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Systematic Review

Self-transfer and mortality amongst adults lost to follow-up in ART programmes in low- and middle-income countries: systematic review and meta-analysis

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Abstract

OBJECTIVE To ascertain estimates of adult patients, recorded as lost to follow-up (LTFU) within antiretroviral treatment (ART) programmes, who have self-transferred care, died or truly stopped ART in low- and middle-income countries.

METHODS PubMed, EMBASE, Web of Science, Science Direct, LILACS, IndMed and AIM databases (2003–2013) and IAS/AIDS conference abstracts (2011–2013) were searched for tracing studies reporting the proportion of traced patients found to have self-transferred, died or stopped ART. These estimates were then combined using random-effects meta-analysis. Risk of bias was assessed through subgroup and sensitivity analyses.

RESULTS Twenty eight studies were eligible for inclusion, reporting true outcomes for 10 806 traced patients attending approximately 258 ART facilities. None were from outside sub-Saharan Africa. Twenty three studies reported 4.5–54.4% traced LTFU patients self-transferring care, providing a pooled estimate of 18.6% (95% CI 15.8–22.0%). A significant positive association was found between rates of self-transfer and LTFU in the ART cohort. The pooled estimates for unreported deaths were 38.8% (95% CI 30.8–46.8%; 27 studies) and 28.6% (95% CI 21.9–36.0%; 20 studies) for patients stopping ART. A significant decrease in unreported deaths from 50.0% (95% CI 41.5–58.4%) to 30.0% (95% CI 21.1–38.9%) was found comparing study periods before and after 31 December 2007.

CONCLUSIONS Substantial unaccounted for transfers and deaths amongst patients LTFU confirms that retention and mortality is underestimated where the true outcomes of LTFU patients are not ascertained.

keywords Human immunodeficiency virus, antiretroviral therapy, lost to follow-up, mortality, continuity of care, systematic review

Introduction

Retention in care is a key measure of the success of HIV treatment programmes. In sub-Saharan Africa, around a third of patients are reported as lost to follow-up (LTFU) within 3 years of initiating antiretroviral therapy (ART) (Fox & Rosen 2010). LTFU is a general term for largely unknown outcomes of patients who have not returned to a particular clinic to collect their next supply of ART. True outcomes for such patients can be divided into three categories: patients who have self-transferred to another facility, those who have died and those who have discontinued treatment (Brinkhof *et al.* 2009; McMahon *et al.* 2013).

With expanding ART coverage, increased decentralisation of ART services to primary health care and growing patient confidence to select where to access ART, patients are increasingly transferring between ART-providing facilities (Geng *et al.* 2010b; Nglazi *et al.* 2013). These transfers may be formal or undocumented, and the latter are referred to in this study as 'self-transfers'. Self-transfers may occur for both health system and personal

reasons including facility congestion and perceptions of depersonalised services, permanent or temporary relocation, lack of patient awareness of transferring processes and ease of transferring without documentation due to increasing numbers of ART providers (Mben *et al.* 2012; Nglazi *et al.* 2013; Wubshet *et al.* 2013). Failure to account for patients self-transferring care can result in underestimated retention in ART care. Accurate retention outcomes are essential to ensure appropriate forecasting, costing and supply chain management of human resource requirements, drugs and laboratory investigations, and to measure the success of ART scale-up (Tweya *et al.* 2013).

True outcomes of patients classified as LTFU are generally determined by either active tracing or data linkage to national death registries (Geng *et al.* 2010b; Van Cutsem *et al.* 2011). While some ART programmes in low- and middle-income countries conduct tracing routinely, this is not generally done due to resource constraints. More commonly, tracing studies have been conducted at a specific time point on either all or a sample of patents who are LTFU, to improve classification of unknown outcomes and link patients back into care (Geng *et al.* 2010a; Rosen & Ketlhapile 2010; McMahon *et al.* 2013).

Two previous reviews have highlighted the substantial numbers of self-transfers amongst LTFU patients. The first, a systematic review, reported self-transfer rates of 12–54% amongst patients found alive (Brinkhof *et al.* 2009). The second, a narrative review, estimated a crude unweighted median self-transfer rate of 48.5% amongst those reported in 14 cited studies as LTFU (Geng *et al.* 2010b).

We systematically reviewed outcomes reported in tracing studies of adult ART patients who are reported as LTFU in low- and middle-income countries (LMICs) to provide an updated assessment of the extent to which self-transfers – a positive outcome – contributed to the overall proportion of people considered to be lost to care.

Methods

Search strategy

We followed the approach set out in the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (Moher *et al.* 2009). Using a predetermined study protocol (see Web Appendix), we searched seven databases – PubMed, EMBASE, Science Direct, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), Indian Medlars Centre (IndMed) and African Index Medicus (AIM) – from 1 January 2003 to 31 December 2013 to identify observational cohort studies reporting true outcomes of patients LTFU in LMICs. Randomised and non-randomised controlled trials were excluded as these cannot provide representative estimates of LTFU rates in programme settings. Highly sensitive search strategies were developed for each database with the assistance of a professional librarian (Umscheid 2013), as detailed in the study protocol.

We also searched the conference abstract sites of all conferences of the International AIDS Society from 2011 to 2013 to enable inclusion of data from studies not published to date. All systematic reviews and editorial articles were identified, and selected studies' reference lists were manually searched to identify further studies for eligibility assessment (Liberati *et al.* 2009; Moher *et al.* 2009).

Study selection and data extraction

Studies reporting on HIV patients on ART in LMICs with LTFU as an outcome were included, provided true outcomes of all or a subset of LTFU patients were ascertained by tracing. We excluded studies that reported on infant, paediatric, adolescent or prevention-of-mother-to-child transmission (PMTCT)-specific cohorts, as well as studies that reported LTFU amongst patients prior to initiating ART, unless ART outcomes were also reported and able to be disaggregated.

Where more than one study reported on the same cohort, the study reporting on the largest cohort was included. Where identical cohorts were published, the study with the latest publication date was included to obtain the most updated data. Study eligibility assessment was carried out by one reviewer (LW) and confirmed by a second reviewer who assessed 10% of titles and 100% of full articles for eligibility (NF); any discrepancies were resolved by a third reviewer (JSW). Data were extracted by one reviewer (LW) and verified by a second reviewer (OA) using a standardised data extraction form. Information was extracted on study and programme characteristics (study period, location and country of study, urban or rural setting and provider type); cohort characteristics (number of adult patients initiated on ART; definition of LTFU; number of reported deaths or formal transfers and number meeting the LTFU definition) and outcomes (number of patients in the tracing study, number traced, tracing methods, reasons for failed tracing and outcomes). Where discrepancies arose, these were resolved in consultation with a third reviewer (NF).

To provide consistency across studies, the following three standardised approaches were taken. Firstly, patients who could not be traced due to incorrect contact

details or living outside the tracing area were included in the tracing study cohort. Secondly, study participants identified through tracing efforts to have relocated were considered untraceable (their true outcomes remaining unknown). Lastly, study participants reported to be obtaining ART privately were included as self-transfers.

Assessment of heterogeneity and risk of bias in included studies and across studies

Selected studies were assessed for study-level and outcome-level risk of bias using the following criteria, which if not met or uncertain whether met, indicated a risk of bias: published in peer-reviewed journal; prospective study design; all or a random sample of LTFU patients included; more than two-thirds of study participants traced; disaggregated adult data reported; and method of tracing included home visits where the patient could not be reached by telephone. Where the study did not trace all or a random sample of patients, had limited tracing success or only traced by telephone, there is a risk that true outcome results of the study may be affected by selection bias. Where the study aggregated tracing outcomes for adults and children, there was an increased risk that LTFU, tracing success rates and tracing outcomes may be biased by the paediatric cohort. Risk of bias categories were not scored for purposes of the meta-analyses due to the inherent subjectivity in such approaches, but the potential influence of various study characteristics was explored through subgroup or sensitivity analysis (Jüni *et al.* 1999; Umscheid 2013).

The risk of bias assessment (Web Appendix) was used as part of the overall assessment of the quality of the evidence.

Statistical analysis and data synthesis

This study's primary outcome is the percentage of traced LTFU patients determined to have self-transferred care in each included study. The secondary outcomes are the percentage determined to have died and stopped ART. Point estimates and 95% confidence intervals (CI) were calculated for individual studies and combined using random-effects meta-analysis on the arcsin scale, then back-transformed prior to pooling (Freeman 1950; Miller 1978). Combined estimates were transformed back to percentages. Heterogeneity between included studies was assessed visually by forest plot and statistically by estimating the τ^2 statistic (Higgins *et al.* 2003; Rücker *et al.* 2008).

The association between the primary outcome and the proportion LTFU in the ART cohort was explored using univariate random-effects meta-regression. In addition, subgroup analyses were undertaken to determine the potential influence risk of bias covariates, study period and LTFU period on the primary and secondary outcomes. Study period stratification was grouped into those ending before and after 31 December 2007. 2008 was the year in which the WHO recommended decentralisation of ART services (WHO 2008), and by which time a number of high-burden HIV countries had already started implementing decentralisation, including Malawi, Mozambique, South Africa and Swaziland (Boulle *et al.* 2008; Lowrance *et al.* 2008; Decroo *et al.* 2011; van Schalkwyk *et al.* 2013). LTFU period was stratified into less or more than 3 months from the patient's last visit due to most studies defining LTFU for tracing purposes as less than 6 months and approximately half defining such period as less than 3 months. Sensitivity analyses were carried out to determine the potential influence of studies that combined outcomes for adults and children and studies that reported outcomes on an incomplete or non-random sample of patients.

Analyses were carried out in STATA version 13(StataCorp 2013).

Results

Study selection and characteristics of inclusions

From the initial search, 2597 published items were retrieved, and another 364 items were identified from other sources, including 3 from reference lists and 361 from conferences. Of these, 36 met the eligibility criteria, including 29 full text journal articles and 7 abstracts from conferences (Figure 1). Eight studies reported on the same cohort of traced patients. This systematic review therefore included 28 studies that described true outcomes of 10 806 LTFU patients attending approximately 258 ART-providing facilities.

A total of 12 countries were represented, all in sub-Saharan Africa, with a third (9/28) from South Africa. Twelve study cohorts were drawn from urban areas, 6 from rural and 10 included both urban and rural cohorts. The vast majority of studies were conducted in public sector facilities with only 2 from the private sector, one of which was a workplace programme (Dahab *et al.* 2011). Fifteen studies were conducted in adult cohorts, five reported data for adults and children, and the remainder did not specify. Study characteristics are summarised in Table 1.

Cohort size varied from 352 (Kato *et al.* 2013) to 47 858 (Toure *et al.* 2012) patients initiated on ART. These cohorts were drawn from 1 to 138 healthcare facilities. The percentage of patients classified as LTFU for tracing purposes ranged from 2.7% (Maskew *et al.* 2007)

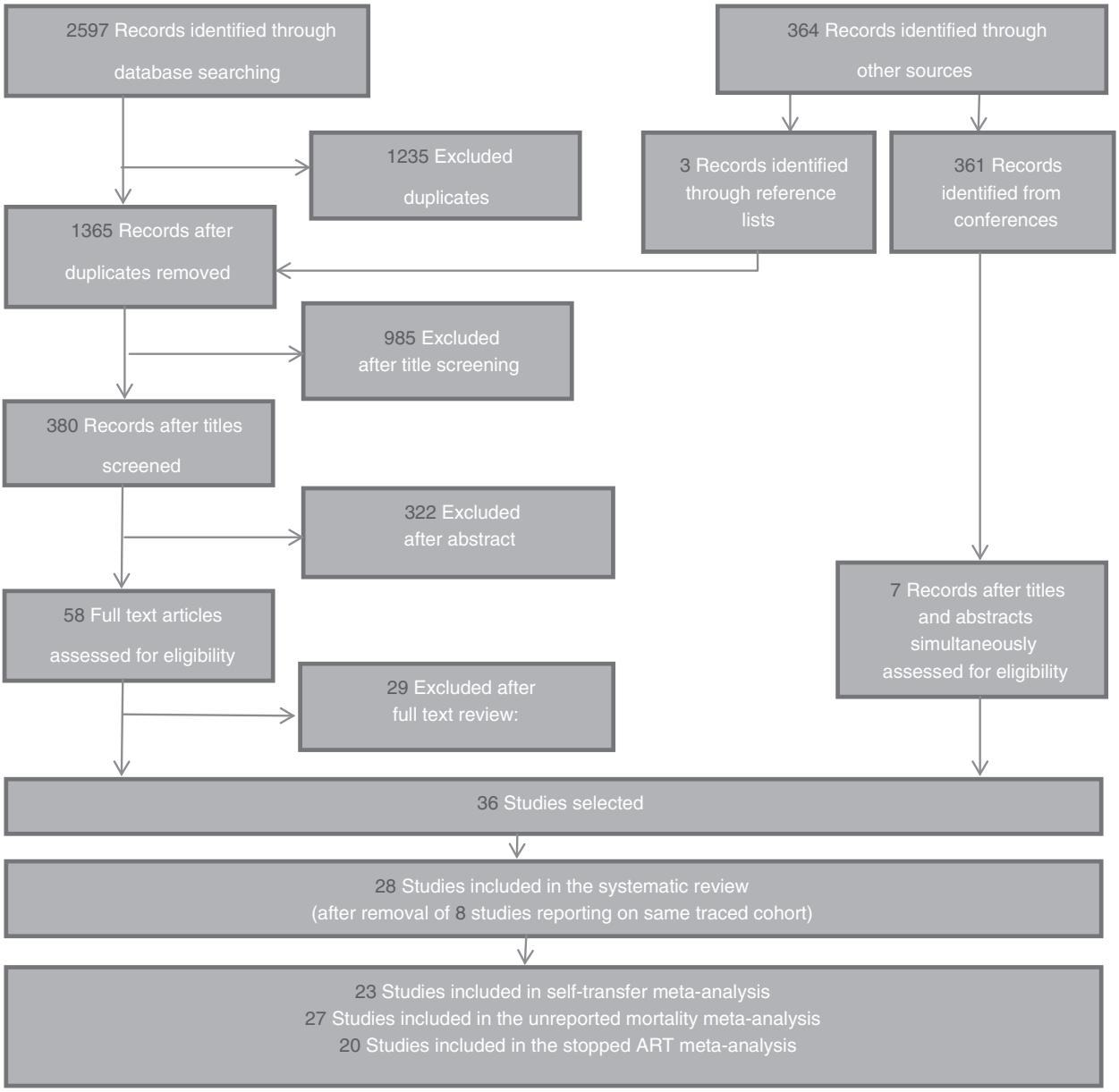

Figure 1 Identification and selection of studies flow diagram.

to 55.4% (Alamo *et al.* 2012b). Most tracing studies attempted to trace all LTFU patients, with 3 studies tracing a random sample of patients, two studies tracing a non-random sample (Krebs *et al.* 2008; Omotoso 2011) and 1 study only reporting on the number of patients traced (Mben *et al.* 2012).

There was an extensive variability in LTFU definitions applied for the purposes of determining the study cohort for tracing. The period for which a patient was missing before they were considered LTFU ranged from 1 week to 6 months. This period also varied from either time since last visit (6 studies) or time since missed appointment (16 studies). Two studies provided no definition for LTFU. Reporting of tracing methods was also heterogeneous and not well described in a number of studies; five studies only attempted to contact patients by telephone, 21 studies attempted to trace by home visit either after failed telephone contact or not, and two

Table 1 Characteristics of included studies and cohorts

No.	First author/ Year	Study period	Location	Setting	Sector	Study population age	No. sites in cohort	LTFU definition for tracing purposes	Tracing method	No. start ART in study cohort	No. LTFU (%)	No. in tracing study (%)
1	Alamo *et al.* (2012b)	2001–2010	Kampala, Uganda	Urban	NGO	Adult	1	Missed appointment >3 months	2 home visits	2713†	1502† (55.4)	164‡ (10.9)
2	Bisson *et al.* (2008)	2003	Gaborone, Botswana	Urban	Public	Adult	1	Missed appointment > 1 month	3 telephone call attempts, if unsuccessful home visit	410	68 (16.6)	68 (100)
3	Caluwaerts *et al.* (2009)	2002–2007	Tete, Mozambique	Urban	Public	Adult/ Paediatric	1	Missed appointment >2 months	If volunteer knew outcome recorded, otherwise home visit	2818	594 (21.1)	594 (100)
4	Chima and Lupondwana (2011)	2008–2009	Vryheid, South Africa	Urban	Public	Mixed	1	Missed appointment	Telephone calls and home visits	NR	343	343 (100)
5	Dahab *et al.* (2011)	2005–2007	Gauteng & Northwest, South Africa	Rural & Urban	Public & Private	Adult	2	Missed 6-m appointment >1 month	3 attempts made to trace patient (methods NR)	411	95 (23.1)	95 (100)
6	Dalal *et al.* (2008)	2004–2005	Johannesburg, South Africa	Urban	Public	Adult	1	Missed appointment > 6 weeks	Telephone calls, if unsuccessful home visit	1631	267 (16.4)	267 (100)
7	Deribe *et al.* (2008)	2005–2007	Jimma, Ethiopia	Urban	Public	Adult	1	Missed >2 appointments	Telephone calls and home visits	1796	161 (9.0)	173 (100)
8	Geng *et al.* (2011)	2006–2007	Mbarara, Uganda	Rural	Public	Adult	1	No visit > 6 months	Home visit	3628	829 (22.9)	128‡ (15.4)
9	Gunguwo *et al.* (2012)*	2010	Bulawayo, Zimbabwe	Urban	Public	Adult§	1	No visit > 3 months	Home visit	1796§	161 (9.0)	161 (100)
10	Kato *et al.* (2013)*	2010	Mumbwa district, Zambia	Rural	Public	NR	> 2	Not defined	Home visit	352¶	53 (15.1)	53 (100)
11	Krebs *et al.* (2008)	2005	Lusaka, Zambia	Urban	Public	NR	12	Missed appointment 1 week to 1 month (facility dependent)	Telephone calls and home visits	16 198	3408 (21.0)	654 (19.2)
12	Maskew *et al.* (2007)	2006–2007	Johannesburg, South Africa	Urban	Public	NR	1	Missed appointment > 1 month	Telephone call	5821	154 (2.7)	154 (100)
13	Mben *et al.* (2012)	2006–2007	Yaounde, Cameroon	Urban	Public	NR	1	Missed appointment > 1 month	3 attempts made to trace patient (methods NR)	NR	NR	NR

Table 1 (*Continued*)

No.	First author/ Year	Study period	Location	Setting	Sector	Study population age	No. sites in cohort	LTFU definition for tracing purposes	Tracing method	No. start ART in study cohort	No. LTFU (%)	No. in tracing study (%)
14	McGuire *et al.* (2010)	2004–2007	Chiradzulu, Malawi	Rural	Public	Adult/ Paediatric**	11	Missed appointment > 1 month	1–3 home visits	106 33§	1186 (11.2)	1186 (100)
15	Miller *et al.* (2010)	2008–2009	Limpopo and Gauteng, South Africa	Rural & Urban	Public	Adult	2	Missed appointment > 1 month	Telephone calls, if unsuccessful home visit	528	40 (7.6)	40 (100)
16	Mutevedzi *et al.* (2013)	2004–2012	Hlabisa, South Africa	Rural	Public	Adult	17	No visit >6 months	Telephone calls and home visits‡‡	4674	558 (11.9)	558 (100)
17	O'Connor *et al.* (2011)	2007–2009	Johannesburg, South Africa	Urban	Public	NR	4	Missed appointment at down-referral site > 6 weeks	3 telephone call attempts, if unsuccessful home visit	3336	490 (14.7)	490 (100)
18	Omotoso (2011)*	2008–2010	Adamawa state, Nigeria	Rural	Public	NR	5	Missed appointment > 3 months	Home visit	2350††	380 (16.2)	185 (48.7)
19	Onoka *et al.* (2012)	2007	Enugu state, Nigeria	Rural & Urban	Public & Private	NR	2	Missed 3 appointments	Telephone calls and home visits	1034	219 (21.2)	219 (100)
20	Peltzer *et al.* (2011)	2007–2008	Uthukela district, South Africa	Rural & Urban	Public	Adult	3	Missed 2 consecutive or 6-/12-m appointment	5 telephone call attempts, if unsuccessful up to 3 home visits	727	169 (23.3)	169 (100)
21	Rosen and Ketlhapile (2010)	2004–2009	Johannesburg, South Africa	Urban	Public	Adult	1	Missed appointment > 1 month	1–8 Telephone calls	11 678	869 (7.4)	493‡ (56.8)
22	Saka *et al.* (2013)	2008–2011	Togo	Rural & Urban	Public & Private & NGO	Adult	28	No visit >4 months	Telephone calls	16 617	1216 (7.3)	1216 (100)
23	Sie *et al.* (2011)*	2010	Cote d'Ivoire	Rural & Urban	Public	NR	12	Not defined	Telephone calls	NR	4221	4221 (100)
24	Toure *et al.* (2012)*	2004–2011	Cote d'Ivoire	Rural & Urban	Public	NR	138	No visit > 3 months	Telephone calls	47 858	11 051 (23.1)	11 051 (100)
25	Tweya *et al.* (2013)	2006–2010	Lilongwe, Malawi	Rural & Urban	Public	Adult	2	Missed appointment > 3 weeks	Telephone calls and home visits	21 370	3510§§ (16.4)	3510 (100)
26	Weigel *et al.* (2011)	2002–2005	Lilongwe, Malawi	Rural & Urban	Public	Adult/ Paediatric	1	Missed appointment > 2 weeks	Up to 3 attempts. Telephone calls and home visits	3846	1840 (47.8)	1800 (97.8)

Table 1 (*Continued*)

No.	First author/ Year	Study period	Location	Setting	Sector	Study population age	No. sites in cohort	LTFU definition for tracing purposes	Tracing method	No. start ART in study cohort	No. LTFU (%)	No. in tracing study (%)
27	Wubshet *et al.* (2013)	2005–2010	Gondar, Ethiopia	Rural	Public	Adult	1	Missed appointment > 3 months	Home visits	3012	551 (18.3)	551 (100)
28	Yu *et al.* (2007)	2005–2006	Northern Malawi	Rural & Urban	Public	Adult/ Paediatric	4	No visit for > 3 months	Home visits	5009	253 (5.1)	253 (100)

NR, not reported
*Conference abstract.
†Disaggregated ART data from (Alamo *et al.* 2012a).
‡Random sample of LTFU patients.
§Corresponding author provided data not reported in publication/conference abstract (see Acknowledgements).
¶Data from conference poster download attached to conference abstract.
**Disaggregated adult data reported for primary and secondary outcomes.
††Abstract does not state whether ART/pre-ART cohort. Unable to contact author. Assumed ART cohort.
‡‡Surveillance database maintained by semi-annual household survey (Bor *et al.* 2013).
§§LTFU patients less 613 formal transfers.

Table 2 True outcomes of LTFU patients traced

No.	First author	No. in tracing study	No. traced (%)	No. self-transfers (%)	No. still at same ART facility (%)*	No. stopped care (%)	No. alive (%)	No. died (%)
1	Alamo	164	158 (96.3)	86 (54.4)		56 (35.4)	142 (89.9)	16 (10.1)
2	Bisson	68	46 (67.7)	NR			6 (13.0)	40 (87.0)
3	Caluwaerts	594	214 (36.0)	43 (20.1)	7 (3.3)	46 (21.5)	96 (44.9)	118 (55.1)
4	Chima	343	251 (73.2)	NR			120 (47.8)	131 (52.2)
5	Dahab	95	67 (70.5)	3 (4.5)		40 (59.7)	43 (64.2)	24 (35.8)
6	Dalal	267	173 (64.8)	30 (17.3)		60† (34.7)	90 (52.0)	83 (48.0)
7	Deribe	173	108 (62.4)	19 (17.6)		89† (82.4)	108 (100)	NR‡
8	Geng	128	111 (86.7)	35§ (31.5)		13§ (11.7)	79 (71.2)	32 (28.8)
9	Gunguwo	161	111 (68.9)	6 (5.4)	16 (14.4)	11 (9.9)	33 (29.7)	78 (70.3)
10	Kato	53	48 (90.6)	10 (20.8)	8 (16.7)	15 (31.3)	33 (68.8)	15 (31.3)
11	Krebs	654	417 (63.8)	NR			225 (54.0)	192 (46.0)
12	Maskew	154	70 (45.5)	10 (14.3)		41† (58.6)	51 (72.9)	19 (27.1)
13	Mben	NR	231	22 (9.5)		111† (48.1)	133 (57.6)	98 (42.4)
14	McGuire	1186	344 (29.0)	63 (18.3)		48† (14.0)	111 (32.3)	233 (67.7)
15	Miller	40	38 (95.0)	16 (42.1)	2 (5.3)	13¶ (34.2)	31 (81.6)	7 (18.4)
16	Mutevedzi	558	394 (70.6)	NR			303 (76.9)	91 (23.1)
17	O'Connor	490	374 (76.3)	71 (19.0)	281 (75.1)	15 (4.0)	367 (98.1)	7 (1.9)
18	Omotoso	185	151 (81.6)	10 (6.6)		27**¶ (17.9)	132†† (87.4)	19 (12.6)
19	Onoka	219	100 (45.7)	15 (15.0)	4 (4.0)	30¶ (30.0)	49 (49.0)	51 (51.0)
20	Peltzer	169	147 (87.0)	58 (39.5)		7 (4.8)	65 (44.2)	82 (55.8)
21	Rosen	493	260 (52.7)	79 (30.4)	56 (22.0)	70 (26.9)	205 (78.9)	55 (21.2)
22	Saka	1216	202 (16.6)	NR		NR	114 (56.4)	88 (43.6)
23	Sie	4221	1038 (24.6)	77 (7.4)		NR	907 (87.4)	131 (12.6)
24	Toure	11 051	2294 (20.8)	200 (8.7)		NR	2104 (91.7)	190 (8.3)
25	Tweya	3510‡‡	2254 (64.2)	121 (5.4)		§§	1302 (57.8)	952 (42.2)
26	Weigel	1800	534 (29.7)	128 (24.0)	157 (29.4)	32 (6.0)	317 (59.4)	217 (40.6)
27	Wubshet	551	486 (88.2)	118 (24.3)		135 (27.8)	253 (52.1)	233 (47.9)
28	Yu	253	185 (73.1)	20 (10.8)	1 (0.5)	37 (20.0)	58 (31.4)	127 (68.7)

NR, not reported.
*Upon tracing found patients still receiving ART at the same facility. Patient records either incorrect or patients returned to care between LTFU classification and tracing.
†No. of patients who stopped ART not reported. Ascertained from % breakdown of reasons provided for stopping ART.
‡Author confirmed that deaths determined upon tracing were included in those not traced (not in reported deaths).
§Only directly interviewed 48/79 patients found alive. True outcomes for remaining 31 patients unknown.
¶Patients who upon interviewing refused to answer/denied their HIV status have been added to those reported to have stopped ART.
**Patients reported to have returned to care after tracing not included.
††Reported alive categories add up to 139 (more than those traced less died). Assumed alive = traced less deaths.
‡‡Study reports cases traced not patients. Corresponding author provided data not reported (see Acknowledgements).
§§LTFU cases not patients that stopped ART reported.

studies only reported the number of tracing attempts not the method.

Overall, the quality of evidence contributing to the assessment of true outcomes of traced LTFU patients was considered to be low to moderate, mainly due to the risk of bias within studies, inconsistency in results and imprecision in estimates.

True outcomes of LTFU patients traced

A total of 10 806 patients were traced, representing 16.6–96.3% of the overall tracing study cohort. Table 2 summarises the number of patients traced and their true outcomes. Figures 2–4 summarise the percentage of traced patients who self-transferred, died and stopped ART in each study reporting such outcomes, including confidence intervals (CI) for the point estimates. The combined self-transfer summary estimate from random-effects meta-analysis is 18.6% (95% CI 15.8–22.0%). There was an extensive heterogeneity (τ^2 0.08, $P < 0.000$). The combined summary estimate from random-effects meta-analysis for death was 38.8% (95% CI 30.8–46.8%) and patients stopping ART was 28.6% (95% CI 21.9–36.0%).

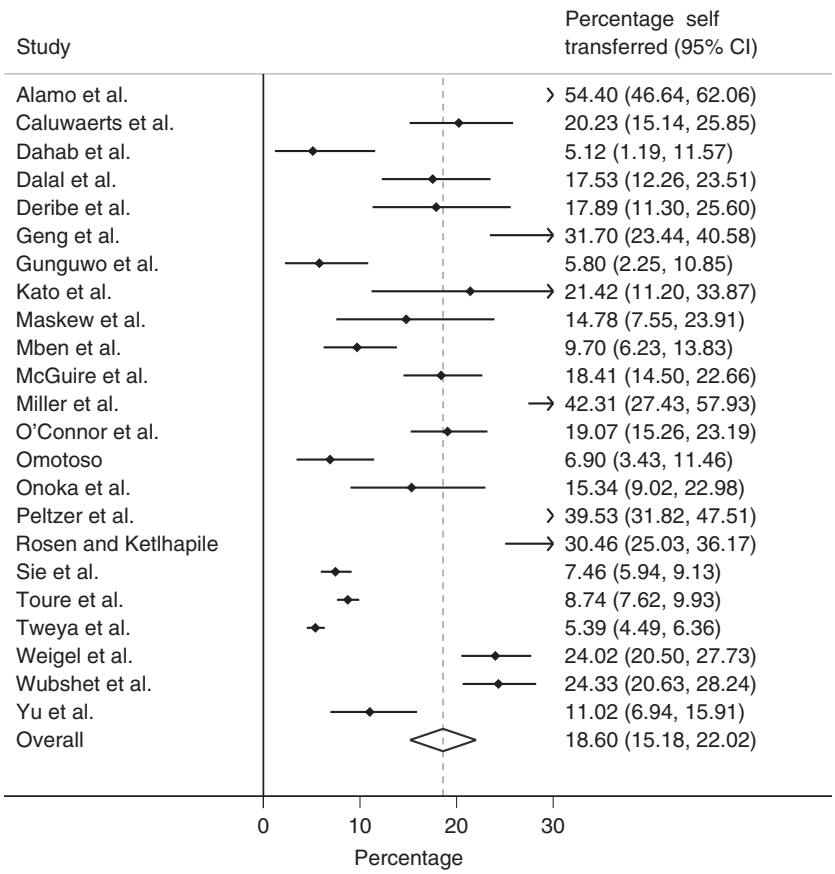

Figure 2 Forest plot – percentage traced LTFU patients found to have self-transferred.

In the random-effects meta-regression (Figure 5), there was a statistically significant positive association between the proportion who self-transferred amongst those traced and the proportion LTFU in the overall ART cohort (β coefficient 0.5, 95% CI 0–0.9).

Subgroup and sensitivity analysis and investigation of heterogeneity

Published studies reported a significantly higher percentage of self-transfers (21.8%, 95% CI 16.2–27.3%) than conference abstracts (8.0%, 95% CI 6.3–9.7%) ($P = 0.03$). Study period and tracing method significantly influenced the percentage of unreported deaths. The percentage of deaths decreased from 50.0% (95% CI 41.5–58.4) to 30.0% (95% CI 21.1–38.9%%) in study periods ending after 31 December 2007, with a lower percentage of deaths ascertained where tracing was only attempted by telephone (21.8%, 95% CI 13.9–29.6% *vs.* 42.6%, 95% CI 31.8–53.5%).

A tendency towards a lower self-transfer percentage was found where study periods ended before *vs.* after 31 December 2007 (16.6%, 95% CI 12.5–20.8% v 20.3%, 95% CI 15.7–25.0%), and where fewer *vs.* two-thirds or more study participants were traced (16.0%, 95% CI 12.3–19.7% v 23.1%, 95% CI 15.0–31.2%).

In sensitivity analysis, exclusion of studies aggregating outcomes for adults and children, or not specifying population age, led to a non-statistically significant increase in percentage of self-transfers (23.8%, 95%CI 15.8–31.8%). Exclusion of non-random tracing cohorts made no difference. There was also no statistically significant difference to the summary estimates of deaths or stopping ART when performing the same sensitivity analyses.

Discussion

This review found that almost one in five ART patients initially reported as LTFU had self-transferred and was retained in ART care. This finding implies that retention in ART care in sub-Saharan Africa is underestimated due to unknown outcomes of LTFU patients. There is

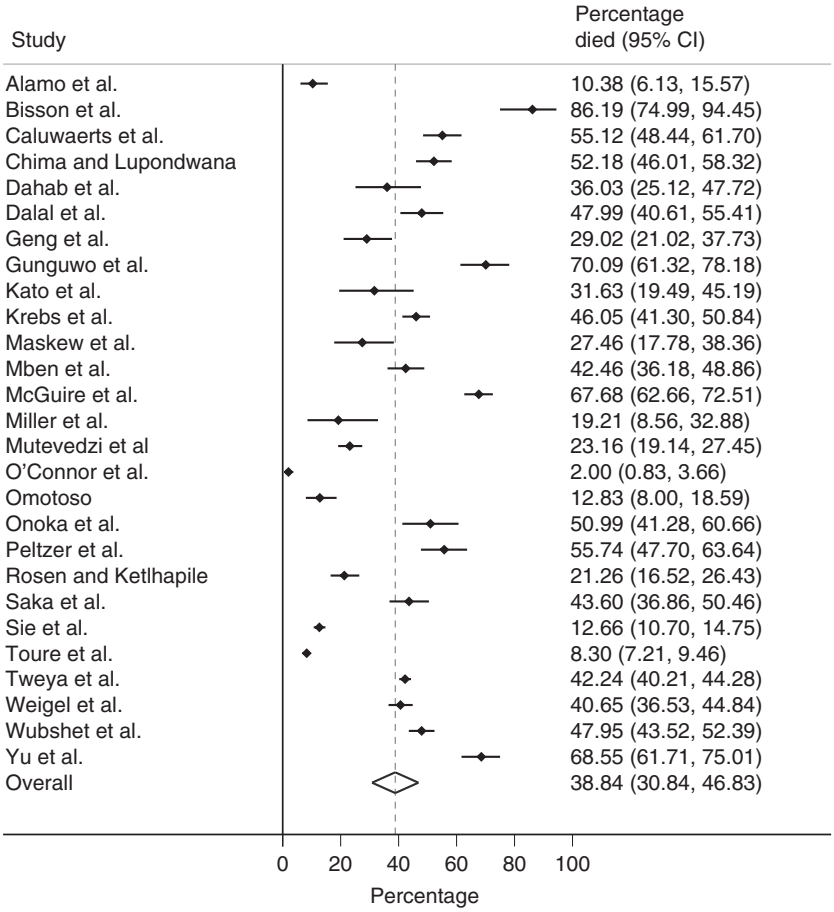

Figure 3 Forest plot – percentage traced LTFU patients found to have died.

evidence that self-transfers have increased after the scale-up of ART coverage and decentralisation. The significant positive association found in our study between self-transfer and LTFU proportions means that programmes with higher LTFU rates can expect higher self-transfer rates and a greater underestimation of retention. Two explanations may provide insight into this finding. Firstly, LTFU rates have been found to positively correlate with ART programme size (Boulle *et al.* 2010) and programme expansion rates (Grimsrud *et al.* 2014), and it is possible that as cohort sizes expand, patients are more likely to self-transfer. Secondly, higher LTFU rates have been found in centralised than primary healthcare facilities (Fatti *et al.* 2010), indicating that patients may self-transfer as the number of facilities offering ART increases and patients are able to access facilities closer to home.

This review also provides an updated summary estimate of 38.8% (95% CI 30.8–46.8%) for mortality amongst ART patients LTFU, compared with 42% (95% CI 34–50%) found previously (Brinkhof *et al.* 2009). Importantly, we found a significant decrease from 50% (95% CI 42–58%) to 30% (95% CI 21–39%) in deaths identified by tracing studies with study periods ending after 31 December 2007. This may be attributable to growing access to ART (Grimsrud *et al.* 2014) and the reduction in the risk of death associated with patients in LMICs initiating ART with higher CD4 counts (Gupta *et al.* 2011; Avila *et al.* 2014).

This review differs in several ways from the previous systematic review of outcomes amongst patients LTFU published in 2009 (Brinkhof *et al.* 2009). We excluded studies reporting pre-ART outcomes; we report the proportion of self-transfers as a percentage of those traced (not of those found alive upon tracing); and we include data up to the end of 2013, which allowed for the inclusion of outcomes for more than double the number of traced patients.

There are inherent limitations to systematic reviews, especially those summarising results from research conducted in routine care settings. This review has a number

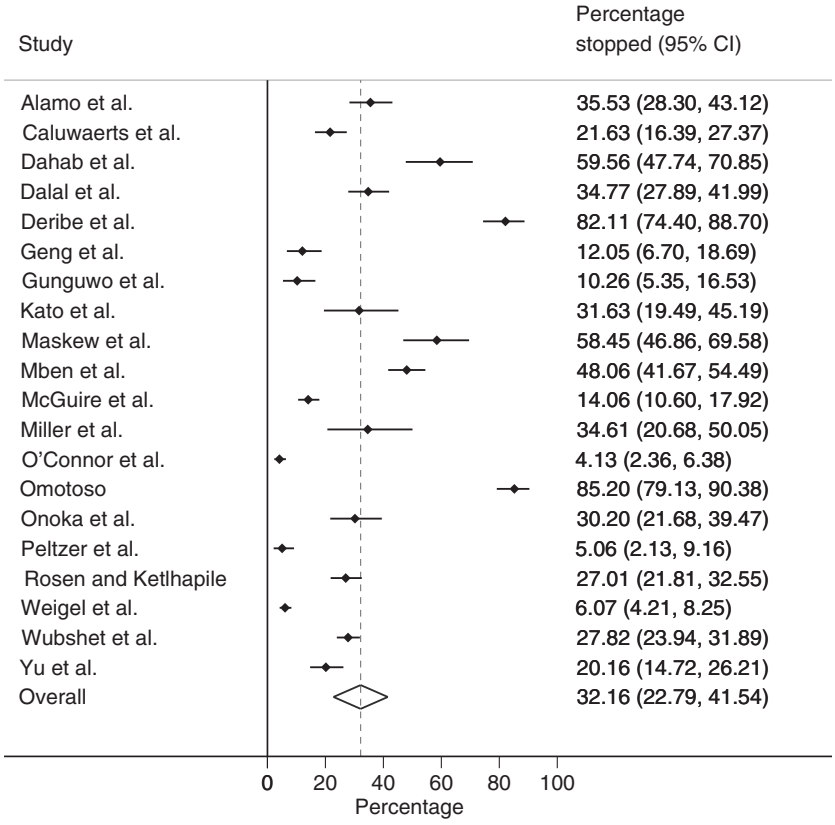

Figure 4 Forest plot – percentage traced LTFU patients found to have stopped ART.

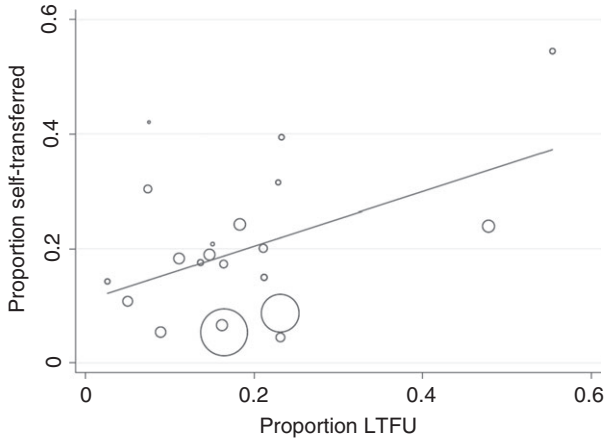

Figure 5 Meta-regression.

of limitations. Firstly, systematic reviews of routine programme outcomes are by definition prone to publication bias, as evidenced by the fact that no studies were identified that reported outcomes from LMICs outside of sub-Saharan Africa. It does not appear, however, that publication bias has favoured the reporting of positive findings as there was a substantial variability between studies, including a number of studies reporting relatively high rates of negative outcomes. Secondly, heterogeneous definitions of LTFU for tracing purposes may mean that studies with shorter intervals were likely to have the number of LTFU patients exaggerated by treatment interrupters (i.e. patients who return to care after a short period of absenteeism) (Shepherd *et al.* 2013), thereby increasing the size of the tracing study cohorts. While the number of patients who self-transferred or died should not change, our LTFU definition may have influenced self-transfer and death rates. Thirdly, the lower self-transfer rate found when limiting the meta-analysis to studies with poor tracing success suggests that large numbers of untraceable patients may underestimate the self-transfer rate (this was not the case for the percentage deaths). Fourthly, it may not be appropriate to assume that the true outcomes of untraceable patients are comparable to those who were traced. Patients with lower socio-economic status are more likely to stop ART than self-transfer (Marson *et al.* 2013), and access to a telephone (which facilitates tracing) may be an indicator

of better socioeconomic status, which in turn may influence survival. Patients who relocate are also less likely to be traced. Due to the risk that true outcome results of tracing studies may be affected by selection bias, correction of retention and mortality should be investigated through sensitivity analysis using a range of plausible self-transfer and mortality estimates. Lastly, tracing studies used heterogeneous approaches to reporting outcomes that may influence the comparability of findings reported.

This review reported tracing a large number of LTFU patients in both rural and urban ART programmes in 12 sub-Saharan African countries, 11 of which are regarded as high HIV prevalence countries (WHO 2013). The vast majority of studies reported on public sector cohorts. These findings may therefore be representative of high-prevalence public sector sub-Saharan African cohorts, but may not be directly generalisable beyond this setting.

These findings confirm the value of tracing patients LTFU, both to ensure appropriate care is provided for the individual and to improve the accuracy of outcome reporting for the overall programme. Due to heterogeneous programmes and contexts, retention and mortality should ideally be reported after tracing all or a random sample of LTFU patients. Where this is not feasible, retention and mortality estimates need to be adjusted to account for self-transferred patients and unreported deaths. The estimates provided by this study can be used to inform outcomes amongst patients recorded as LTFU in sub-Saharan Africa.

In addition, these findings emphasise the importance of health systems accounting for patient mobility and transfer as a normal and expected evolution in ART scale-up. Transfers need to be easily accounted for by monitoring systems so that self-transfers are not counted as LTFU. This could be achieved by encouraging the use of unique patient identifiers that allow tracking of patients across facilities through standardised integrated monitoring systems (Harries *et al.* 2010; Fox *et al.* 2012). Such systems are unfortunately not perfect, and mechanisms need to be put in place to ensure patients are not issued with a new unique identifier at the new facility (McGuire *et al.* 2010). Alternative strategies could include strengthening referral systems and ensuring a regular exchange of information between facilities (Egger *et al.* 2011). As the number of sites providing ART increases, patient mobility is likely to become more common and should be supported by increasing patient awareness and understanding of transfer procedures (Mben *et al.* 2012), removing any pre-conditions for transfer (Wubshet *et al.* 2013), simplifying facility processes for transfer (Miller *et al.* 2010) and providing incentives in the form of a longer supply of ART. Longer ART supply also helps cover the period of moving between facilities thereby limiting unnecessary treatment interruptions (Grimsrud *et al.* 2013; Tweya *et al.* 2013). Health authorities should encourage facilities to be 'transfer friendly' so that patients feel comfortable with communicating their intention to transfer.

This systematic review provides several directions for future research. ART programmes should continue to publish tracing studies undertaken as these provide valuable data to inform future updated systematic reviews and meta-analysis. In particular, tracing studies are required from LMICs beyond sub-Saharan Africa and with study periods after 2010, to further assess whether self-transfers increase and unreported deaths decrease with growing ART access and coverage. Future reviews would be less prone to bias and provide a better quality of evidence if tracing studies followed a standardised approach to reporting outcomes. It is particularly important to report on outcomes of LTFU patients rather than cases traced and not only on deaths ascertained but patients who self-transfer, stop ART and return to care before and after tracing. Tracing studies should further aim to ascertain the reasons for a patient self-transferring care. Patients who have stopped ART should be asked whether they initially intended transferring their care and which obstacles prevented such transfer. This would allow assessment of obstacles to transfer notification and their impact on continuity of care. Lastly, studies describing appropriate retention adjustment models are necessary to provide guidance to those reporting ART cohort outcomes in the future.

In conclusion, ART programmes with high LTFU rates can expect large numbers of self-transfers 'hidden' in the LTFU classification. To protect against inappropriate disinvestment from, and poor forecasting for, ART care provision, retention estimates need to be adjusted to account for self-transfers.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Study protocol.

Appendix S2 Risk of bias assessment.

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