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Retention in Care among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions

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Abstract In resource-limited settings—where a massive scale up of HIV services has occurred in the last 5 years—both understanding the extent of and improving retention in care presents special challenges. First, retention in care within the decentralizing network of services is likely higher than existing estimates that account only for retention in clinic, and therefore antiretroviral therapy services may be more effective than currently believed. Second, both magnitude and determinants of patient retention vary substantially and therefore encouraging the conduct of locally relevant epidemiology is needed to inform programmatic decisions. Third, socio-structural factors such as program characteristics, transportation, poverty, work/child care responsibilities, and social relations are the major determinants of retention in care, and therefore interventions to improve retention in care should focus on implementation strategies. Research to assess and improve retention in care for HIV-infected patients can be strengthened by incorporating novel methods such as sampling-based approaches and a causal analytic framework.

Keywords HIV care and treatment · Retention in care · Resource-limited settings · Loss to follow-up · Access to care

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Introduction

Retention in care is required for optimal clinical outcomes in patients with HIV infection. Among patients who have not initiated antiretroviral therapy (ART), retention in care allows provision of prophylactic medications for opportunistic infections, ongoing staging, prevention of mother-to-child transmission (pMTCT), and prompt initiation of ART once indications arise. For patients on ART, retention in care is necessary to ensure ongoing receipt of ART, evaluate the emergence of medication toxicities, and identify the occurrence of treatment failure when it occurs in order to switch regimens. Finally, retention in care for all patients provides additional benefits through ancillary services, social support, and secondary prevention messages that can help patients navigate a lifelong and complicated infection [1].

The vast majority of the world's 33 million HIV-infected patients—including the over 4 million on ART already—reside in resource-limited settings (RLS) such as sub-Saharan Africa, Asia, and parts of South America where retention in care potentially takes on an even more important role than in industrialized settings. For patients who have tested HIV-positive but who do not yet have indications for ART, poor retention prevents ongoing immunologic and clinical evaluation. This increases the risk of late presentation when opportunistic infections such as tuberculosis and cryptococcosis are already in motion—conditions with particularly high mortality in RLS [2, 3]. In addition, provision of co-trimoxazole prophylaxis also has significant benefits for HIV-infected patients with CD4 counts above the threshold for ART [4]. For patients who have started ART, failures of retention are often tantamount to medication cessation. Once interrupted, the effects of ART are rapidly reversed

and additional harms can accrue through the emergence of drug resistance mutations [5] that limit future drug options and increase mortality [6]. Furthermore, ongoing clinical visits are needed to identify toxicities in order to substitute single offending drugs as well as diagnose treatment failure in order to switch to second-line regimens when indicated. Finally, because medication adherence is relatively in sub-Saharan Africa among patients in care [7, 8], the importance of retention in care may comprise the most important factor in the overall effectiveness of ART programs there.

To date, most studies, including a recent review [9], describing the magnitude and determinants of retention in care for HIV-infected patients have been in industrialized settings. In this article, we focus on the rapidly growing literature from RLS for adult patients and 1) summarize definitions and terminology regarding retention in care; 2) critically review the literature on the extent of retention in care; 3) evaluate determinants of, and strategies to improve, retention in care; and 4) highlight methodological issues that can help to advance the study of retention in care in RLS.

Defining Retention in Care

Reviewing the literature on retention in care begins with summarizing commonly used, yet heterogeneous definitions of the term. Working in the North American HIV epidemic, Messeri et al. proposed that "'Retention in care' implies remaining connected to medical care, once entered" [1]. In RLS, retained patients have been defined as "patients known to be alive and receiving highly active ART at the end of a follow-up period" [10••]. Other authors proposed retention in care to mean "patients alive and on ART at the same facility or those formally transferred out to another ART unit and thus assumed to be on therapy" [11, 12]. Operationally, in industrialized settings, visit frequency has often been used as a measure of retention [13]. In RLS, retention is usually defined as ending at some interval of time after a scheduled appointment. The actual interval, however, is not clearly established and has been set as 14 days [14], 30 days [15], 90 days [16], 6 months [17••], or 1 year [18]. Finally, since ART patients are expected to come to clinic more frequently (eg, monthly) than patients who have not yet initiated ART (eg, semiannual), the optimal interval for the definition may differ for each type of patient.

Existing definitions of retention in care, however, contain several limitations that must first be discussed in order to frame the following review of retention in care. First, most studies focus on patients already on ART, but the public health benefits of continuous and appropriate care begin for HIV-infected patients even before eligibility for ART. Second, retention in care is usually defined from the perspective of the clinic rather than the patient. During scale up and decentralization of HIV care in RLS, patients inevitably access care within a rapidly widening network of sites, many which may be increasingly closer to their residences [19]. Estimates of retention defined by continued presence at a specific clinic are tantamount to *retention in clinic* rather than *retention in care,* and these two metrics will likely differ in both magnitude and significance. Third, the definition of retention in care is often predicated on "known outcomes." In this case, the mechanisms in place to know about outcomes (such as passive vs active tracing, death registries, etc.) can artificially influence estimates of retention in care. For the purposes of this review, therefore, we will consider all patients who have registered at an HIV clinic regardless of ART status to be the population of interest, highlight estimates of patient retention (as opposed to clinic retention) by emphasizing "tracing" studies that seek outcomes among patients lost to follow-up, and remark on the methods of outcome ascertainment whenever possible.

How Good is Retention in Care among HIV-Infected Patients in RLS?

Patients Who Have Initiated ART

A large systematic review in 2007 that surveyed 32 publications on 33 cohorts in 13 countries and contained information on 74,289 patients raised an early alarm about poor retention in care among HIV-infected patients on ART in Africa. Using weighted averages and considering deaths as not-retained, the authors contend that a plausible mid-point estimate of retention 2 years after ART initiation was only 50%, with best and worst case scenarios of 77% and 24% [10••]. The analysis was updated in 2010, and it was found using an additional 39 cohorts and 226,307 patients that the 24-month retention rate was 70.0% and 36-month estimate was 64.8% [20••]. Overall, these studies paint a rather dismal picture of retention in care and led some commentators to call into question the effectiveness of ART programs in RLS [21].

Methodological issues, however, influence our interpretation of these studies and assessment of the magnitude of retention in care. These reports have been conducted from the perspective of clinics and have assumed that patients who are lost to follow-up (ie, who have unknown outcomes) are no longer engaged in care. As discussed above, in the setting of rapid ART scale-up and decentralization of care, this assumption may not always be true. Indeed by design in most countries, ART delivery started in urban

hospital-based referral centers and then later extended to lower-level health centers and rural sites [19, 22]. Some fraction of patients initially accessing care at the centralized sites can be expected to shift in this process. Given the speed and scope of the scale-up in settings without pre-existing integrated medical records, complete capture of patient movement cannot be expected. Therefore, existing estimates of retention in care must be interpreted in light of the specific contexts, definitions, and methods of ascertaining outcomes in order to best understand their implications.

"Tracing" studies that evaluate outcomes among lost patients in the community provide insight into retention in care by documenting patient movement across clinic sites. In many instances, patients who are lost to follow-up continue to receive care at other, more local facilities (Table 1). In rural Uganda, 61%–80% of 111 patients lost between 2004 and 2007 and found alive were in care elsewhere (as defined by both seeing an HIV provider and continuing to obtain ART) [23]. In Kampala, Uganda, investigators found that 50% of patients lost from the Infectious Diseases Institute, a large central clinic, were in care elsewhere [18]. In the Lighthouse clinic in Malawi, among 2253 patients who missed at least one clinic visit by 3 weeks, 1580 (70%) were found to be alive and 55% were still in care and on ART [24]. In Johannesburg, one group noted that 41% of 90 lost patients who were found to be alive were in care elsewhere [25], while a second group found 66% of 260 traced patients who were alive to be in care elsewhere [26]. The fraction of living patients lost from one clinic who remain in care, however, is heterogeneous: a figure of 20% was reported from Ethiopia [27], 20% from an earlier study in Johannesburg, and in Botswana 87% of 46 lost patients were dead, leaving very few who could be retained in care [15]. Overall, however, among 14 studies where outcomes in some patients lost to clinic were reported, a crude unweighted median of 48.5% were in care elsewhere. This suggests that retention in care is on average substantially higher than retention in clinic.

Studies that reveal retention at central, large, hospital-based sites to be worse than at peripheral health centers also provide indirect evidence that apparent retention in care is susceptible to influence from the process of decentralization. In a Medecins Sans Frontieres program in rural Lusikisiki, South Africa, the rate of loss at more peripheral decentralized sites was 2.2% (95% CI: =1.2%–3.7%) versus 19.3% (95% CI=15.7%–23.4%) at the central site [19]. In Malawi, loss from a hospital "hub" was fourfold greater than at the health center "spoke," with an absolute difference of 77% [11]. In the district of Zomba, Malawi, retention was approximately 90% at the decentralized sites and 77% at the hospital site by 3 years [22]. Finally, in a meta-analysis that included 13 cohorts from Africa and Asia, the fraction of patients lost to follow-up correlated to the size of the program [28]. Although these data are consistent with the hypothesis that poorer retention at large, central sites is due in part to decentralization, further confirmation of this hypothesis is an important research priority. Finally, although silent transfers appear to be retained, critical evaluation of the frequency of treatment gaps during this process is also an important operational research question.

Retention in Care for Pre-ART Patients

For patients not yet starting ART, we consider retention to be an issue after registration at an HIV clinic. The fraction of patients who enrolled and who obtained staging through CD4 determination was assessed in two cities in Mozambique during the first 12 months of free ART availability in 2005. The investigators found that 77.1% of those enrolling had a CD4 determination—routine staging mechanism in this setting—within 30 days. Overall, 43% of patients testing positive completed enrollment and staging within 60 days [29]. This study was unique in that only one site in each city provided free CD4 testing and ART; therefore, the fractions reported are likely unbiased by incomplete capture of the outcomes.

Retention for patients without indications for ART appears to be particularly challenging. In a 2005 study among 3370 HIV-infected patients in KwaZulu-Natal in South Africa, only 49.4% of individuals with an initial CD4 cell count >200/cm^3 returned for a subsequent CD4 measurement within the next 13 months [30]. In Witwatersrand, South Africa, investigators found that 75 of 128 (59%) patients who had initial CD4 counts from 251–350 did not return by 1 year and that 169 of 228 (74%) patients with a CD4 >351 did not return by 1 year [31]. In a study in Zambia among 1343 patients who missed a visit, only 11% of the non-ART patients returned whereas 39% of the patients on ART returned [32]. Finally, in western Kenya, patients in the clinic who had a CD4 >200/cm^3 were 3.5-fold more likely to never make a second visit than patients with lower CD4 counts [33]. In Chiradzulu, Malawi, over 3 years 52.5% of pre-ART patients—not distinguished by ART eligibility criteria—failed to be retained compared to 16.1% of patients who had initiated ART [34•]. These estimates, however, do not distinguish retention in program and retention in care. Therefore, the actual estimates provided here can be interpreted as the worst case scenarios.

Among patients with an indication for ART—the subgroup of patients not on ART at highest risk for death—retention has also been found to be suboptimal. Among 2483 patients with CD4-based indications for ART in Jinja (a semi-rural area in Eastern Uganda), 88%

Table 1 Vital status and HIV care status of patients lost to follow-up from HIV care and treatment clinics in resource-limited settings

Study	Setting and patients	Study period	ART status	Patients in the clinic population under consideration, total *n*	Definition of loss to follow-up	Patients lost to follow-up, *n (%)*	Tracing attempted, *n (%)*	Median time (IQR) in months between last visit and tracing
Published articles								
Maskew et al. [42], 2007	Themba Lethu Clinic in Johannesburg, South Africa (urban)	2005	On ART	nr[b]	Missed a single clinic visit during a 2-month interval	154	154 (100)	nr
Yu et al. [37•], 2007	Four public-sector ART facilities in northern Malawi, including one central hospital and three peripheral hospitals	2004–2006	On ART	5009	3 months of absence from clinic	253 (5)	253 (100)	6.4 (IQR nr)
Dalal et al. [25•], 2008	The Johannesburg Hospital adult HIV clinic, Johannesburg, South Africa (urban)	2004–2005	On ART	1631	Missing a scheduled appointment for 6 weeks	267 (16)	267(100)	nr
Krebs et al. [32], 2008	Lusaka ART program, Zambia (urban and rural)	2005	49% on ART, 51% no ART	nr	Missed visit	1343	1343 (100)	nr
Bisson et al. [15], 2008	The Infectious Disease Care Clinics in Gaborone, Botswana (urban)	2003	On ART	410	30 days late for scheduled visit	68 (17)	68 (100)	nr
Deribe et al. [27], 2008	Jimma University Specialized Hospital in semi-rural Jimma zone, Ethiopia (urban and rural)	2003	On ART	1270	Missed 2 or more monthly scheduled clinic appointments	173 (14)	173 (100)	nr
Amuron et al. [35••], 2009	The AIDS Support Organizaiton (TASO) centers in the semi-rural southeastern district of Jinja, Uganda (semi-urban)	2004–2006	Pre-ART	2483	Failure to complete 3 pre-ART visits	637 (26)	637 (100)	11.5 (6.0–17.0)
Bassett et al. [16], 2009	Sinikithemba HIV Clinic at McCord Hospital in Durban, South Africa (urban)	2006	Pre-ART	501	Failure to complete 3 pre-ART visits or initiate ART	82 (16)	82 (100)	nr
Geng et al. [23], 2010	Immune Suppression Syndrome Clinic in Mbarara, Uganda (semi-rural)	2004–2007	On ART	3628	6 months absent for a visit	829 (23)	128 (15)	11.6 (9.4–14.3)
Tweya et al. [24], 2010	Lighthouse Clinic, Lilongwe and Martin Preuss Center in Milawi (urban and semi-rural)	2006–2009	On ART	13,981	3 weeks late for a visit	3098 (22)	3098 (100)	nr
McGuire et al. [34•], 2010	MSF, Chiradzulu, Malawi (rural)	2004–2007	On ART	11,683	1 month late for appointment	1261 (11)	656 (52)	23.2 (14.4–35.1)
McGuire et al. [34•], 2010	MSF, Chiradzulu, Malawi (rural)	2004–2007	Pre-ART	7943	1 month late for appointment	1747 (22)	981 (56)	18.9 (14.1–26.8)
Rosen and Ketlhapile [26], 2010	Themba Lethu Clinic in Johannesburg, South Africa (urban)	2008	On ART	nr	3 months late for appointment	869	493 (57) (random sample)	nr
Abstracts								
Ive et al. [54], 2005	Themba Lethu Clinic, Johanesburg, South Africa	2004–2005	On ART	2400	nr	nr	74	nr
Hochgesang et al. [14], 2006	Lighthouse Clinic, Lilongwe, Malawi	2004–2005	On ART	3840	2 weeks late for an appointment	1843 (48)	727 (39)	nr
Dehab et al. [55], 2008	Public sector HIV ART program in South Africa	nr	On ART	267	1 month late for the 6 month appointment	44	44 (100)	nr
Dehab et al. [55], 2008	Workplace ART program in South Africa	nr	On ART	146	1 month late for the 6 month appointment	53	53	nr
Lurton et al. [69], 2008	Community ART scale-up in Segou, Mali (rural)	2003–2007	On ART	1568	3 months late for appointment	236 (15)	71 (30)	nr

Table 1 (continued)

Study	Setting and patients	Study period	ART status	Patients in the clinic population under consideration, total *n*	Definition of loss to follow-up	Patients lost to follow-up, *n (%)*	Tracing attempted, *n (%)*	Median time (IQR) in months between last visit and tracing
Joshi et al. [40], 2008	Referral Hospital, Jodhpur, India (rural)	nr	On ART	1911	3 months late for appointment	152 (8)	152 (100)	nr
Muwanga et al. [18], 2008	Infectious Diseases Institute, Kampala, Uganda	2004–2007	On ART	6654	3 months late for appointment	831 (12)	831 (100)	nr

Study	*N* (%) of traced in whom no further information obtained (ie, unsuccessfully traced)	*N* (%) of traced with ascertained outcomes (ie, successfully traced)	Patients successfully traced found to have died, *n* (%)	Patients successfully traced found alive, *n* (%)	Living patients not in care elsewhere, *n* (%)	Living patients in care elsewhere, *n* (%)	Living patients whose current care status is unknown or not reported[a], *n* (%)
Published articles							
Maskew et al. [42], 2007	84 (55)	70 (45)	19 (27)	51 (70)	41 (80)	10 (20)	0 (0)
Yu et al. [37•], 2007	68 (27)	185 (73)	127 (67)	58 (23)	37 (64)	21 (36)	0 (0)
Dalal et al. [25•], 2008	94 (35)	173 (65)	83 (48)	90 (52)	34 (38)	42 (47)[c]	14 (16)
Krebs et al. [32], 2008	554 (41)	789 (59)	359 (46)	430 (54)	nr	nr	nr
Bisson et al. [15], 2008	22 (32)	46 (68)	40 (87)	6 (13)	nr	nr	nr
Deribe et al. [27], 2008	65 (37)	108 (67)	29 (27)	79 (83)	59 (75)	20 (25)	0 (0)
Amuron et al. [35••], 2009	109 (17)	528 (83)	181(34)	347 (66)	158 (46)	189 (54)	0 (0)
Bassett et al. [16], 2009	32 (39)	50 (61)	28 (56)	22 (44)	4 (18)	15 (68)	3 (14)
Geng et al. [23], 2010	17 (13)	111 (87)	32 (29)	79 (79)	8 (10)	48 (51)	31 (39)[d]
Tweya et al. [24], 2010	845 (27)	2253 (73)	673 (30)	1580 (70)	909 (58)[e]	671 (38)	nr
McGuire et al. [34•], 2010	205 (31)	451 (69)	244 (54)	207 (44)	nr	nr	nr
McGuire et al. [34•], 2010	287 (29)	694 (71)	343 (71)	351 (51)	nr	nr	nr
Rosen and Ketlhapile [26], 2010	233 (47)	260 (53)	55 (21)	205 (79)	70 (34)	135 (66)[e]	0 (0)
Abstracts							
Ive et al. [54], 2005	26 (35)	48 (65)	26 (54)	22 (46)	nr	nr	nr
Hochgesang et al. [14], 2006	189 (26)	538 (74)	218 (41)	320 (59)	23 (7)	297 (93)	0 (0)
Dehab et al. [55], 2008	9 (20)	35 (80)	18 (51)	17 (49)	14 (82)	3 (18)	0 (0)
Dehab et al. [55], 2008	12 (23)	41 (77)	5 (12)	36 (88)	25 (69)	2 (6)	9 (25)
Lurton et al. [69], 2008	10 (14)	61 (86)	25 (41)	26 (59)	5 (8)	14 (54)	7 (27)
Joshi et al. [40], 2008	46 (30)	106 (70)	13 (12)	93 (88)	nr	nr	11 (10)
Muwanga et al. [18], 2008	450 (54)	381 (46)	159 (40)	234 (60)	117 (50)	117 (50)	0 (0)

[a] Patients who were found alive by tracing can have unknown current care status because it was not asked by the tracing protocol, or it was not ascertainable because patients moved out of the area and informants about vital status were unable to provide information on current care status

[b] Inclusion in this study was defined by clinic visit, not unique patient identifier

[c] Includes 7 patients who were obtaining medications privately, as well as 35 transferred to another facility

[d] A high fraction with unknown treatment status was because patients whose vital status was ascertained through an informant were not asked about current HIV care

[e] This fraction considers 27 patients who had treatment gaps but who returned as being "in care" and 29 patients with no treatment gaps but incorrect record as being "in care"

ART—antiretroviral therapy; nr—not reported.

returned for a second visit and overall 74% returned for a third visit and started ART [35••]. This occurred in a community that was highly sensitized to the beneficial effects of ART. An important strength of this study was that investigators sought outcomes among those lost to follow-up in order to obtain true outcomes. Of the 637 patients who did not start ART, investigators found that 189 (28%) had started ART with a different provider. Therefore, retention in care among pre-ART patients was higher than thought, but overall, nearly 30% of eligible patients did not start ART. In McCord Hospital in Durban, South Africa, 16% of patients with clear indications for ART failed to complete ART training [16]. Among over 22,000 patients with CD4 levels <200/cm^3 enrolling in the Free State ART program, 13% were lost to care before ART initiation [36]. In ART-eligible patients, the risk of death is high and reaches 28%–34% at 1 year in these studies; hence failures of retention in this group are likely to have a marked impact on survival.

Improving Retention in Care

A number of studies have sought to understand the determinants of retention through identifying factors associated with retention. Although this section summarizes the findings of these studies, the effect of unknown outcomes that we raise with regard to the estimates of the magnitude of retention in care also apply to analyses that seek to identify the determinants of retention in care. In other words, factors associated with retention in clinic may not always be an accurate proxy for retention in care.

Transportation to Clinic

Distance to clinic and transportation are major barriers to retention in care in a wide variety of settings in Africa and Asia. In rural Uganda, among 111 patients lost to follow-up, the most common reasons for absence were lack of transportation in 50% and excessive distance in 42% [23]. In rural Malawi, 35% of patients who were lost and traced cited the high cost of transport to the clinic as the reason for absence [37•]. The International Center for AIDS Care and Treatment (ICAP) performed a multisite analysis in Western, Eastern, and Southern Africa using a 6-month absence as the outcome. The study found that if travel time to clinic exceeded 2 hours, the risk of non-retention was doubled [38]. In Cambodia, among 6688 patients of whom 4150 were on ART, living out of province was the only risk factor for failure to return to clinic [39]. In Rajasthan, India, among 106 patients who failed to return for 3 or more months, 20% cited distance and lack of transportation [40]. In pre-ART patients in Jinja, Uganda, 44% of patients who were eligible for ART but did not start cited transportation as the major reason for failure to initiate [35••]. In Western Kenya, one study found that among pre-ART patients, travel time was only significantly associated with failure of retention among women (OR=1.07; 95% CI=1.00–1.16) [33]. The consistent relationship between transportation and distance on retention has prompted the only randomized trial we are aware of studying retention. In this trial, conducted in Mbarara, Uganda, individuals were randomized to receive a cash transfer of 10,000–15,000 Uganda Shillings ($5–$8) to be used for transportation. Only 14 (18%) patients were lost from the intervention group, versus 23 (34%) lost from the control group (P=0.04) [41].

Poverty

Financial constraints also figure prominently in non-retention and "tracing" studies. Lost patients consistently report finances as a limiting factor: 34% in a South African study [42] and 35% in rural Ugandans. Among poor families, work and childcare responsibilities can compete with retention in care. In over 50,000 patients in The Academic Model Providing Access to Healthcare (AMPATH) programs in Kenya, 21% of women cited family commitments for missing a clinic appointment and 24% of men cited work commitments [33]. Lack of food or hunger—particularly concurrent with reversal of cachexia and improving health after ART initiation—has been cited as a reason for poor adherence [43], and may compromise retention in care as well. In Jimma zone in Ethiopia—an area that has faced food shortages in the last decade—17.6% of patients who defaulted reported lack of food as a reason for absence from clinic [27].

Social Support, Stigma, and Disclosure

In RLS, social determinants of retention in care have also been found to be important in a number of settings. Ware et al. [7] conducted the largest qualitative study to date in Africa on patterns of accessing care among HIV-infected patients in Nigeria, Uganda, and Tanzania through 252 qualitative interviews. Patients reported that social relationships can help in overcoming barriers to care through the force of social expectations and can also be used to obtain material benefits that make remaining in care possible [7]. In Tanzania, qualitative interviews with 42 patients revealed that many felt fulfilling responsibility to their children formed a motivating factor for retention in care [44]. Social support interventions for vulnerable groups appear to be promising interventions to improve retention. In a study from Kenya, a targeted program providing social support for youths found retention was better at the intervention clinic with 70% remaining in active care versus 55% at the

general site for the same age group [45]. Disclosure—which has been hypothesized to be a marker of social support—was found to be associated with a 70% rise in the odds of retention in 3362 patients in the pMTCT Plus network supported by ICAP [38]. Although qualitative interviews from South Africa found stigma did not represent a big challenge to retention [46], in a study from Malawi, stigma led to non-retention in 45.8% of pre-ART and 25% of on-ART patients [34•].

Models of Care

Certain program strategies have been associated with greater retention in care. Given that structural barriers such as distance and transportation play large roles in retention in care, programs that deliver care in a more decentralized way or provide home-based therapy may improve retention in care. The multinational organization AIDS Relief reported on an association between four different models of care and retention among 13,391 patients at 27 facilities in eight countries from August 2004 to June 2005. They found that, compared to groups that received adherence counseling only, programs with home visits and community health worker involvement had loss to follow-up of 5% and 1% compared to 14% [47]. In Malawi, Massaquoi et al. [11] demonstrated that a centralized "hub" lost patients faster than a "spoke" site. In the rural district of Lusikisiki in South Africa, the rate of loss to follow-up among patients who started ART at decentralized sites was 8.8-fold lower than in centralized sites [19]. As discussed previously, however, it is not possible to completely disentangle retention in care from patient movement during centralization. Although ancillary services have not been extensively studied in RLS, among 122,405 patients in 216 facilities supported by the ICAP, the better retention was associated with presence of peer support groups (173 vs 315 losses per 1000 patient-years) and outreach services (120 vs 231 losses per 1000 patient-years), but not with food supplementation [48].

CD4 Level

Low and higher CD4 counts have both been associated with worse retention. In 11 cohorts in West Africa, the retention probability was lower for patients with baseline CD4 count <50 cells/mm^3 (HR=2.27; CI=1.96–2.64; $P<0.001$) compared to CD4 >200 cells/mm^3 [49]. Interestingly, among 50,275 pre-ART patients in Kenya, a CD4 >200/cm^3 increased the risk of non-retention by 3.49-fold [33]. Likewise, in the China National Treatment cohort, lower baseline CD4 was associated with lower rate of missed visits in on-ART patients [50]. The bidirectional nature of this association may be because patients with high CD4 counts are more likely to move for work but those with low CD4 levels are at risk for unascertained deaths that appear to be failures of retention.

Sex

Male sex has emerged as a predictor of poor retention in a number of settings. In a South African study, even though 30% of the clinic were men, 42% of missed visits during a 2-month window were by men ($P<0.05$) [42]. In a large multisite study from West Africa, males had a 14% higher rate of loss than females. In western Kenya, combining those on and not on ART, the rate of loss among men was 28.1/100 person-years but 23.8 among women [33]. In a study focused on teachers in Malawi, men had an unadjusted 73% higher rate of loss to follow-up [51]. In the West Africa IeDEA consortium, with 13,102 patients from 11 cohorts from Benin, the Ivory Coast, Gambia, Mali, and Senegal, men had a 10% higher hazard of failure to retain [52]. Again, given the overall higher likelihood that men travel for work—particularly in professions of truck drivers, fishermen, and migrant agricultural workers—the observed association between men and loss to follow-up may be due at least in part to migratory labor patterns [53]. These generalizations, however, are not universal. In China, which has a concentrated rather than a generalized epidemic, women were more likely to miss visits during the first 6 months of ART [50].

Toxicities of ART

Toxicities appear to be a relatively less common reason for disengagement from care. In the Themba Lethu Clinic in Johannesburg, among 70 patients who were lost to follow-up (defined here as a single missed visit), only 1.4% cited side effects as a reason for failure to return to clinic [42] and in a later study at the same site, only 4.1% reported toxicity as a reason for absence [26]. In another clinic in Johannesburg, only 2.9% of 90 lost patients reported toxicity as a reason for absence [25•]. However, in another Johannesburg study, among 30 lost patients, 19% noted medication toxicity [54]. Among 49 defaulting patients in Malawi, 12.8% reported toxicity [34•].

Other

A few other reasons for failure to retain in care have been cited by studies in fewer numbers of patients. These include feeling well and not needing ART [32, 55], use of alternative medicines in Malawi and India [40, 55], younger age in western Kenya, and discordance in Ethiopia [27]. Low pretherapy hemoglobin has also been associated with death or loss to follow-up [52]. Pregnant women have been

found to have a high rate of loss to follow-up in South Africa [56] and other settings, and this may be due to increased burden of attending both antenatal clinics as well as HIV clinics.

Methodological Issues and Research Agenda

The study of retention in care can lead to several immediately relevant findings. First, retention in care is a primary metric of the conduct of routine, day-to-day health care delivery at the front lines. For this reason, *describing the magnitude* of retention in care is central to understanding the comparative effectiveness of HIV care and treatment programs in RLS. Second, enhancing retention in care requires knowledge about the chain of events that leads to failures of retention; therefore, studies to *identify determinants of retention* are needed to target the right interventions to the right people. Third, *estimating the causal effect of retention* on mortality is needed to appropriately prioritize retention among many health care delivery aims. Fourth, operational research on the programmatic determinants of retention—including the processes to optimize transfers of care without treatment interruptions and with appropriate medical documentation—is urgently needed. Novel methodological approaches can strengthen each of these avenues of research.

Estimating the magnitude of retention in care requires a strategy to account for patient movement within the system but outside of the clinic. A sampling-based approach is one such strategy. Reports of transfers between clinics are rarely complete—an unsurprising fact given that the roll out of care and treatment for HIV-infected patients in Africa is massive in scale, emergent in nature, and was initiated without the benefit of previously established health records infrastructures. Sampling-based approaches track a numerically small but representative sample of patients with unknown outcomes and use supplemental data on outcomes thus obtained to adjust program-level estimates of mortality and retention in care. In initial work, the sampling-based approach has found estimates of retention in care at a single site in Uganda to be 70% higher than believed at 2 years [57••]. Sampling is a potentially efficient and scalable strategy that allows us to disentangle what we care about (retention in care) with our insufficient ability to measure what we care about (ie, ascertainment of outcomes).

Understanding the determinants of retention requires epidemiologists to move away from nominal statistical "associations" to causal inferences. In short, it has been well established that a large fraction of patients lost to follow-up have died [58], but this numerical association glosses over two distinct causal relationships. First, patients who die despite adequate engagement in care often subsequently appear to not be retained because deaths are systematically underreported in most of Africa [59, 60]. On the other hand, failure to retain in care eventually leads to clinical deterioration and high risk of death. These patients, for whom the absence from clinic itself contributes to death, must be identified, epidemiologically characterized, and systematically targeted for outreach activities.

Third, attempts to estimate the effect of retention on survival must take into account that retention in care is a longitudinal exposure likely subject to time-dependent confounding [61–63]. In other words, time-varying factors such as deteriorating health status may act both as mediators of the effect of past missed clinic visits on mortality and confounders of the effect of future missed clinic visits on mortality. Confounding of this nature is not amenable to adjustment using standard regression-based adjustment [63]. Further, strategies such as defining the exposure to be retention during a restricted interval and the outcome to be survival in a subsequent interval [13, 50] may not capture the full effect of retention in care on survival. Control for time-dependent confounding can be accomplished through the use of alternative analytic approaches that employ marginal structural models and inverse probability weights [64]. Of note, however, control for time-dependent confounding requires that time-updated covariates be measured in both subjects that do and do not return to clinic. Such measurements are available only in cohorts that are followed both clinically and by research studies (such as the CHAIN cohort in New York City) and may be less common in RLS [65].

Fourth, program-level factors (eg, role of peer educators, adherence support, outreach, other ancillary services, staffing ratios, approaches to appointments, mechanisms to facilitate transfers, etc.) are likely to play a key role in patient retention. Yet to date, measurement of these key programmatic elements has not been highly featured and is not widely standardized. In particular, given the magnitude of both documented and undocumented transfers, mechanisms to ensure smooth conveyance of patient information and continuation of uninterrupted ART across sites are priority research questions. Research on program-level determinants of retention requires both standardized measures of program characteristics as well as hierarchical, multilevel models in epidemiology to "bring context" into analyses [66]. Standardized approaches to measurement and analysis of key processes that make up day-to-day implementation of HIV care can eventually yield public health "best practices" and optimize patient retention.

Conclusions

In summary, our reading of the literature is that retention in care among ART patients in RLS requires further charac-

terization but is likely higher than commonly publicized estimates. The reasons for underestimation to date of retention in care in RLS is because many patients who have unknown outcomes are accessing care within the wider network of public health ART clinics. Furthermore, few studies have attempted to address deaths that are clearly not a result of failures of retention (eg, late ART initiation, treatment failure, opportunistic infections, etc.) [57••]. Also, it is clear that marked differences in retention exist and this underscores the importance of "knowing your epidemic" and the conduct of locally relevant epidemiologic studies in diverse settings. For example, the fraction of living patients among those lost to follow-up has been found to be between 70% [42] and 13% [15], and the fraction of living patients who report being in care ranges from 93% [14] to 20%–25% [27, 42, 55]. These wide differences mean that caution is required before extrapolating from one setting to another. These differences also underscore the fact that in many situations clinic retention is a poor proxy for patient retention.

In data from RLS, factors associated with poor retention are often structural, such as transportation, poverty, and work/child care responsibilities. Associations between retention and individual psychosocial or behavioral factors have not been extensively documented [67]. Improving retention in care in RLS, therefore, begins with addressing the relevant social, economic, geographical, and political forces. Key steps include strengthening information management strategies, reducing deaths, preventing stock-outs, reducing regimen toxicity, decentralization, and reducing ancillary costs [68]. Finally, more research that focuses on retention in care (as opposed to retention in clinic), includes pre-ART as well as ART patients, and that employs sampling-based and causal approaches, can deepen our understanding of the effectiveness of care and treatment for HIV-infected patients in RLS.

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