Retention of Adult Patients on Antiretroviral Therapy in Low- and Middle-Income Countries: Systematic Review and Meta-analysis 2008–2013

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Background: We previously published systematic reviews of retention in care after antiretroviral therapy initiation among general adult populations in sub-Saharan Africa. We estimated 36-month retention at 73% for publications from 2007 to 2010. This report extends the review to cover 2008–2013 and expands it to all low- and middle-income countries.

Methods: We searched PubMed, Embase, Cochrane Register, and ISI Web of Science from January 1, 2008, to December 31, 2013, and abstracts from AIDS and IAS from 2008–2013. We estimated retention across cohorts using simple averages and interpolated missing times through the last time reported. We estimated all-cause attrition (death, loss to follow-up) for patients receiving first-line antiretroviral therapy in routine settings in low- and middle-income countries.

Results: We found 123 articles and abstracts reporting retention for 154 patient cohorts and 1,554,773 patients in 42 countries. Overall, 43% of all patients not retained were known to have died. Unweighted averages of reported retention were 78%, 71%, and 69% at 12, 24, and 36 months, after treatment initiation, respectively. We estimated 36-month retention at 65% in Africa, 80% in Asia, and 64% in Latin America and the Caribbean. From lifetable analysis, we estimated retention at 12, 24, 36, 48, and 60 months at 83%, 74%, 68%, 64%, and 60%, respectively.

Conclusions: Retention at 36 months on treatment averages 65%–70%. There are several important gaps in the evidence base, which could be filled by further research, especially in terms of geographic coverage and duration of follow-up.

Key Words: retention, attrition, loss to follow-up, HIV, antiretroviral therapy, meta-analysis, systematic review, low- and middle-income countries

(*J Acquir Immune Defic Syndr* 2015;69:98–108)

INTRODUCTION

The success of national antiretroviral therapy (ART) programs in expanding access to treatment for HIV/AIDS in low- and middle-income countries (LMICs) is undisputed. As of the end of 2013, some 11.7 million adults and children were estimated to be on ART,[1] representing almost two-thirds of those eligible for ART under current guidelines.[2] Recent studies have observed large reductions in mortality and corresponding increases in life expectancy in some of the hardest hit countries and populations.[3,4]

A large and growing body of research, conducted largely since 2008, has identified poor retention in HIV care, both before and after ART initiation, as one of the most important factors in determining the overall impact of treatment. Systematic reviews of retention after ART initiation in sub-Saharan Africa, conducted by the authors in 2007[5] and 2010,[6] estimated 24-month retention to average 62% in the years leading up to 2007 and 76% between 2007 and 2009. The remaining one quarter to one-third of all patients initiated on treatment were either known to have died or were lost to follow-up with unknown outcomes. Of these, some unknown proportion likely "self-transferred" to another facility and are alive and in care, a proportion estimated in a recent pooled analysis to average 18.6% of those lost to follow-up.[7] Still, the loss of up to a third of patients over 2 years—and of more in each year after that—is regarded as a threat to the sustainability of HIV treatment programs and an important target for intervention.[2]

Although average retention in sub-Saharan Africa seemed to improve between the earlier reviews, there were also substantial differences in the volume and methods of the articles included. It is thus difficult to determine whether the observed difference is a real improvement or is merely an

Received for publication September 22, 2014; accepted December 17, 2014.
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Supported by the World Health Organization, the National Institutes of Health and USAID. WHO originated the review, including formulating the review PICO questions, and defining the outcome and scope of the review as well as funding the review.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

M.P.F. designed the study, oversaw data collection, drafted parts of the article, and approved the final version. S.R. also designed the study, drafted parts of the article, and approved the final version. M.P.F. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The funders had no role in the study design, the collection, analysis, and interpretation of data, in the writing of the report, approval of the article, or in the decision to submit the article for publication.
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artifact of research. These previous reviews were limited, moreover, to sub-Saharan Africa through mid-2009. Current retention rates reported by the World Health Organization (WHO) vary widely between countries and regions,[1] and there have been important changes in both WHO guidelines and national ART programs since 2008. To assist policy makers, program managers, and funding agencies in understanding and targeting their efforts, we updated and expanded the previous reviews to estimate retention on ART among general adult populations from all low- and middle-income regions from 2008 to 2013.

METHODS

Our goal was to estimate all-cause attrition from and retention in care for adult patients receiving first-line ART in routine service delivery settings in World Bank-defined LMICs. All-cause attrition was defined as death or loss to follow-up. When such data were reported, we excluded patients who transferred to other sites, as their outcomes are unknown. Patients who were reported as stopping treatment but remaining in care were counted as retained.

We included observational studies describing retention in HIV treatment programs published or presented in 2008 or later. We included cohorts receiving standard first-line ART at any type or level of facility that followed prevailing national treatment guidelines. We excluded clinical trials, intervention evaluations (including home-based care), and studies providing care that patients wouldn't receive under usual practice, as indicated by each study's authors. We included standard-of-care arms from studies evaluating interventions in nonrandomized trials. Cohorts where ≥50% of patients were reported to be from high-risk or "key" populations—men who have sex with men, injection drug users, prisoners, female sex workers—cohorts that limited enrollment to pregnant women, and subsets of the general population with low CD4 counts or tuberculosis were excluded. These will be reported on in a separate publication. Cohorts combining adults and pediatric or adolescent patients that did not stratify results by age groups were included only if over 50% were ≥18. We have reported on pediatric patients separately.[8]

Where multiple reports described a single cohort, we chose the one with the most complete data and/or longest follow-up. If a report described multiple cohorts, we included it only if the data could be stratified by country and there was no other report of any of the cohorts individually. If the data were disaggregated by cohort, only cohorts that were also reported in other sources were excluded. We required that studies follow patients from ART initiation to a mean or median of at least 6 months of follow-up. Studies had to report or provide enough information to estimate all-cause attrition (death and loss) for at least one of the following time points: 6, 12, or 18 months, or a later 12-month interval after treatment initiation. We placed no restrictions on how cohorts assessed mortality among patients lost but excluded studies that reported mortality but not loss to follow-up.

To identify studies, we searched PubMed, Embase, the Cochrane Register, and ISI Web of Science from January 1, 2008, to July 28, 2013, for English language publications. Within each index, we combined "antiretroviral" and any of "Africa"/"Asia"/"Central America"/"Mexico"/"South America"/"Middle East"/"Eastern Europe"/"Caribbean Region" with any of the following: "retention"/"attrition"/"adherence"/"mortality"/"loss to follow-up"/"efficacy"/or "evaluation." We searched conference abstracts from AIDS and IAS conferences from 2008 to 2013 using "attrition," "retention," or "loss to follow-up" (we did not search CROI as its website archives were unavailable throughout the review process).

We then conducted three secondary searches. First, to capture journals that are not MeSH indexed, we searched again in PubMed, substituting region names with individual country names for all LMICs for which we did not initially include at least two cohorts. Second, we searched PubMed to determine whether any conference abstracts identified in the primary search had been published as full-text articles. Finally, we repeated each search in PubMed for the period from August 1, 2013, to January 9, 2014, when the database for the search was closed.

M.P.F. supervised the primary search and S.R. conducted the secondary searches. After excluding those whose titles were not relevant, abstracts were read to determine eligibility. Full-text articles were reviewed by both authors to confirm eligibility. Uncertainties were resolved through consensus of both authors.

Statistical Analysis

For cohorts reporting retention to a particular time point (as a proportion or Kaplan–Meier estimate), retention at each point was defined as that reported by the cohort. For cohorts that did not report retention at specific time points but provided data on attrition (numbers of subjects lost or died), retention was defined as the proportion alive and in care and assigned to the time closest to the median follow-up.

For analysis, countries were grouped into 4 regions: Africa (including North Africa); Asia (including Pacific island states); Europe and Central Asia (ECA); and Latin America and the Caribbean (LAC) (including South and Central America and Caribbean island states).

Analysis of Reported Retention Proportions

We estimated mean retention across cohorts using simple averages unweighted by sample size. As each cohort reported to different time periods, we also interpolated any missing time period possible. For example, if a cohort reported 12- and 24-month retention, we interpolated 6- and 18-month retention, assuming a linear decline between two points.

Meta-analysis of Retention Rates

We synthesized the data in a meta-analysis stratified by last time period reported to. We plotted each retention estimate and its 95% confidence interval (CI) using forest plots and combined estimates using a random effects regression with a Freeman and Tukey arcsine transformation.[9] We created a patient-level data set for each study with all attrition occurring at the time period when it was reported. We summarized retention using Kaplan–Meier curves and

TABLE 1. Median Follow-up and Rates of Patient Attrition, From Antiretroviral Treatment Programs

Study Code	N	Median or Mean Follow-up (mo)	Died (A), %	Lost to Follow-up (B), %	Total Attrition From ART (C) (C = A + B), %	Total Retained (D) (D = 1 − C), %	Transferred Care (E), %	Total Retained at Original Site (F) (F = D − E), %
Africa								
Botswana 1	633	41.9	23.4	19.9	43.4	56.6	19.1	37.5
Botswana 2	102,713	35.0	10.0	14.9	24.8	75.2		75.2
Burkina Faso 1	4255	22.6	11.4	8.2	19.6	80.4	3.6	76.7
Burkina Faso 2	5608	23.2	12.8	7.4	20.2	79.8	3.7	76.1
Burkina Faso 3	867	11.2	5.7	8.5	14.2	85.8		85.8
Cameroon 1	600	12.0	2.8	50.0	52.8	47.2	10.7	36.5
Cameroon 2a	330	12.0	4.5	30.0	34.5	65.5		65.5
Cameroon 2b	295	12.0	2.4	13.9	16.3	83.7		83.7
Cameroon 3	1187	58.0	35.0	6.1	41.1	58.9	18.5	40.4
Cameroon 4	2920	6.2	5.6	39.5	45.1	54.9	0.3	54.5
Cameroon 5	141	12.0	9.6	34.6	44.1	55.9	3.5	52.3
Cote d'Ivoire 1	1573	6.0	9.2	13.1	22.2	77.8	1.4	76.4
Cote d'Ivoire 2	10,211	7.7	11.5	14.0	25.5	74.5	3.0	71.5
Cote d'Ivoire 3	3682	36.0	12.1	6.9	19.0	81.0		81.0
Cote d'Ivoire 4	1008							
Cote d'Ivoire 5	247	17.3	4.7	12.7	17.4	82.6		82.6
DRC 1	68	19.0	6.2	18.3	24.5	75.5	1.4	74.1
DRC 2	1450		16.4	14.9	31.3	68.7	1.5	67.2
Ethiopia 1	1540	24.0	6.4	15.6	22.0	78.0	12.5	65.6
Ethiopia 2	1709	24.0	11.1	22.6	33.7	66.3	7.9	58.4
Ethiopia 3	1537	24.0	6.4	15.6	22.0	78.0	12.5	65.5
Ethiopia 4	37,466	24.0						
Ethiopia 5	321		18.6	8.2	26.8	73.2	1.2	71.9
Ethiopia 6	1428	17.7	12.8	15.2	28.0	72.0	12.0	60.0
Gambia 1	308	12.1	19.6	3.8	23.4	76.6	7.1	69.4
Ghana 1	3054	30.0	7.7	20.4	28.1	71.9		71.9
Ghana 2	290	18.0	2.4	14.1	16.6	83.4		83.4
Ghana 3	91	36.0	21.7	8.4	30.1	69.9	8.8	61.1
Guinea Bissau 1	2351	20.5	10.3	44.1	54.4	45.6	3.5	42.1
Kenya 1	1307	9.0	4.2	14.8	19.1	80.9		80.9
Kenya 2a	120	12.0	5.8	12.5	18.3	81.7		81.7
Kenya 2b	120	12.0	0.8	19.2	20.0	80.0		80.0
Kenya 2c	120	12.0	5.8	10.0	15.8	84.2		84.2
Kenya 3	830	18.0		29.4	29.4	70.6		70.6
Kenya 4	301	12.0	5.2	7.6	12.7	87.3	3.3	84.0
Kenya 5	1676		3.2	42.5	45.7	54.3	6.4	47.9
Lesotho 1	3394	13.0	3.0	7.0	10.0	90.0		90.0
Lesotho 2	4064	12.0	9.3	2.5	11.8	88.2		88.2
Lesotho 3	3747	17.4	11.2	15.0	26.2	73.8		73.8
Malawi 1	12,004	12.0						
Malawi 2a	397	6.0						
Malawi 2b	1868	6.0						
Malawi 2c	2142	6.0						
Malawi 2d	1893	6.0						
Malawi 2e	3164	6.0						
Malawi 2f	1264	6.0						
Malawi 2g	6994	6.0						
Malawi 3	253,154							
Morocco 1	412		3.6	11.4	15.0	85.0		85.0

TABLE 1. (*Continued*) Median Follow-up and Rates of Patient Attrition, From Antiretroviral Treatment Programs

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Mozambique 1	142	22.2						
Mozambique 2	11,793	7.4	14.9	17.4	32.3	67.7	6.1	61.6
Mozambique 3	471	6.0	16.4		16.4	83.6	2.8	80.9
Mozambique 4	2005	24.0						
Mozambique 5	7636							
Mozambique 6	2596							
Mozambique 7	1417	120.9						
Mozambique 8	9692	13.1						
Nigeria 1	4785	28.1	3.0	21.7	24.7	75.3	5.1	70.2
Nigeria 2	1034	13.8	3.6	21.2	24.8	75.2	0.1	75.1
Nigeria 3	5760	7.1		25.9	25.9	74.1		74.1
Nigeria 4	12,764	6.0						
Rwanda 1	306	12.0	7.4	3.3	10.7	89.3	2.3	87.0
Senegal 1	403	98.0	30.5	9.4	40.0	60.0		60.0
South Africa 01	3162	28.8	11.8	20.9	32.7	67.3	10.3	57.0
South Africa 02	47,285	14.8	6.3	9.5	15.8	84.2		84.2
South Africa 03	1154	17.4	6.6	20.2	26.8	73.2	16.3	56.9
South Africa 04	226				12.8	87.2		87.2
South Africa 05	267	6.0	7.6	8.0	15.5	84.5	1.1	83.3
South Africa 06	9102	12.0	12.9	14.2	27.1	72.9	2.1	70.8
South Africa 07	735	12.0	12.1	14.0	26.1	73.9	7.9	66.0
South Africa 08	2102		1.9	15.4	17.3	82.7	0.3	82.4
South Africa 09	15,060	21.6	18.2	27.6	45.7	54.3	15.2	39.1
South Africa 10	49,383							
South Africa 11	40,176	20.5	14.2	22.9	37.1	62.9	6.0	56.9
South Africa 12	6411	18.4	8.4	10.3	18.7	81.3	4.8	76.6
South Africa 13	1380	12.0	2.1	14.1	16.2	83.8		83.8
South Africa 14	1353	24.0	9.6	2.7	12.3	87.7	4.7	83.0
South Africa 15	609	12.0	18.6	14.6	33.2	66.8		66.8
South Africa 16a	1794	76.8	18.1	28.2	46.3	53.7	9.9	43.8
South Africa 16b	2154	44.3	18.5	32.0	50.5	49.5	10.4	39.1
South Africa 16c	2617	38.0	15.9	31.3	47.2	52.8	10.5	42.3
South Africa 16d	1996	31.0	15.3	28.5	43.8	56.2	9.4	46.8
South Africa 16e	2185	25.0	14.4	21.3	35.7	64.3	7.7	56.6
South Africa 16f	2481	17.3	10.2	20.3	30.6	69.4	6.0	63.5
South Africa 17	684	36.0	18.7	5.5	24.2	75.8	4.1	71.7
South Africa 18	309	8.4	15.9	7.4	23.3	76.7		76.7
South Africa 19	2835	22.0						
South Africa 20	2817	24.0	2.0	11.2	13.2	86.8		86.8
South Africa 21	4674	33.2	17.4	10.6	28.0	72.0	5.6	66.5
South Africa 22	11,397	13.1	14.8	20.6	35.4	64.6	16.7	47.9
Swaziland 1	769	12.0		17.2	17.2	82.8		82.8
Swaziland 2	2510							
Tanzania 1	1463	12.0	8.8	12.9	21.7	78.3		78.3
Tanzania 2	255,143		11.0		11.0	89.0		89.0
Tanzania 3	320	10.9	33.3	10.9	44.2	55.8	10.9	44.9
Tanzania 4	12,842	8.8	13.1	22.7	35.8	64.2		64.2
Tanzania 5	1458							
Togo 1	16,617	6.0		1.7	1.7	98.3		98.3

(*continued on next page*)

TABLE 1. (*Continued*) Median Follow-up and Rates of Patient Attrition, From Antiretroviral Treatment Programs

Study Code	N	Median or Mean Follow-up (mo)	Died (A), %	Lost to Follow-up (B), %	Total Attrition From ART (C) (C = A + B), %	Total Retained (D) (D = 1 − C), %	Transferred Care (E), %	Total Retained at Original Site (F) (F = D − E), %
Uganda 1	399	12.0	4.3	17.5	21.8	78.2		78.2
Uganda 2	8835	37.0	3.8	3.7	7.6	92.4		92.4
Uganda 3	3628			22.9	22.9	77.1		77.1
Uganda 4	22,315	31.0	6.7	6.4	13.1	86.9		86.9
Uganda 5	5633	22.5	8.4	11.3	19.8	80.2	1.2	79.0
Uganda 6	289	72.0	3.5	4.8	8.3	91.7	0.0	91.7
Uganda 7	1763	48.0	15.6	21.4	37.0	63.0	8.2	54.8
Uganda 8	27,425							
Uganda 9	1472							
Zambia 1	3902	12.0						
Zambia 2	89,339	10.0	9.5	13.7	23.2	76.8		76.8
Zambia 3	1084		11.9	6.4	18.3	81.7	6.0	75.8
Zambia 4	1457							
Zimbabwe 1	592	15.2	9.5	12.3	21.8	78.2		78.2
Zimbabwe 2	3919	16.3						
Zimbabwe 3	3030	120.9						
Asia								
Cambodia 1	2840	48.0	13.9	6.4	20.3	79.7	3.0	76.7
Cambodia 2	1010	30.0	7.2	8.0	15.2	84.8	2.0	82.9
Cambodia 3	549	28.8	10.4	12.3	22.7	77.3		77.3
Cambodia 4	467	13.2	7.1	4.2	11.4	88.6	5.5	83.2
China 1	67,732	20.0	10.9	14.7	25.6	74.4		74.4
China 2	1014		9.0	2.7	11.6	88.4		88.4
India 1	230	12.0	10.8	5.2	16.0	84.0	7.8	76.1
India 2a	150		8.1	14.1	22.2	77.8	10.0	67.8
India 2b	148		9.5	21.2	30.7	69.3	7.4	61.9
India 3	631	21.0	13.8	24.8	38.6	61.4	11.3	50.2
India 4	972	24.0	12.8					
India 5	717		3.8	32.4	36.1	63.9		63.9
India 6	239	41.4	10.0	43.5	53.6	46.4		46.4
India 7	142	44.0	12.0		12.0	88.0		88.0
India 8a	43	6.0	20.9	18.6	39.5	60.5		60.5
India 8b	44	6.0	6.8	15.9	22.7	77.3		77.3
India 8c	43	6.0	7.0	46.5	53.5	46.5		46.5
India 9	3159	26.0	15.1	15.5	30.6	69.4		69.4
Indonesia	96	8.2	19.8	14.3	34.1	65.9	5.2	60.7
Laos 1	913	21.7	13.1	4.9	18.0	82.0	10.7	71.2
Myanmar 1	5963	36.0	14.3	6.8	21.0	79.0	3.5	75.4
Nepal 1	1049	19.1	14.1	4.6	18.7	81.3	18.9	62.4
Papua New Guinea 1	993	24.0						
Thailand 1	36		0.0	0.0	0.0	100.0		100.0
Thailand 2	213,753	42.0	9.7	10.6	20.3	79.7		79.7
Vietnam 1	466	16.5	8.6	2.1	10.7	89.3		89.3
Vietnam 2	11,432							
Vietnam 3	1604							
LAC								
Brazil 1	541		0.4	5.2	5.5	94.5		94.5
Brazil 2	516		0.2	5.4	5.6	94.4		94.4
Brazil 3	522	12.0	3.6	5.2	8.8	91.2		91.2
Brazil 4	702	22.0	1.4	6.1	7.5	92.5		92.5

TABLE 1. (*Continued*) Median Follow-up and Rates of Patient Attrition, From Antiretroviral Treatment Programs

Study Code	N	Median or Mean Follow-up (mo)	Died (A), %	Lost to Follow-up (B), %	Total Attrition From ART (C) (C = A + B), %	Total Retained (D) (D = 1 − C), %	Transferred Care (E), %	Total Retained at Original Site (F) (F = D − E), %
Dominican Republic 1	1207	20.0	15.0	12.8	27.8	72.2		72.2
Guyana 1	25	72.0	16.7	16.7	33.3	66.7	4.0	62.7
Haiti 1	4717	27.0	12.7	12.8	25.4	74.6		74.6
Honduras 1	328	12.0	10.1	0.6	10.7	89.3		89.3
Jamaica 1	476	40.0	8.0	16.2	24.2	75.8		75.8
Nicaragua 1	166	14.4	21.6	2.0	23.5	76.5	8.5	68.0
Peru 1	873	12.0	8.8	3.1	11.9	88.1		88.1
Peru 2	55		18.2	10.9	29.1	70.9		70.9
All (averages)	10,096	22.7	10.6	15.0	24.7	75.3	6.8	71.7

estimated retention over time using lifetable analysis. We report no confidence intervals for these estimates as the sample size creates misleadingly narrow intervals.

Sensitivity Analysis

We plotted mean retention by last time period reported to assess whether cohorts reporting to longer time periods were more likely to report higher retention at earlier time periods than cohorts reporting to shorter time periods. If they were, it would suggest publication bias in later years of follow-up, in that cohorts with worse retention stopped reporting after shorter durations of follow-up than those with better retention. To create upper and lower bounds on true retention, given the varying time periods reported to, we conducted a sensitivity analysis to consider the best-case, worst-case, and midpoint scenarios for retention. The best-case scenario assumed no additional attrition from the last period reported through 60 months. The worst-case scenario assumed retention continued along the same linear trend as was observed between baseline and the last time period reported. The midpoint scenario is the average of the two.

RESULTS

Our primary search identified 3517 unique articles and 6846 abstract citations; an additional 1236 articles were identified by our secondary searches. Of these, 123 met the inclusion criteria (97 articles, 26 abstracts, as depicted in Appendix S1 (see Supplemental Digital Content, http://links.lww.com/QAI/A634). These studies reported on 154 patient cohorts, described in Appendix S2 (see Supplemental Digital Content, http://links.lww.com/QAI/A634 and 1,554,773 patients.

A total of 42 countries were represented: 24 in Africa (114 cohorts), 10 in Asia (28 cohorts), and 8 in LAC (12 cohorts). Nearly 75% of all cohorts were from Africa. Within Africa, 24% of cohorts, about 18% of all included cohorts, were from South Africa. In Asia, nearly half of the cohorts came from India, but large cohorts from Thailand and China accounted for 68% and 22% of all patients from Asia, respectively. One-third of the LAC cohorts came from Brazil and nearly half the LAC patients came from Haiti. We found no studies from the Middle East, Eastern Europe, or Central Asia reporting on general population adult cohorts. The Europe and Central Asia region (ECA) is therefore not included in the results below.

Most patients initiated ART in their early to mid 30s, with CD4 counts well below 200 cells per cubic millimeter (see Appendix S2, Supplemental Digital Content, http://links.lww.com/QAI/A634). Just under two-thirds of patients in Africa were female, whereas in all other regions >50% were male. Although not perfectly monotonic, there is some trend toward higher starting CD4 counts over time, with average or median CD4 counts at 113 cells per cubic millimeter among patients initiating in 2001/2 and 154 cells per cubic millimeter for those starting in 2009/10 (mean difference, 41.2; 95% CI: 9.4 to 72.3). Most (74%) cohorts had relatively short follow-up of 1 or 2 years, whereas the rest reported to 3 or 4 years (20%) or longer (6%).

Attrition from each cohort by the end of that cohort's follow-up, stratified by reason for attrition, is reported in Table 1. For cohorts that distinguished between deaths and losses (n = 113), an unweighted average of 43% of patients not retained were known to have died, whereas the remaining 57% were lost. Definitions of loss to follow-up ranged from 1 to 12 months late for the next scheduled clinic visit and 1–16 months since the last clinic visit. The most common definition was to categorize patients as lost if they were ≥3 months late for a scheduled visit or did not return for >6 months after the last completed visit (definitions in Appendix S3, Supplemental Digital Content, http://links.lww.com/QAI/A634).

Retention on ART as Reported

Table 2 shows retention at each time period reported to, by country. Simple average retention for select time points is plotted in Figure 1. Details are presented in Figure 2, which

TABLE 2. Summary of Retention at Specified Time Points After ART Initiation, by Country

	Retained at Months on ART, %									
Country	**6**	**12**	**18**	**24**	**36**	**48**	**60**	**72**	**84**	**96**
Africa										
Botswana		74			70		51			
Burkina Faso		75		80						
Cameroon	66	65		47		35	47			
Cote d'Ivoire	78	81	67	74	71	48				
DRC	81	75		65	57		63			
Ethiopia	76	74	72	73						
Gambia		82		75	73					
Ghana			83		71					
Guinea Bissau			46							
Kenya	80	80		64	58	55	45	39	36	
Lesotho		89		80	67					
Malawi	83	80	77	72	68	64	54			
Morocco	85									
Mozambique	83	72	65	56	51	60				
Nigeria	77	75			75					
Rwanda		89								
Senegal										60
South Africa	85	77	71	75	67	50	74	63		
Swaziland	84	82	77	74	69	66				
Tanzania	82	68	64	61	56	49			38	
Togo	98									
Uganda	88	83	86	76	79	69	57	92		
Zambia	81	79	72	68	59	54				
Zimbabwe	91	80	79	72	64					
Regional average	82	76	71	69	67	57	61	64	37	60
Asia										
Cambodia		89		77	85	80				
China	94	91	87	86			76			
India	66	81		78	67	75	74			
Indonesia	66									
Laos		88								
Myanmar	92	89			82		72			
Nepal			81							
Papua New Guinea		80		73	68	63				
Thailand	100				80					
Vietnam	87	81	89	74	67	63				
Regional average	77	84	86	79	72	71	74			
LAC										
Brazil	94	91		92						
Dominican Republic			72							
Guyana								67		
Haiti				75						
Honduras		89								
Jamaica					76					
Nicaragua			76							
Peru		79								
Regional average	94	85	74	84	76			67		

illustrates retention rates and 95% CIs at 12, 24, 36, and 48 months using forest plots. Simple average retention with no interpolation of missing values averaged 78% at 12 months, 71% at 24 months, and 69% at 36 months across all regions.

To determine whether average retention changed over calendar time, we compared attrition at 12 months in the 66 cohorts completing enrollment before 2008 to 12-month attrition in the 19 starting enrollment on or after 2008.

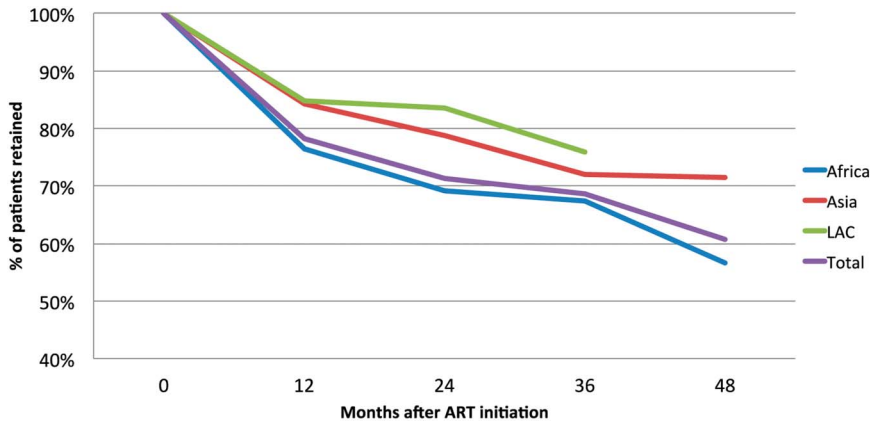

FIGURE 1. Average retention at specified time points, by region. Note: *y* axis starts at 40%.

Retention was slightly lower in the later (post-2008) cohorts, averaging 74.3% vs. 78.4% in earlier cohorts.

We looked for publication bias by plotting weighted average attrition by last time point reported to. Studies with shorter follow-up periods reported higher attrition at any given time point than did studies with longer follow-up (see Appendix S4, Supplemental Digital Content, http://links.lww.com/QAI/A634). Studies reporting only to 12 months, for example, retained an average of 84% of patients at 12 months, whereas those reporting to 36 months retained an average of 91% of patients at 12 months. This suggests some publication bias; had the studies that reported retention at 12 months continued to follow their cohorts, they would likely have had poorer 36-month retention than those that did report to 36 months.

Meta-analysis of ART Retention

We plotted Kaplan–Meier survival curves by region (Figs. 3A–D) and estimated retention by lifetable analysis. These may be regarded as the most accurate of our aggregate estimates of retention, as they take into account the full set of data available. From this analysis, we estimate 12-, 24-, 36-, 48-, and 60-month retention at 83%, 74%, 68%, 64%, and 60%, respectively. Asia fared better than Africa or LAC in these estimates, with 36-month retention of 80% in Asia, 65% in Africa, and 64% in LAC.

Sensitivity Analysis

Both publication bias and the possibility that cohorts with resources to publish also have more resources for retaining patients suggest that simple averages may overestimate true retention. However, reported loss to follow-up may overestimate true loss to care, as patients who self-transfer to other facilities are often reported as lost. We undertook a sensitivity analysis in which we modeled expected attrition under best-case, worst-case, and midpoint scenarios (see Appendix S5, Supplemental Digital Content, http://links.lww.com/QAI/A634). As we previously found for adults in sub-Saharan Africa, there is little variation among the three scenarios up to 24 months on ART. By 36 months, the difference widens, and continues to expand through 60 months. The midpoint estimate of retention at 36 months is 67%. The worst- and best-case estimates at the same time point are 62% and 72%, respectively.

DISCUSSION

This review of 154 general adult patient cohorts comprising 1,554,773 patients from 42 LMICs published or presented from 2008 to 2013 allowed us to estimate ART retention with excellent precision. We found that adult 36-month retention averaged 65% in Africa, 80% in Asia, and 64% in Latin America and the Caribbean. Although average starting CD4 counts seem to be rising, attrition also shows some evidence of increasing over time. In considering change over time, however, it should be noted that most cohorts in this review enrolled patients under earlier, more restrictive treatment eligibility guidelines (ie, CD4 count threshold of 200 cells per cubic millimeter rather than the 350 threshold that is common now).

Since our first two reviews, several reviews have considered other aspects of retention and other regions or populations. These include syntheses of reasons for stopping treatment[10,11] and pooled analyses of data from multiple cohorts in a region.[12] Quantitative results have generally been similar to ours, although several authors have noted that the definition of loss can influence estimated rates.[13,14] Of importance in interpreting this review is work on the ultimate outcomes of patients categorized as lost.[15] Studies that actively track lost patients suggest that although many have died or are untraceable, a large minority have reinitiated ART at another site (self-transferred). The term "lost to follow-up" should therefore be regarded as a catchall that includes informal self-transfers and undocumented deaths. It may overestimate national treatment program attrition, while also underestimating the proportion of deaths.

Unlike our previous reviews, for which long-term data were scarce, our current review provides a robust estimate of retention beyond two years. Our lifetable results estimated overall adult retention at 83%, 74%, 68%, 64%, and 60% after 12, 24, 36, 48, and 60 months on ART, respectively. We saw a steady reduction in annual attrition after 24 months, suggesting annual attrition slows but is not eliminated in later years on ART. A 2013 WHO report on LMICs found similar

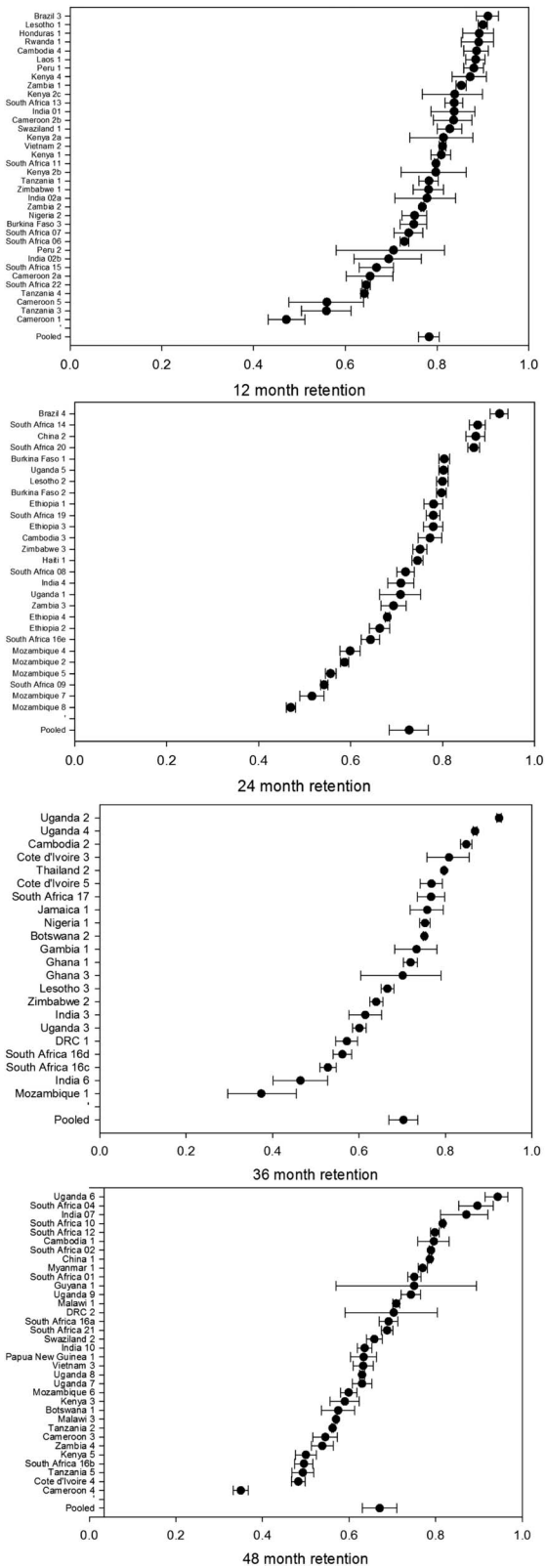

FIGURE 2. Forest plots of retention by time period reported to at 12, 24, 36, and 48 months on ART. Figure of 48-month retention includes 48-month retention (sometimes interpolated) for all cohorts reporting beyond 48 months.

12-month retention (86%) but estimated 60-month retention at 72%.[2] These estimates come from 23 cohorts of ≥2000 patients and therefore may not be representative of typical cohorts in resource-limited settings. Alternatively, as the countries included do not perfectly overlap our analysis and mainly report on recent retention, they could indicate retention is highly variable over long-term follow-up. Longer follow-up in nationally representative cohorts is needed to discern the reasons for these differences.

In this review, we included counties outside of sub-Saharan Africa, which allowed us to investigate regional differences in retention. We found some variation, with lifetable estimates of 36-month retention estimated at 65% in Africa, 80% in Asia, and 64% in LAC. Our review was not able to explain these differences, although they may have to do with differences in patient care-seeking behavior, socioeconomic status, experiences with the health care system, distances to the clinics, or baseline disease status. We also note that although we excluded studies where >50% of patients were explicitly reported to be drawn from key populations, it is likely that cohorts in Asia and Latin America and the Caribbean, where most countries have concentrated HIV epidemics, included much larger proportions of men who have sex with men and injection drug users, in particular, than those from Africa. Future work is needed to define more accurately the specific populations from which study cohorts are drawn, confirm the variation between regions and populations, and explain its implications for retention.

As noted above, we found a modest chronological trend toward increasing attrition in later years. Average 12-month retention for cohorts enrolling all patients before 2008, 78%, was higher than for cohorts that started enrolling in 2008 or later, 74%. Because the included cohorts vary widely, by location, population, and other factors, it is impossible to know whether this difference reflects a real trend toward poorer retention or is an artifact of the review. These results suggest that at a minimum, there is no broad trend toward improvement in retention over time. Although our finding of increased attrition over time was not robust, it is consistent with findings from the South Africa national treatment program[16] and other African treatment programs.[17] There are many possible explanations for this. It is possible, for example, that as programs scale up, they are less able to focus on retention. It is also possible that earlier treatment initiation, as reflected in many countries' treatment guidelines starting in 2008, is associated with less mortality but more loss to follow-up.[17] We note that reviews like this cannot readily address questions of the impact of guideline changes, largely because estimates of retention are rarely reported by either calendar year or patients' year of ART initiation. This precludes ascribing any cohort's retention estimate to a specific time period in relation to prevailing guidelines. We encourage future cohort studies to report outcomes by year of treatment initiation.

Our review identified some important gaps in the retention literature. Roughly 70% of all included studies were African cohorts. Although our inclusion criteria covered all LMICs, we found relatively few cohorts reporting in English

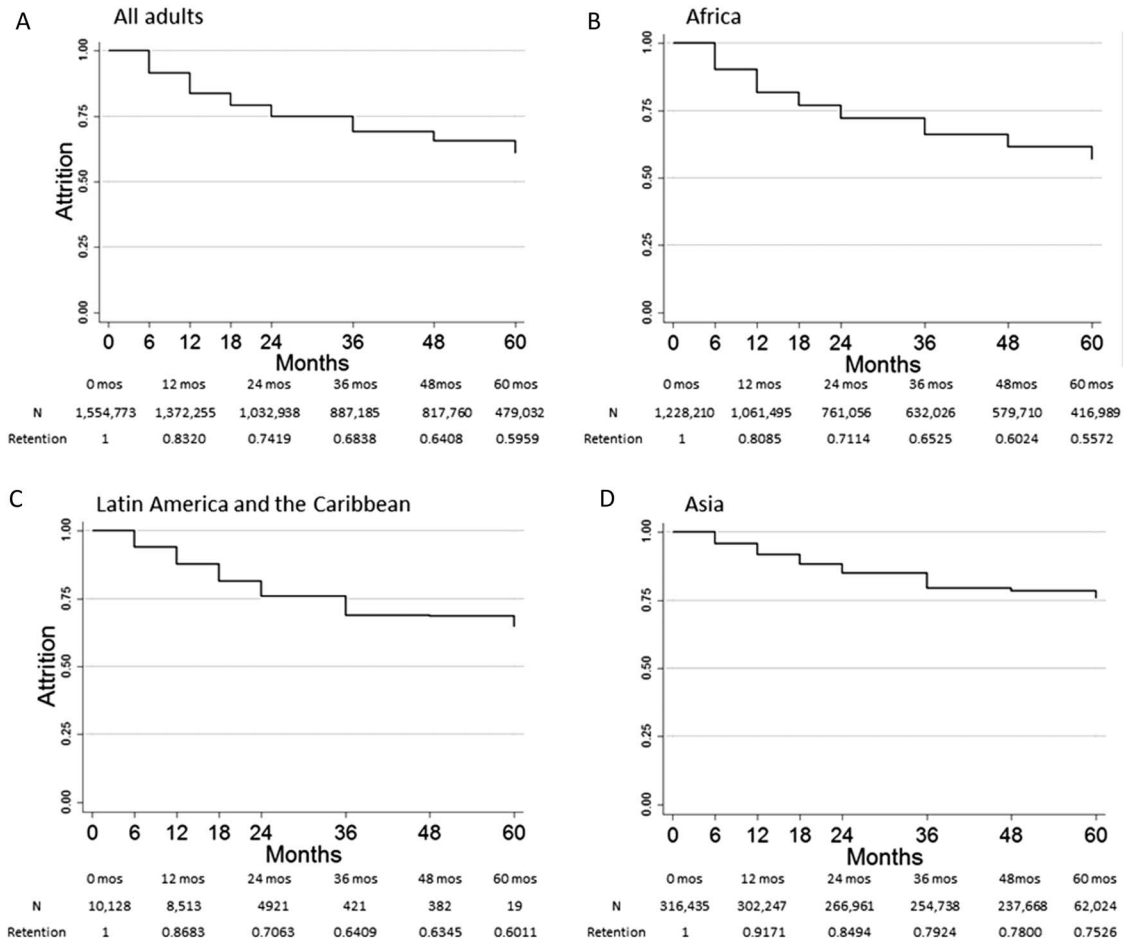

FIGURE 3. A–D, Kaplan–Meir curves of time to attrition for all adults and stratified by region. Kaplan-Meir data use interpolated estimates.

outside Asia and Africa. It is understandable that a majority of research is done in Africa, which has the majority of HIV-infected individuals. We identified no studies meeting our inclusion criteria reporting on general adult populations from Europe and Central Asia. A parallel review of retention in high-risk, rather than general, populations found only one eligible study from the ECA region.[18] Although we stratified our analysis by geographic region, both Asia and LAC had limited country variation, modest numbers of studies, and smaller cohorts. Within Africa, North Africa provided only 1 cohort, and most studies came from Southern or Eastern Africa, with minimal representation from Central and West Africa. Within Asia, the Middle East is missing entirely, and several very large countries (Malaysia, Pakistan, Bangladesh, and Indonesia) had only one or no studies available (these countries were also absent from or poorly represented in the parallel high-risk populations review). Finally, few cohorts reported retention beyond 36 months. Although 12- or 24-month follow-up captures the high attrition immediately after starting treatment, it does not shed light on the long-term effects of resistance, toxicities, treatment fatigue, and treatment failure, which may only develop after 5 years or more.

This review has several limitations. First, as noted, we identified publication bias that would be expected to overestimate retention as cohorts with worse attrition were systematically underrepresented. Second, for cohorts reporting overall retention along with median follow-up duration, we ascribed retention to the period closest to the median. This can have an unpredictable effect on estimates; in some cases it will overestimate and in others underestimate retention. Third, large cohorts (eg, Malawi, China, Thailand) may have had overly strong influence on the results. Fourth, in cases where we calculated cohort retention, we excluded transfer patients. Cohorts that reported Kaplan–Meier analyses often censored patients at transfer, which could bias retention estimates. In addition, many patients who transfer care informally are likely reported as lost. Fifth, we accepted each report's own definition of loss to follow-up as we did not have access to primary data that would have allowed us to apply a common definition. The definition of loss to follow-up certainly matters, as has been made clear by other authors.[13,14] It is unclear, however, how the lack of a standard definition affected our aggregate estimates, as whatever standard definition was applied would have led to some studies overestimating and some underestimating attrition. Sixth,

our results, particularly retention at 6 and 12 months, could be biased by the fact that we were forced to interpolate data between time points not reported and chose linear interpolation as the best approach. Although attrition is often linear after the first year on treatment, it tends not to be during the first year. For the cohorts where 6- and/or 12-month retention was interpolated, this would likely cause an overestimate of early retention. Seventh, we excluded non-English language publications, which may explain the limited data outside Asia and Africa. Eighth, some cohorts used patient tracing, which could have influenced retention rates. Finally, the keywords and MeSH terms used to index publications about ART retention are not consistent across publications. As a result, it is difficult to construct searches in databases such as PubMed that are both inclusive and precise.

In conclusion, we found that among 1,554,773 general population patients from LMICs, overall retention at 12, 24, and 36 months was estimated to be 83%, 74% and 68%, respectively. There seem to be substantial regional differences, with 36-month retention estimated at 65% in Africa, 80% in Asia, and 64% in LAC. As most of the reviewed cohorts came from sub-Saharan Africa, more retention data from LMICs outside sub-Saharan Africa are needed to create a robust picture of retention throughout resource-limited settings.

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