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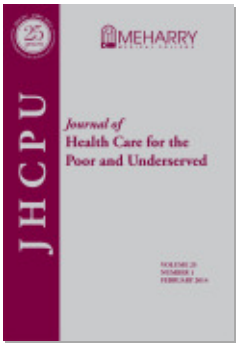

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Abstract: Efforts to scale-up HIV care and treatment have been successful at initiating large numbers of patients onto antiretroviral therapy (ART), although persistent challenges remain to optimizing scale-up effectiveness in both resource-rich and resource-limited settings. Among the most important are very high rates of ART initiation in the advanced stages of HIV disease, which in turn drive morbidity, mortality, and onward transmission of HIV. With a focus on sub-Saharan Africa, this review article presents a conceptual framework for a broader discussion of the persistent problem of late ART initiation, including a need for more focus on the upstream precursors (late HIV diagnosis and late enrollment into HIV care) and their determinants. Without additional research and identification of multi-level interventions that successfully promote earlier initiation of ART, the problem of late ART initiation will persist, significantly undermining the long-term impact of HIV care scale-up on reducing mortality and controlling the HIV epidemic.

Key words: Late ART initiation, sub-Saharan Africa, scale-up, conceptual framework, retention.

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An estimated 34 million people are infected with HIV worldwide, the majority in developing countries.[1] Efforts to scale-up access to HIV care and treatment have been successful at initiating large numbers of patients on antiretroviral therapy (ART). Sub-Saharan Africa is the most affected region, constituting 69% of people living with HIV/AIDS and 70% of HIV/AIDS deaths worldwide.[1] The estimated number of people on ART in the region increased from 100,000 people in 2003 to 8 million by the end of 2011, reaching an estimated 44% of those in need.[1] Despite these successes, there remain persistent challenges to optimizing the effectiveness of HIV care and treatment scale-up in the region. Among the most important of these are very high rates of late ART initiation (i.e., in the advanced stages of HIV disease)[2,3] which in turn drive high rates of mortality soon after initiation of ART (early mortality).[4,5] A three-to-four fold difference in mortality rates is apparent in the first year after ART initiation in resource-limited as compared with resource-rich settings.[6] There are also very high mortality rates prior to ART initiation among people already diagnosed and enrolled in care.[2] Late ART initiation is also associated with a longer infectious period, and earlier ART initiation substantially reduces onward HIV transmission.[7]

The aim of this review is to draw on relevant literature from around the world to examine and discuss the magnitude of the late ART initiation problem in sub-Saharan Africa, including precursors of late ART initiation (late HIV diagnosis and late enrollment into HIV care). We discuss the pathways to late ART initiation, which may in turn be associated with different determinants and interventions, and present a conceptual framework to help guide future discussions and inform studies aimed at identifying determinants and interventions that ultimately increase the effectiveness of HIV care and treatment scale-up.

International treatment guidelines and definition of late ART initiation. With few exceptions, national guidelines in the sub-Saharan African region during 2004–2009 specified ART eligibility for patients with CD4+ counts <200 cells/μL.[8] In 2009, the World Health Organization (WHO) revised its guidelines for ART eligibility to start patients on ART earlier: CD4 count ≤350 cells/μL (irrespective of WHO stage) and WHO stage 3 or 4 (irrespective of CD4 count).[9] Subsequently, many sub-Saharan African countries have updated their HIV national guidelines to reflect these new recommendations. National guidelines, however, still vary greatly and while they are an important reference point, most patients in sub-Saharan Africa have historically initiated ART at levels well below international and national guidelines that were in effect at the time of ART initiation (e.g., median of 80–212 cells/μL).[10–32]

For the purposes of this review, we broadly define late ART initiation as initiating ART in the advanced stages of HIV infection, irrespective of the reason. We do not put forth an operational definition, given the relative variability across countries and contexts. Rather, we frame our discussion of what constitutes late as being on the low end (e.g., lowest 25% or 10%) of the distribution of CD4 count or clinical stage at ART initiation in a given setting. However, as a reference point, operational definitions used in epidemiologic studies include WHO stage 4[33–35] or CD4 ≤200 cells/μL[17,33,35–40] to define *late* and CD4 <50 cells/μL to define *very late*.[37–40] In the past years, some attempts have been made to create consensus on these definitions,[41–43] but given that international guidelines tend to evolve and CD4 count at ART initiation is not universally available

among HIV patients in sub-Saharan Africa, it is advisable to use both CD4 and clinical stage information when operationally defining late ART initiation.

Methods

We conducted a literature review to identify the extent to which studies had been published on the magnitude of the late ART initiation problem, its precursors (late HIV diagnosis and late enrollment into HIV care) and their determinants in sub-Saharan Africa. English-language, peer-reviewed publications from 2005 to 2011 were searched in PubMed, using the terms (late OR delay) AND antiretroviral AND initiation. Additional articles were identified from references in published papers and abstracts from major international AIDS conferences. The PubMed search yielded 148 articles. We only included reports of observational ART cohorts in sub-Saharan Africa reporting CD4+ cell count and/or WHO/CDC clinical staging. We excluded data from controlled clinical trials and from special populations, such as female sex workers and intravenous drug users, as the findings are likely not generalizable to all people with HIV. Table 1 presents results from 27 studies from 18 African countries reporting the median CD4 and/ or clinical staging at HIV diagnosis, enrollment into care, and ART initiation among patients enrolled in care and treatment between 1998 and 2009, as well as the definition and proportion considered late when available.

Results

The magnitude of the late ART initiation problem in sub-Saharan Africa. Despite more expansive guidelines for ART eligibility, most patients in sub-Saharan Africa initiate ART at very low CD4 counts,[2,6,10,12,13,19,21,22,27,28,44,45] with substantial variability in the CD4 count at ART initiation across sites and settings.[8,28] We observed a range of median CD4 counts from 87 to 212 cells/μL at ART initiation (Table 1) in our review of the published literature in sub-Saharan Africa from 2005 to 2011. Table 1 also notes median CD4 count at the key milestones on the pathways towards ART initiation (HIV diagnosis and enrollment into care). In an analysis from the ART-LINC collaboration, which included 36,715 patients from 17 centers in 12 low-income countries, the median CD4 count at ART initiation was 122 cells/μL (IQR 53-194) among the sub-Saharan African patients.[19,28] Some of the most recent publications on scale-up programs for which CD4 and stage information are available suggest that, while the median CD4 count at ART initiation is increasing, they remain quite low among sub-Saharan African ART patients.[19,27,28] For example, one recent analysis of 121,504 patients initiating ART from 267 clinics in eight sub-Saharan African countries found that the median CD4 cell count at ART initiation increased modestly from 115 to 143 cells/μL during 2004–2008.[28]

The very low CD4 counts at which populations in sub-Saharan Africa are initiating ART reflects, among other things, the emergency nature of HIV scale-up in the region,[46] treatment prioritization of the sickest individuals, and absorptive capacity of the health care system to meet the overwhelming demand for treatment through scale-up and decentralization. However, once past the initial emergency phase, as ART coverage and

Table 1.

MAGNITUDE OF THE LATE ART INITIATION PROBLEM IN SUB-SAHARAN AFRICA, 2005–2011

	Author, year	Country	N	Females	Median (IQR) CD4 cell count (cells/μL)[ab]	Proportion with advanced clinical staging (WHO 4 or CDC C)[a]	Year(s) of ART Initiation	Definition[a]	Proportion delayed[a]
Delayed Diagnosis	Forbi et al., 2010	Nigeria	588	314 (53.4%)	—	—	—	Advanced immunosup.: 200–349 cells/μL; Severe immunosup.: <200 cells/ μL	130 (22.1%) advanced immunosup.; 292 (49.7%) severe immunosup.
	Okome-Nkoumou et al., 2005	Gabon	150	94 (62.7%)	242 (102–394)	28.0% CDC C	—	>124 days between first HIV-related symptoms and HIV diagnosis	66 (44.0%)
Delayed Enrollment into Care	Pati et al., 2011	Mozambique	37,352	—	452 (345–611)	—	—	—	—
	Ingle et al., 2010	South Africa	44,844	29,898 (66.7%)	170 (76–318) 26.0% missing	—	—	—	—
	Kranzer et al., 2010	South Africa	885	622 (70.3%)	—	—	—	>6 months between HIV diagnosis and CD4 testing	331 (37.4%)
	Larson et al., 2010	South Africa	352	235 (66.8%)	184.5 (67.5–353.5)	—	—	>12 weeks between HIV diagnosis and CD4 testing	230 (65.3%)
	Kigozi et al., 2009	Uganda	2,311	1,487 (64.3%)	—	5.1% WHO 4	—	WHO Stage 3 or 4	928 (40.2%)
	Marcellin et al., 2009	Cameroon	3,151	2,239 (71%)	336 (208—448)	—	—	≥6 months between HIV diagnosis and 1st HIV consultation	477 (15%)
Delayed ART Initiation	Bassett et al., 2010	South Africa	1,474	—	159 (65—299)	—	2006–2008	—	—
	Boulle et al., 2010	South Africa	7,323	4,961 (67.7%)	101 (45–164)	35.5% WHO 4	2001–2007	—	—
	Charurat et al., 2010	Nigeria	5,760	3,375 (58.6%)	121 19.6% missing	—	2005–2006	—	—

(Continued on p. 363)

Table 1. *(continued)*

	Author, year	Country	N	Females	Median (IQR) CD4 cell count (cells/μL)[ab]	Proportion with advanced clinical staging (WHO 4 or CDC C)[a]	Year(s) of ART Initiation	Definition[a]	Proportion delayed[a]
Delayed ART Initiation (continued)	De Beaudrap et al., 2010	Senegal	404	221 (54.7%)	128 (54–217) 2.2% missing	55.5% CDC C	1998–2008	—	—
	Ekouevi et al., 2010	Benin, Cote d'Ivoire, Gambia, Mali, Senegal	14,352	8,810 (61.4%)	131 (48–221) 14.8% missing	28.9% CDC C or WHO 3/4	<2004–2008	—	—
	Ford et al., 2010	Lesotho	1,177	801 (66.7%)	212 (120–285) 4.2% missing	—	2008–2009	CD4 ≤200 cells/ μL	538 (45.7%)
	Bassett et al., 2009	South Africa	501	281 (56.0%)	96 (39–158)	—	2006	—	—
	Lahuerta et al, 2012	Mozambique	36,411	22,680 (62.2%)	150 (72–219) 24% missing	13% WHO 4	2005–2009	CD4 <100 cells/μL or WHO Stage 4	14,010 (38%)
	Lahuerta et al., 2011	Mozambique	51,269	32,200 (62.8%)	144 (69–221)	14% WHO 4	2004–2009	—	—
	Lawn et al., 2009	South Africa	2,423	1624 (67.0%)	101 (48–157)	23.0% WHO 4	2002–2007	—	—
	Lowrance et al., 2009	Rwanda	3,194	2071 (64.8%)	141 (80–199.5)	—	2004–2005	—	—
	MacPherson et al., 2009	South Africa	1353	907 (67.0%)	93 (37–148)	—	2005–2007	—	—
	Rougemont et al., 2009	Cameroon	312	198 (63.5%)	104 (50–177) 4·2% missing	14.1% CDC C	2006	—	—
	Sanne et al., 2009	South Africa	7536	5,011 (66.5%)	87 (31–158) 8.5% missing	—	2004–2007	—	—
	Sieleunou et al., 2009	Cameroon	1187	527 (44.4%)	105 (40–173) 10.6% missing	90.4% WHO 3/4	2001–2006	—	—

(Continued on p. 364)

Table 1. *(continued)*

	Author, year	Country	N	Females	Median (IQR) CD4 cell count (cells/μL)[ab]	Proportion with advanced clinical staging (WHO 4 or CDC C)[a]	Year(s) of ART Initiation		Definition[a]	Proportion delayed[a]
Delayed ART Initiation (continued)	Fairall et al., 2008	South Africa	14,267	9,320 (65.3%)	—	3.6% WHO 4	2004–2005		—	—
	Keiser et al., 2008	Cote d'Ivoire, Kenya, Malawi, Rwanda, Senegal, South Africa, Uganda, Zambia	30,056	19,571 (65.1%)	111 (45–184)	56.5% CDC C or WHO 3/4	2001–2006	—		—
	Nash et al., 2011	Total	16,170	10,895 (67.4%)	—	—	2005–2008	—		—
		Ethiopia		—	122.0 (133.5, 125.0)	—	2006–2008	—		—
		Kenya		—	105.0 (102.0, 108.0)	—	2006–2008	—		—
		Lesotho		—	107.5 (105.3, 122.5)	—	2005–2008	—		—
		Mozambique		—	149.5 (140.5, 154.8)	—	2005–2008	—		—
		Nigeria		—	153.0 (130.3, 158)	—	2005–2008	—		—
		Rwanda		—	178.3 (162.4, 195.5)	—	2005–2008	—		—
		South Africa		—	117.5 (116, 118.3)	—	2005–2008	—		—
		Tanzania		—	116.5 (100.0, 125.8)	—	2005–2008	—		—
	Stringer et al., 2006	Zambia	16,198	9,864 (60.9%)	Mean CD4 (SD): 143 (123)	11.6% WHO 4	2004–2005	—		—

[a]CD4+ cell count, WHO/CDC (World Health Organization/Centers for Disease Control and Prevention) Stage, definition, and proportion delayed correspond to the time of diagnosis, enrollment into care, or Antiretroviral Therapy (ART) initiation as specified.
[b]When available, proportion missing a CD4 cell count is also noted.
IQR = Interquartile Range

absorptive capacity reach a steady state equilibrium, an important question is whether the late ART problem will persist and whether there are structural interventions at the population and clinic-levels that could promote the earlier initiation of ART among people with HIV, such that the individual and population-level effectiveness of HIV treatment scale-up can be further optimized.

The consequences of late ART initiation. A recent randomized control trial from Haiti showed a four-fold higher risk among those for whom ART initiation was delayed until after CD4 counts dropped below 200 cells/μL compared with those who started with CD4 counts between 200–350 cells/μL.[35] Late ART initiation translates into substantial early mortality after the initiation of ART. Low CD4 count and advanced stage of disease are the most important predictors of clinical progression and poor survival after ART initiation,[2,17,27,47–52] and these were a factor in nearly all deaths through the first year after ART initiation in one South African study.[2] A large review article of early mortality following ART initiation by Lawn et al.[4] found that 8 to 26% of patients initiating ART died within one year, with most dying in the first few months after ART initiation often with tuberculosis (TB) related complications.[53,54] The range in median CD4 counts at ART initiation across the clinics was 43–147 cells/μL.[4,53,54] Another landmark study compared mortality rates in the two years following ART initiation among people initiating ART in four sub-Saharan African countries to non-HIV-related mortality rates in the general population, observing 20–50 times higher mortality among patients who initiated with CD4 $<$100 cells/μL and WHO stage 4 than in the general population.[5] The authors conclude that much of the excess mortality could be prevented by timely ART initiation. Finally, another study found that 50% of the excess in death rates in the first two years after ART initiation among patients treated in Uganda over those treated in London was due to late ART initiation, even after accounting for serious opportunistic infections.[55]

Patients who initiate ART at low CD4 count remain at risk for opportunistic infections for a substantially longer period than patients starting ART at higher CD4 counts,[53] increasing their risk for serious morbidity and death, with TB being the most common opportunistic illness.[8,53] While information on underlying causes of death among people on ART is lacking in sub-Saharan Africa, one study found 86% of deaths in the first year following ART initiation to be HIV-related (CNS infections, TB, Kaposi's sarcoma, pneumonia, and mitochondrial toxicity), with 7% due to immune reconstitution syndrome.[56]

Early mortality in patients who initiate ART is an extension of very high mortality rates in ART-eligible patients who are enrolled in care but have not initiated ART. Importantly, we note that only a handful of studies, all from South Africa, have reported on patient outcomes prior to ART initiation,[2,11,18,57] all of which found the mortality rates to be very high (e.g., 36 deaths per 100 person-years). In fact, deaths among pre-ART patients accounted for 66% of deaths (Cape Town)[2] and 87% of deaths (Free State)[16] in the entire clinic population. This in turn underscores the need for more research on patients at the time of enrollment and in the care phase prior to ART initiation.

Population-level consequences. Recent clinical trial data (HPTN 052) demonstrated that earlier initiation of ART results in near complete interruption of HIV transmission, with a 96% reduction in HIV transmission in serodiscordant couples.[7] It is estimated

that around two to three new infections occur for every one person placed on ART,[58] and it has long been known that late stage HIV infection is associated with higher rates of HIV transmission due to elevated viral load levels.[59,60] A study with serodiscordant couples from a cohort in Rakai, Uganda, estimated that the probability of HIV transmission during late-stage infection increases by four to eight times during the two years before death.[61,62] Hence, earlier diagnosis, enrollment into HIV care, and more timely ART initiation can prevent onward HIV transmission,[63–66] both by reducing an individual's infectiousness through ART and by promoting safer sexual behaviors.

Pathways to late ART initiation. We have delineated four distinct pathways to ART initiation (Figure 1), and key milestones along these pathways: HIV diagnosis and enrollment into care. Pathways A, B and C all converge on late ART initiation, but through different mechanisms. Pathway D (timely diagnosis → timely enrollment into care → timely ART initiation) is the optimal scenario, with 'timely' meant to imply prior to the onset of advanced stages of HIV disease. While all of these pathways are operating to some degree or another in a given clinic or context, they are very different with respect to their determinants and therefore the types of interventions to be identified and implemented. Further, the relative contribution of each Pathway (A–C) to the overall burden of late ART initiation in sub-Saharan Africa is not well understood.

Late diagnosis of HIV/AIDS (Pathway A). Late diagnosis (defined as low CD4 count or advanced clinical stage [e.g., AIDS-defining illness]) is an extremely common and

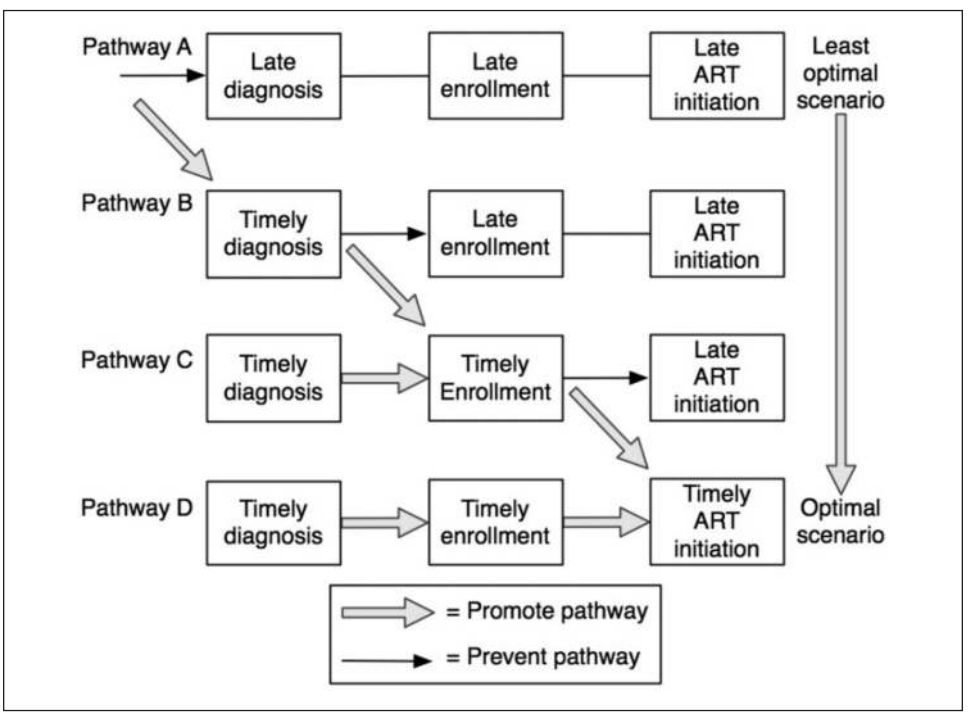

Figure 1. Pathways to and points of intervention to promote timely Antiretroviral Therapy (ART) initiation.

persistent problem in both resource-rich[33,34,40,67–75] and resource-limited settings.[29,38,76–81] In sub-Saharan Africa, HIV testing uptake is variable, but generally low throughout the region; only 4–27% of adults report receiving an HIV test and receiving the results in the past 12 months,[82] despite the increasing availability of testing opportunities and ART. This suggests that late diagnosis is a major contributing factor to late ART initiation in the region. In a study conducted in Nigeria, for example, 50% of HIV-infected individuals had CD4 <200 cells/μL at HIV diagnosis.[81] Similarly, in a peri-urban community near Cape Town, South Africa, 36% of HIV-infected individuals had CD4 <200 cells/μL and 31% presented HIV-related symptoms (WHO stage 3/4) at the time of diagnosis.[83] Furthermore, and despite the increase in the annual population HIV testing rates in this community from 4% in 2001 to 20% in 2006, the proportion that was diagnosed late did not change with time. While many studies in sub-Saharan Africa have described CD4 count and stage *at ART initiation*, the scarcity of data on CD4 count and stage *at diagnosis* makes it difficult to quantify the contribution of late diagnosis to the problem of late ART initiation relative to the other pathways in Figure 1. However, these data suggest that late diagnosis is a major contributor to late ART initiation in the sub-Saharan African region.

Late enrollment in care (Pathway B). Little is known about the factors associated with delayed or late enrollment in HIV care among diagnosed HIV-positive people. In a study evaluating linkages to care in Cape Town, South Africa, 63% of individuals had a CD4 cell count measurement indicative of care linkage within six months of testing HIV positive, with those testing at sexually transmitted infection services having the highest likelihood (84%) and those testing in VCT services having the lowest likelihood (54%) of linkage to HIV care.[20] An analysis of a national cross-sectional cohort of Cameroonian HIV-positive adults (ANRS-EVAL study) observed that 30% of participants reported delays of three months and 15% waited more than six months before enrolling in care.[84] A Ugandan study of newly diagnosed HIV-positive adults who enrolled in HIV care found that 40% had advanced AIDS-defining disease (WHO Stage 3 or 4).[79] Finally, a recent case-control study in Ethiopia observed that HIV-positive adults who lived with their families, lived in a rented house, perceived many ART side effects or HIV-related stigma, tested with sickness/symptoms, did not disclose their HIV status to their partner, or had frequent alcohol use were more likely to enroll in care late.[85]

Late ART initiation despite early enrollment into care (Pathway C). Although late ART initiation remains a pervasive problem in sub-Saharan Africa, there are very few published data on outcomes following early enrollment into care. Perhaps one of the most important reasons why some people may initiate ART late, despite having enrolled into HIV care early, is the prioritization of sicker patients for ART initiation, and that clinics are often overburdened and lack the absorptive capacity to treat anyone but the sickest of the sick.[86,87] While this phenomenon may improve with time as the sickest patients are treated, as ART coverage increases, and as HIV services are decentralized to primary health centers, it may also persist if the sickest patients cannot be treated quickly enough.

Despite the limited data available, death prior to ART initiation remains a major concern.[4,11,88] Poor retention,[11,89,90] waiting lists,[91,92] lengthy or onerous ART eligibility procedures,[11] lack of integrated TB diagnosis and disease management,[93] ARV

stock-outs,[39] and inadequate immunologic and clinical monitoring[11] have all been documented and are potentially important contributing factors to late ART initiation. However, the degree to which each of these factors may contribute to the overall burden of late ART initiation at the individual or clinic-levels, and the extent to which they can be addressed, has not been described.

A large proportion of patients enrolled in HIV care in sub-Saharan Africa (perhaps 40–50%[10,21,94]) have not been determined to be ART-eligible and have not yet initiated ART; among these individuals, even less is known about the magnitude and determinants of non-retention in care and regular clinical and immunological monitoring to help ensure timely ART initiation and OI prophylaxis. A systematic review of pre-ART retention in care in Africa suggests that less than one-third of patients testing positive for HIV and not yet eligible for ART when diagnosed are retained continuously in care.[95] Among HIV-infected individuals not yet eligible for ART in a rural area of South Africa, overall retention was only 45% and younger patients and those at earlier stages of the infection had lower odds of being retained, increasing the likelihood that these patients will only return for treatment once they develop clinical symptoms, a sign of advanced HIV disease.[57] The WHO-recommended expansion of ART eligibility guidelines in resource-limited settings further highlighted the problem of retention because newly eligible patients could not be located.[96] Indeed, the fact that most published studies on outcomes in HIV care programs have focused primarily on outcomes after ART initiation makes it difficult to infer or draw conclusions about outcomes prior to ART initiation.[42]

In summary, for each of the pathways to late ART initiation there are likely structural and systemic solutions to some of the problems mentioned above that could increase the likelihood of earlier ART initiation among the patient population at many clinics, as well as that of future patients in their catchment areas. There is great concern regarding the diminishing proportion of people who test HIV positive that are retained along the cascade from HIV diagnosis to ART treatment initiation.[95] Box 1 summarizes several potentially promising strategies that could reduce the problem of late ART initiation at different milestones. In the next section, we provide a conceptual framework for and review the literature on the determinants of late ART initiation.

Conceptual framework for determinants of late ART initiation. The determinants of late ART initiation likely operate at multiple levels. To help delineate these determinants we have developed a conceptual framework for late ART initiation (Figure 2) drawing upon the Behavioral Model of Health Services Use,[97–99] which has been used extensively and adapted to understand the factors that predict use (or non-use) of medical care services.[100,101] Elements of this model include predisposing factors, described as pre-existing characteristics of individuals such as age and gender; enabling factors, which can include health system factors (e.g., cost of care), as well as individual, family and community resources that support or constrain use of care; and need for care, described as the individual's perception of need. The framework includes factors measured at the contextual (nationwide or sub-national), clinic, and individual levels, which are hypothesized to influence late ART initiation and the relative timing of one or more of the upstream milestones on the pathway to late ART initiation—diagnosis and enrollment into HIV care.

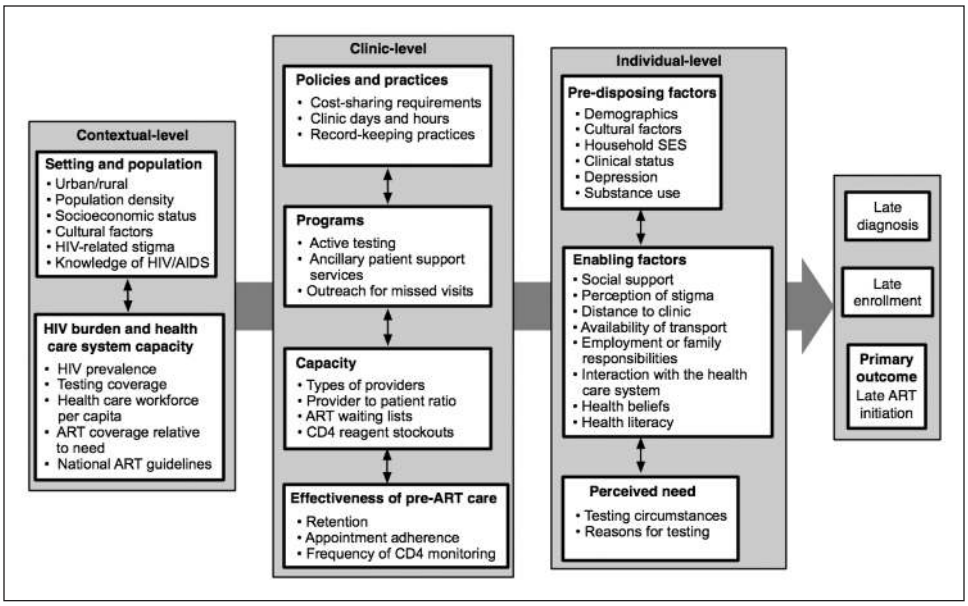

Figure 2. Multi-level factors associated with late HIV diagnosis, late enrollment into care, and late Antiretroviral Therapy (ART) initiation.

Contextual-level factors. Contextual factors include characteristics of the setting and population where the HIV epidemic is occurring (e.g., urban/rural, population density, socioeconomic status, levels of stigma and HIV knowledge), as well as, indicators of HIV burden and health care system capacity (e.g., HIV prevalence, percent of population tested for HIV, health care workforce *per capita*, ART coverage relative to need, and national treatment guidelines).

Characteristics of the setting and general population. HIV-related stigma, routinely measured as part of Demographic and Health Surveys (DHS) in sub-Saharan Africa,[82] continues to be pervasive. Anticipated stigma from the community or perceived discrimination in the health care system is likely to inhibit care-seeking,[102,103] but only a few studies in sub-Saharan Africa have focused on how stigma influences the decision to seek testing or medical care.[39,104] Qualitative studies in Tanzania, Ethiopia, and Zambia found that perceived stigma was a barrier to seeking treatment for infections closely associated with HIV,[105,106] and in Botswana, stigma was associated with ART adherence difficulties.[107] A qualitative study in Uganda observed that perceived stigma and misconceptions about ARVs contributed to delays in ART initiation,[39] however, whether and to what extent population-level stigma influences HIV-related health-seeking behaviors among HIV positive people (e.g., testing, enrollment, and ART initiation) has not been extensively examined in sub-Saharan Africa.

The type of community (urban *vs*. rural) can also be a factor, since differences exist in community characteristics in terms of density of population, distance to and availability of clinics and hospitals and infrastructure within clinics (e.g., availability of CD4 testing).[22,28] A study by Ingle et al. in South Africa observed that patients in rural

clinics had lower rates of starting ART treatment and higher mortality than patients in urban/peri-urban clinics,[18] but more studies evaluating this association in different contexts are needed. DHS data,[82,108] as a source of contextual information, linked with contemporaneous routinely collected HIV program outcome data[110] may be particularly useful to this end. For example, one recent study found that higher levels of HIV testing coverage and AIDS knowledge were associated with a lower likelihood of late ART initiation among populations of people initiating ART.[28]

National HIV burden and health care system capacity. The health care worker shortage in the sub-Saharan African region is well-documented,[109,110]and concerns about meeting the demands of scale-up have been raised.[111] The capacity of the health care system to respond to the burden of HIV in a community, district or catchment area are also likely to have important influences on the timing at which individuals reach each of the key milestones in pathways to ART initiation (Figure 1). In one large study, provider to patient ratio was associated with a lower median CD4 count among cohorts of patients initiating ART in 8 sub-Saharan African countries.[28] In a cohort of HIV-infected children in South Africa, insufficient human resources in the clinics was noted as the second most common reason for delays in ART initiation.[103] Finally, national HIV care and treatment guidelines that specify the CD4 count and clinical stage at which patients are considered eligible for ART vary somewhat from country to country and likely influence the timing of ART initiation among populations of individuals enrolled in care.

Clinic-level factors. Clinic factors including clinic policies and practices, programs (e.g., ancillary services), capacity, and pre-ART care effectiveness likely have a direct impact on each of the milestones on the pathway to late ART initiation. There may be strategies that clinics can adopt to promote timely ART initiation among their existing and future patients, some of which could represent effective and scalable intervention strategies.[28,72]

Clinic policies and practices. Clinical policies, such as the number of clinic days and clinic hours, have not been examined in detail but substantial variability exists and it is possible that limited clinic days and hours could hinder enrollment, retention, and appointment adherence for some patients.[68,111] Certain record-keeping practices, such as keeping appointment books and attendance registers, are associated with improved appointment adherence and more timely outreach for patients who miss visits.[28,112]

Costs of care attendance. It has been shown that those receiving ART in clinics providing it free of charge have significantly lower mortality than patients from clinics where a fee is charged,[6] although others have shown that free care is not enough, especially for vulnerable populations.[113] Cost of transportation to the clinic can also pose substantial practical barriers to keeping clinic appointments, especially since it is a recurrent cost.[114] Furthermore, to avoid being seen by neighbors or recognized by clinic staff, some patients may enroll in care at a clinic farther from their home,[115,116] exacerbating the problem of transport.

Programmatic approaches. Programmatic approaches used by clinics—including active testing and the provision of ancillary patient support services such as adherence support, peer education, and outreach for patients who miss clinic visits—may have direct effects on patient behaviors and are feasible to implement and sustain in sub-

Saharan Africa, as they are already being widely implemented in sub-Saharan African settings.[28] Outreach programs have proven to be effective at returning patients who were lost to follow-up to care in several studies, and could therefore have a positive effect in reducing the proportion initiating ART late.[117–120] Cohorts of patients initiating ART at clinics that provide care adherence support services targeted at pre-ART patients have been shown to be less likely to have low median CD4 count at ART initiation.[28]

Clinic capacity and effectiveness of pre-ART clinical care. The type and number of staff providing HIV care (e.g., physicians, nurses, clinical officers) and the provider-to-patient ratio are also potentially important clinic-level factors. For example, in a study conducted in South Africa, patients at clinics with a lower staff-to-patient ratios had lower rates of starting ART treatment than those with higher staff-to-patient ratios.[18] Another study of cohorts of patients initiating ART in eight sub-Saharan African countries found lower provider to patient ratio to be associated with a lower median cohort CD4 count at ART initiaton.[28] Similarly, heavy workloads and long waiting times at the clinic could also impact the care received by pre-ART patients and reduce the frequency of visits, which would consequently affect the determination of ART eligibility, as well as retention in pre-ART care. In fact, waiting times have been reported in several studies as one of the major challenges that patients face for appointment adherence.[114,121,122]

Individual-level factors. Individual factors, beyond clinical parameters, may have a major impact on timely ART initiation. We have grouped these into predisposing factors, enablers/barriers, and perceived need among HIV infected people.

Predisposing factors. Pre-existing characteristics of individuals such as demographics, socioeconomic status, mental disorders or substance abuse might also affect the timing of each milestone along the path to ART initiation. For example, on average, women initiate ART at an earlier stage of HIV disease than men.[27,123] The reasons likely include that women have more regular contact with the health care system and associated opportunities for HIV testing, especially *via* antenatal care, or holding different health-related beliefs. Additionally, both individual and household socioeconomic status may predispose individuals to delay care-seeking or to default from care, most notably through the competing demands and opportunity costs of care. In a study conducted in Uganda, financial constraints were found to be a reason for delay in ART initiation.[124] Competing work- or home-life demands (such as the inability to take time off from work or leave a child or elderly person at home) would likely also play a role in delaying care. In a study looking at loss to follow-up among pre-ART patients in South Africa, patients who were unemployed were nearly twice as likely to be lost from care before ART initiation as those employed.[11] Finally, in areas with highly mobile populations, relocation was also reported as a reason for non-retention.[125]

Enablers/barriers. These include parts of an individual's health-related knowledge/beliefs, social environment as well as characteristics of the health care system—as perceived by or engaged with by the patient—that could support or hinder timely care-seeking.

Treatment-related knowledge. Individuals with higher levels of HIV-related "health literacy," or knowledge concerning HIV disease (the importance of CD4 monitoring and ART regimens) may be less likely to initiate ART late and this can be influenced by clinic level factors such as peer education programs.[126]

Health beliefs, norms, and self-efficacy related to care-seeking. As health beliefs have been shown to be important predictors of ART adherence,[127–129] they may also be associated with timely enrollment and retention in care. Given the gender differences in late ART initiation that have been observed in sub-Saharan Africa,[27,123] and gender differences in internalized HIV-related stigma,[130] there is a need to enhance our understanding of gender-related beliefs around care-seeking for HIV symptoms.

Characteristics of the social environment. Well documented in the literature is that family and social support are associated with better psychological adjustment, medication adherence, and slower progression to AIDS.[131–134] In particular, social network members may facilitate behavioral change by transmitting beliefs and motivations concerning treatment to the patient.[136] Network support may also result in increased logistical support and/or an emboldened sense of moral support.[136,137] Social support may be particularly relevant to timely ART initiation because policies in many sub-Saharan countries require a patient to have someone who might be called a *treatment supporter* before being initiated on ART. Therefore, individuals with limited networks, or those who are unwilling or unable to disclose, may delay enrolling in or may drop out of care. Anticipated stigma appears to be a barrier to HIV testing [138–139] and may also be a barrier to enrolling in care once tested, and experienced stigma might be related to dropping out of care.

Perceived need. An individual's perception of need is an important determinant of their decision to use care. It is likely that people seek testing because they believe they may be infected and those who are also symptomatic will be more likely to enroll promptly in care. One South African study showed that being referred for testing by a provider was associated with a lower likelihood of linking to long-term HIV care compared with patients who made their own decision to test.[140]

Conclusions

In summary, the published literature points squarely to late ART initiation as a major contributor to the problem of early mortality and morbidity following ART initiation in sub-Saharan Africa, which threatens to substantially limit the effectiveness of HIV care and treatment scale-up in the region, including its direct effect on individuals with HIV[35] and its indirect effect on HIV incidence.[7] The considerable variability in late ART initiation across clinics and settings[8,28] and its persistence over time points to the complex and multi-level nature of the problem. While several studies from sub-Saharan Africa have documented low median CD4 count at ART initiation, surprisingly little is known about the multi-level (i.e., individual, clinic, and contextual) determinants of late ART initiation.[28] Importantly, very few studies have examined factors relevant to important and distinct upstream milestones along the pathway to ART initiation—HIV diagnosis and enrollment into HIV care. Although many different strategies to reduce late ART initiation are being utilized across sites and settings in sub-Saharan Africa, more evidence is needed on their relative effectiveness and cost-effectiveness. In particular, more research is needed to identify the structural determinants that may be amenable to intervention. Future research should focus on strategies to diagnose, engage, retain, and monitor current and future patients, and this will likely only be

accomplished through structural interventions at the societal, policy, and clinic-levels. Some strategies to consider that could potentially contribute to reducing late ART initiation in sub-Saharan Africa are listed in Box 1.

In the U.S.[142] and in New York City,[143] the epicenter for HIV in the U.S., HIV treatment has been widely available for more than 15 years. Yet, approximately 26% of people diagnosed with HIV have concomitant diagnosis of AIDS at the time of HIV diagnosis, and delayed access to HIV care after HIV diagnosis is common.[144–147] For example, a recent study in NYC showed that nearly 20% of newly diagnosed individuals had not yet enrolled in HIV care one year later,[148] and this figure may be as high as 30%–40%

Box 1.

STRATEGIES THAT COULD POTENTIALLY CONTRIBUTE TO REDUCING LATE ART INITIATION IN SUB-SAHARAN AFRICA

Promote early HIV diagnosis	Expand provider-initiated counseling and testing
	Offer mobile, home-based or work-based services for HIV counseling and testing
	Implement partner-testing services as well as active-testing approaches
	Increase HIV/AIDS knowledge to reduce community stigma
	Advertise ART availability to contribute to further expansion of testing
Improve linkage to care for timely enrollment into care	Optimize and simplify the referral process across services (e.g., reduce the number of return visits newly-diagnosed people need to make before becoming enrolled in a care and treatment site)
	Provide peer supporters to escort and provide emotional support to newly-diagnosed individuals through the linkage-to-care process.
	Use SMS or other reminder systems to follow-up individuals who test positive but are not known to have not enrolled in HIV care within 30 days
	Implement information systems to be able to track patients across sites
Reduce late Antiretroviral Therapy (ART) initiation	Implement point-of-care CD4 testing to allow for faster determination of ART eligibility
	Increase retention of pre-ART patients by improving support services such as peer educator programs, nutritional support, and transport assistance
	Shorten programmatic delay from CD4 testing to ART initiation (e.g., by streamlining clinical and non-clinical aspects of the eligibility determination process)

(Continued on p. 374)

Box 1. ***(continued)***

Operations research	Use a systematic approach to track and detect bottlenecks in the HIV care process from HIV diagnosis to treatment and follow-up
	Investigate upstream determinants beyond the individual-level.
	Capitalize on significant existing aggregate-level data collected as part of routinely service delivery or ministry/donor reporting as well as DHS data to generate hypotheses regarding the association between promising program and contextual level factors and early diagnosis, enrollment into care and ART initiation.
	Collect data to examine the influence of promising clinic/program-level factors that are already being used or will soon be rolled out by many clinics (e.g., outreach or point of care CD4 testing) to assess their relationship to the outcomes of CD4 at enrollment to care and CD4 count at ART initiation at the individual and aggregate levels.

SMS = Short Message Service, text message
DHS = Demographic and Health Survey
HIV = Human Immunodeficiency Virus
ART = Antiretroviral Therapy

nationwide.[70,144,149] Thus, in sub-Saharan Africa, a major concern is that the problem of late ART initiation will reach a sub-optimal steady state similar to the United States, where, despite substantial investment and near universal availability of HIV-related services, an unprecedented number of people living with HIV (including undiagnosed HIV[150]) and several important service and programmatic gaps[151] continue to drive HIV incidence, and HIV-related morbidity and mortality at the population-level.[152,153,154] Given that millions of Africans will be initiating ART in the coming decade, the number of lives potentially saved, directly and indirectly, by reducing late ART initiation would be substantial over the long term.[155] Very recent data indicating that Rwanda has the second highest mean CD4 count at ART initiation in the world (after the U.S.) are very encouraging and provide hope for the entire region.[156] However, the threat of decreased international commitment to HIV/AIDS in sub-Saharan Africa associated with the global financial crisis, combined with persistently low testing coverage, low rates of linkage to care after HIV diagnosis, and poor retention in HIV care after enrollment and ART initiation all have the potential to perpetuate the problem of late ART initiation, and severely limit the full future potential of HIV scale-up in the region.

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