently reported, regardless of the WHO recommendation (Option A or B) as shown in a meta-analysis [24] and also under the more recent Option B+ as found in Malawi [25].

As noted by several authors [13, 14, 18, 21], misclassification of care transfers, incorrectly considered as failures to continue care, may have led to underestimate the rates of retention in HIV care. This may be particularly the case in the study conducted in Guinea-Bissau, where many people worked outside the city of Bissau during the crop season [16]. Indeed, patients not retained in the study clinic may have continued HIV care elsewhere without informing their doctor or nurse. Only one study tried to account for this concern, using a tracking method to establish the updated status of a random sample of patients not retained in the initial study clinic setting [20]. Once the vital status of people who were firstly considered as lost-to-follow-up was verified, the authors estimated a corrected rate of retention in HIV care prior to ART eligibility of 90%, much higher than the uncorrected estimate of 70%.

This literature review confirms that retention in HIV care prior to ART eligibility is lower in younger individuals [12, 14, 16-19, 21, 23] and in men [12, 14, 19], as it has been already reported in previous literature reviews exploring retention in HIV care overall [3, 26]. Some papers included in our review also suggest that biological and clinical factors are associated with retention in pre-ART care. Indeed, it was shown that patients who are co-infected with tuberculosis [12, 14], those who have anemia [16] or those with low CD4 count [12, 19] are more likely to be retained in pre-ART care than patients without these characteristics. These results suggest that it is important for programs to focus attention during pre-ART care on younger individuals, men in general, and also on individuals with less advanced HIV disease, who may feel healthier. While tuberculosis co-infection [27] and anemia [28] are HIV-related diseases, the association between these complications and retention in pre-ART care is only supported by limited evidence so far and needs to be further explored.

This literature review highlights several gaps in knowledge on retention in HIV care prior to ART eligibility. First, 10 of the 12 studies identified were conducted in Eastern and Southern

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Africa; reports from West Africa where healthcare systems have been described as less efficient, are lacking. Second, three of these studies reported that, among patients with a second CD4 measurement, about 70% of individuals were still not ART-eligible at that time [14, 19, 21]. However, only one paper focused on retention in HIV care beyond the second CD4 measurement [15] and three others reported retention in HIV care prior to ART eligibility regardless of the number of CD4 measurements [12, 20, 22]. As the consensus is that individuals should be diagnosed as early as possible in the course of HIV infection before becoming eligible for ART [11], and bearing in mind that the CD4 threshold for ART initiation has been recently enlarged [10], the period between HIV diagnosis and ART initiation is a critical one for optimizing the care plan. Longer-term retention in HIV care prior to ART eligibility should thus be further documented. Thirdly, further methods such as tracking by peer educators and use of mobile technologies could contribute to better retention and more correct estimations of retention [20], accounting for people who are retained in care in the overall health system, but outside a given study clinic. Lastly, the 12 studies included in our review showed that retention in pre-ART care was associated with socio-demographic and clinical individual factors. However, the role of programmatic and logistic factors (such as time/distance to clinic, waiting time in clinic, costs for transportation or looking after the children) was very rarely studied, as well as perceptions on HIV care at individual and community levels. And yet, as discussed by Boyles et al [8], reasons for low retention in pre-ART care may include the lack of availability of comprehensive HIV care services and the perception that ART is only necessary in individuals who become sick, suggesting that these factors should be further explored as potential barriers to pre-ART care.

The results of our review highlight the urgent need to continue designing and evaluating interventions aimed at improving retention in HIV care, especially for people not-yet eligible for ART. To date, several interventions have targeted the improvement of ART adherence, e.g. reminder services (such as mobile phones, text messaging and diary cards) [29, 30] and treatment supporters [30]. These interventions should now be adapted for improving retention in pre-ART care, and especially before ART eligibility, too. Some interventions such as CD4 point-of-care [31] and involvement of community health care workers and peers counsellors [32] have already been shown to improve retention in pre-ART care but are insufficiently used. A combination of different interventions [32, 33], adapted to the setting will most often be necessary in helping the majority of people to remain in care up to ART initiation.

A limitation of this review is that we only found a few number of published studies exploring retention in HIV care prior to ART eligibility. Although we aimed to conduct an exhaustive review of published literature, we cannot exclude that we missed some that did not correspond to our search equation; however, we have searched three different and large databases and enlarged our search to HIV conferences abstracts. Another limitation was that definition of retention in HIV care prior to ART eligibility substantially varied across the studies reviewed, making it challenging to compile and compare the retention rates reported in the various studies.

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Considering the small number of studies included and the non-standardized definitions of retention in HIV care prior to ART eligibility, we could not conduct a meta-analysis. Finally, the generalizability of these findings need to be done with caution; indeed, it is possible that only HIV programmes with better resources have analysed and published their data.

In conclusion, this literature reviews shows that, as more and more subjects are offered HIV testing earlier in the course of HIV infection and as ART eligibility criteria are enlarged over time, rates of retention in HIV care prior to ART eligibility remain insufficient. Large-scale community randomized trials are currently evaluating the effectiveness of universal test and treat interventions, where ART initiation is initiated immediately after HIV testing, regardless of immunological or clinical criteria [34, 35]. Such an approach would a *priori* solve the issue of retention in HIV care prior to ART eligibility and a recent report has shown good feasibility and acceptability in rural South Africa [36]. However, even if test and treat strategies are shown to be effective in reducing HIV incidence at population levels, the timeframe until their large-scale implementation is unclear. Thus in the medium-term, HIV care prior to ART eligibility does remain a challenge for health care systems and societies and deserves further consideration in sub-Saharan Africa. Longitudinal follow-up of newly HIV-diagnosed individuals tested under various circumstances would contribute to better characterize and understand attrition for those not yet eligible to ART in order to better guide local HIV care programs. Finally, innovative support interventions, home or clinic-based, will need to be evaluated on their capacity to retain this population in comprehensive HIV care services up to ART initiation and thus prepare them better to life-long ART and case management.

3272 words, 2 tables and 3 figures

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Contributorship statement
Conceived and designed the review: MP, JOG, RDS. Analyzed the data: MP. Wrote the paper: MP, RDS, JOG, FD.

Competing interests
The authors have no competing interest to declare.

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Data sharing
No additional data available.

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Table 1. Characteristics of the 12 sub-Saharan Africa studies included in the review of retention in HIV care prior to antiretroviral therapy (ART) eligibility

Country *(Reference)*	Year of the study	Urban / Rural	Programmatic context	ART eligibility criteria	Population	Overall population size in pre-ART care	Population size prior to ART eligibility
PAPERS							
Kenya, Malawi, Uganda [12]	2004-2011	Rural and urban	HIV programmes supported by a NGO	Until January 2007: CD4 <200 or WHO stage IV Since January 2007: CD4 <200 or WHO stage III/IV Since March 2010: CD4 <350 or WHO stage III/IV	≥15 years old	N = 55,789	N = 10,314
South Africa [13]	2010-2011	Urban	Clinic operated by a NGO	CD4 ≤350	Pregnant women ≥18 years old	N = 271	N = 112
South Africa [14]	2010-2011	Urban	Clinic operated by a NGO	CD4 ≤350	Non pregnant adult ≥18 years old	N = 842	N = 155
Kenya [15]	2008-2010	Rural	Public health care institution	CD4 <200 OR WHO stage III/IV OR no CD4 count and WHO staging at baseline	≥15 years old and with HIV diagnosis <3 months before registration in care	N = 530	N = 530
Guinea-Bissau [16]	2005-2012	Urban	National hospital	Undefined	≥16 years old	N = 484	N = 484
Kenya [17]	2005-2007	Urban	Clinic supported by a NGO	CD4 <250 or WHO stage III/IV	Not clear	N = 1,024	N = 1,024
South Africa [18]	2004-2009	Peri-urban	Public clinic	CD4 <200	≥18 years old	N = 419	N = 419
South Africa [19]	2007-2008	Rural	Public HIV programme	CD4 <200	≥16 years old	N = 4,223	N = 4,223
Mozambique [21]	2005-2009	Rural and urban	National ART programme	WHO stage IV OR WHO stage III and CD4 <350 OR CD4 <200	≥15 years old	N = 17,598	N = 12,992

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Uganda [20]	2008-2011	Semirural and urban	Public HIV programme	CD4 <350	≥18 years old	N = 6,473	N = 6,473
CONFERENCES ABSTRACTS							
Nigeria [22]	2009-2012	Urban	Unknown	CD4 <350	≥18 years old	N = 414	N = 191
Zambia [23]	2009-2010	Rural and urban	District hospital	CD4 <250 OR WHO stage III/IV	≥15 years old	N = 145	N = 145

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Table 2. Retention in pre-ART care among patients who are not-yet eligible for antiretroviral therapy (ART). Twelve studies in sub-Saharan Africa.

Country *(reference)*	Period when retention was studied	Definition of retention	Retention time point	Rate of retention	Consideration of deaths and transfers for calculating the rate	Factors associated with retention in pre-ART care	Factors investigated but not associated with retention in pre-ART care
PAPERS							
Kenya, Malawi, Uganda [12]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	Having missed an appointment for more than 6 months	Median: 18.4 months (IQR*=8·5-32·2)	68·4%	Deaths excluded Transfers excluded when reported	Being old, female gender, BMI >18.5, low CD4 cell count, being diagnosed with TB, entry in VCT or PMTCT vs in or outpatient services or medical referral, not eligible for ART at enrollment	
South Africa [13]	Between the 1st and the 2nd CD4 measurements	Receiving a repeat CD4 count after delivery	12 months	23·2%	Transfers excluded when reported No deaths reported		
South Africa [14]	Between the 1st and the 2nd CD4 measurements	Receiving a second CD4 test within one year after the first CD4 staging	12 months	57·4%	Transfers excluded when reported Deaths not excluded	≥30 years old, female gender, receiving a TB treatment	Nationality, being employed, CD4 cell count
Kenya [15]	Between the 1st and the 2nd CD4 measurements	Not being more than 60 days late for the scheduled appointment	Undefined	81·9%	Deaths excluded Transfers excluded when reported	Living ≤5km from the main road, Not being single	Gender, age, entry point in care, religion, education level, season, population density, WHO staging, BMI
	After the 2nd CD4 measurement	Not being more than 60 days late for the scheduled	Undefined	63·2%	Deaths excluded Transfers excluded when reported	Low education level, living ≤5km from the main road, wet season	Gender, age, marital status, entry point, religion, population

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		appointment after the second visit					density, WHO staging, BMI, CD4, Hb
Guinea-Bissau [16]	Between the 1st and the 2nd CD4 measurements	Being less than one month late for the scheduled appointment	Median: 147 days (IQR*=7-653)	27·2%	Deaths excluded Transfers excluded when reported	>30 years old, having anemia, attending school, being infected by HIV-1 (vs HIV-2)	Sex, BMI, marital status, religion
Kenya [17]	Undefined	Returning to clinic less than 30 days after the next scheduled pharmacy or clinic appointment	12 months	75·5%	Transferred excluded when reported Deaths not systematically taken into account	Being older, high BMI, enrolled after free cotrimoxazole provision	Sex, TB status, baseline CD4 count
South Africa [18]	Between the 1st and the 2nd CD4 measurements	Having a repeat CD4 count before 2009	Undefined	46·3%	Undefined	≥30 years old	Sex, year of HIV test
South Africa [19]	Between the 1st and the 2nd CD4 measurements	Repeating CD4 count within 13 months of the initial test	13 months	44·9%	No exclusion of deaths and transfers	Female gender, >25 years old, ≤350 CD4 cells/µL, not out-migrant, not full-time employed, not living in a household size >10	
Mozambique [21]	Undefined	Having less 12 months elapsed since the last documented clinic visit	12 months	37·6%	Transfers and deaths excluded	Non-pregnant female, >25 years old, having at least finished primary school, weight >56kg, no WHO stage I	Marital status, number of children, socio-economic status, CD4 count,
Uganda [20]	From enrolment in the HIV program to end of the study	Having seen an HIV provider in the 6 months before the interview	30 months	88·2%	Using of a weighing method for correcting the rate, taking into account	High income, employment, high weight, urban setting	Age, sex, CD4 level, education level, marital status, calendar date at

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	regardless of the number of CD4 measurements				all outcomes (transfers, deaths) after tracking		enrollment
CONFERENCE ABSTRACTS							
Nigeria [22]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No clinic appointment missed for three consecutive times	Undefined	52·8%	No exclusion	Intervention package: provision of free cotrimoxazole prophylaxis, harmonized pharmacy and laboratory appointments, task-shifting to nurses and data-clerks, same-day CD4 monitoring and receipt of results, integrated clinic services	
Zambia [23]	From enrolment in the HIV program to end of the study regardless of the number of CD4 measurements	No fail to return for an appointment on two and more occasion	12 months	51%	No détail provided	≥30 years old, >20 km from the hospital	Gender, marital status, education level, monthly outcome, partner's HIV status, WHO clinical stage, CD4 cell count

**IQR: Interquartile Range*

BMI: body mass index, Hb: hemoglobin, PMTCT: prevention of mother-to-child transmission of HIV, TB: tuberculosis, VCT: voluntary counseling and testing

LTFU: Loss to Follow Up.

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Figure 1. Search strategy for the systematic literature review on retention in HIV care in sub-Saharan Africa. January 2014.

Figure 2. Flow chart of literature search on retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. January 2014.

Figure 3. Rates of retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. Twelve studies in sub-Saharan Africa. Bubble size proportional to population size.

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Medline/Pubmed

((hiv AND retention AND ("Sub-Saharan Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "Sudan" OR "Tanzania" OR "Uganda" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR "Benin" OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea Bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo")) AND ("2002"[PDAT] : "2014"[PDAT]))

Scopus

TITLE-ABS-KEY*(HIV) AND* ***TITLE-ABS-KEY****(retention)* ***AND TITLE-ABS-KEY****({sub-Saharan Africa} OR {Burundi} OR {Djibouti} OR {Eritrea} OR {Ethiopia} OR {Kenya} OR {Rwanda} OR {Somalia} OR {Sudan} OR {Tanzania} OR {Uganda} OR {Cameroon} OR {Central African Republic} OR {Chad} OR {Congo} OR {Democratic Republic of Congo} OR {Equatorial Guinea} OR {Gabon} OR {Angola} OR {Botswana} OR {Lesotho} OR {Malawi} OR {Mozambique} OR {Namibia} OR {South Africa} OR {Swaziland} OR {Zambia} OR {Zimbabwe} OR {Benin} OR {Burkina Faso} OR {Cape Verde} OR {Cote d'Ivoire} OR {Gambia} OR {Ghana} OR {Guinea} OR {Guinea-bissau} OR {Liberia} OR {Mali} OR {Mauritania} OR {Niger} OR {Nigeria} OR {Senegal} OR {Sierra Leone} OR {Togo}) AND PUBYEAR > 2002*

Web of Sciences

TOPIC: *(hiv AND retention AND ("sub-Saharan Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "Sudan" OR "Tanzania" OR "Uganda" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR "Benin" OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo")) AND* **YEAR PUBLISHED:** *(2002-2014)*

Figure 1. Search strategy for the systematic literature review on retention in HIV care in sub-Saharan Africa. January 2014.
210x297mm (300 x 300 DPI)

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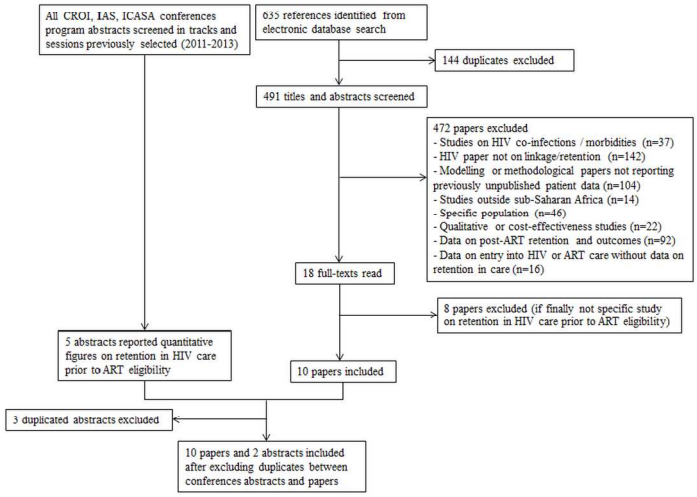

Figure 2. Flow chart of literature search on retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. January 2014.
297x210mm (300 x 300 DPI)

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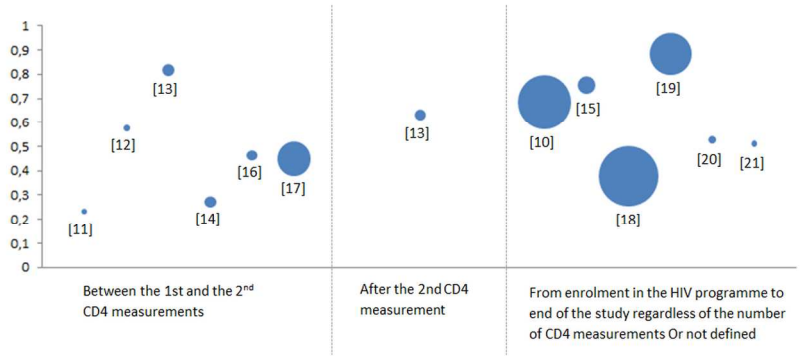

Figure 3. Rates of retention in HIV care prior to antiretroviral therapy (ART) eligibility in sub-Saharan Africa. Twelve studies in sub-Saharan Africa. Bubble size proportional to population size.
297x210mm (300 x 300 DPI)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not concerned
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p.5, Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not concerned
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not concerned

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not concerned
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not concerned
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.6. Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p.6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not concerned
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p.6, p.7. Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not concerned
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not concerned
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not concerned
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p.7, p.8, p.9.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.9.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.9, p.10.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.11 (see Acknowledgments)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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