JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000000075

Tracing of patients lost to follow-up and HIV transmission: Mathematical modelling study based on two large ART programmes in Malawi

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Abstract 250 words, main text 3456 words, 3 tables, 2 figures and 1 Supplementary Digital Content text file including 7 tables

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Preliminary results of this study were presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012), March 2-5, 2012 in Seattle, WA, United States.

This work was supported by a PROSPER fellowship to O.K. for O.K. and J.E. (grant 32333B_131629) and a PhD fellowship to O.K. and M.E. for N.B. (grant PDFMP3_137106) from the Swiss National Science Foundation; an Operational Research Fellow fellowship to H.T. from the International Union against Tuberculosis and Lung Disease; and the National Institutes of Health (grant 5U01-AI069924-05).

The authors have conflicts of interest to declare

Running head: Tracing and HIV transmission in Malawi

Abstract

Objectives: Treatment as prevention depends on retaining HIV-infected patients in care. We investigated the effect on HIV transmission of bringing patients lost to follow up (LTFU) back into care.

Design: Mathematical model.

Methods: Stochastic mathematical model of cohorts of 1000 HIV-infected patients on antiretroviral therapy (ART), based on data from two clinics in Lilongwe, Malawi. We calculated cohort viral load (CVL; sum of individual mean viral loads each year) and used a mathematical relationship between viral load and transmission probability to estimate the number of new HIV infections. We simulated four scenarios: 'no LTFU' (all patients stay in care); 'no tracing' (patients LTFU are not traced); 'immediate tracing' (after missed clinic appointment); and, 'delayed tracing' (after six months).

Results: About 440 of 1000 patients were LTFU over five years. CVL (million copies/ml per 1000 patients) were 3.7 (95% prediction interval [PrI] 2.9-4.9) for no LTFU, 8.6 (95% PrI 7.3-10.0) for no tracing, 7.7 (95% PrI 6.2-9.1) for immediate, and 8.0 (95% PrI 6.7-9.5) for delayed tracing. Comparing no LTFU with no tracing the number of new infections increased from 33 (95% PrI 29-38) to 54 (95% PrI 47-60) per 1000 patients. Immediate tracing prevented 3.6 (95% PrI -3.3-12.8) and delayed tracing 2.5 (95% PrI -5.8-11.1) new infections per 1000. Immediate tracing was more efficient than delayed tracing: 116 and to 142 tracing efforts, respectively, were needed to prevent one new infection.

Conclusion: Tracing of patients LTFU enhances the preventive effect of ART, but the number of transmissions prevented is small.

Keywords: antiretroviral therapy; transmission; sub-Saharan Africa; lost to follow-up; mathematical model

Introduction

Despite the recent decrease in HIV incidence, an estimated 2.5 million people were newly infected with HIV worldwide in 2011[1]. One promising intervention to fight the global HIV epidemic is antiretroviral therapy (ART)[2,3]. HIV-1 RNA (viral load) and infectiousness are strongly associated[4,5]; successful ART suppresses viral load to undetectable levels and makes onward transmission unlikely. However, replication of HIV in patients who interrupt therapy or whose ART fails will rebound and increase the risk of transmission. The full benefit of treatment as prevention can only be sustained if patients are retained in care, have good adherence, and if treatment failures are identified in time[6].

In 2006, to actively trace patients lost to follow-up (LTFU), two public ART clinics in Malawi introduced the 'Back-to-Care' (B2C) programme. Almost 30% of patients who missed an appointment and were found by tracing had stopped or never started ART[7,8]. Two-thirds of the patients found alive outside official treatment programmes eventually returned to care. Although the main goal of the B2C programme is to improve survival and quality of life of patients on ART, this intervention may also reduce transmission. The effect of tracing programmes on transmission is however unclear, and has not been explored.

We investigated the effect of interrupting ART on the risk of HIV transmission at the population level, and the effect of bringing patients LTFU back into care using different strategies of tracing. To this end, we developed a mathematical model based on data from the B2C programme in Malawi.

Methods

'Back-to-care' tracing programme: Study setting and tracing procedure

By the end of 2012, 405,000 patients were on ART in 651 ART clinics in Malawi[9]. The B2C programme[8] was introduced in 2006 at the Lighthouse Clinic[10,11] and the Martin Preuss Centre (MPC)[12], the two largest public ART programmes in Lilongwe. Together they treat about 7% of all patients in Malawi. Under B2C, patients are declared LTFU three weeks after a missed appointment. The B2C team then attempts to contact the patient by phone or personal visit. If the patient died or is receiving ART from another provider, the outcome (death or transfer-out) is updated in the patient records. If the patient is not found, the outcome remains LTFU. Transfers among patients LTFU may be official (recorded in the patient's health passport but missing from the clinic records) or self-transfers (patient changes clinics without informing the original clinic). If the patient discontinued or interrupted ART, or received ART from sources other than official clinics (e.g. friends, relatives, unlicensed vendors), the tracing clerk will, with the patient's consent, schedule a new appointment at Lighthouse or MPC to restart ART. Herein, we refer to ART with gaps and ART from unofficial sources as 'irregular ART' (see **Table S1, Section 1.1, Supplemental Digital Content**, http://links.lww.com/QAI/A493).

Data characteristics and statistical analyses

The characteristics of the dataset have been described in detail by Tweya *et al*[8]. The dataset included 23,137 adult patients (aged ≥16 years) with a median follow-up time of 1.3 (interquartile range 0.4-2.8) years (see **Table S2, Section 1.1, Supplemental Digital Content**, http://links.lww.com/QAI/A493). At the end of follow-up, 13,302 patients were alive and in care, 1706 had died, 539 were alive without ART, 4335 had transferred out to another ART clinic, and 3262 were LTFU. A total of 4851 LTFU cases were discovered during the study period and in 4805 (99%) of these tracing was attempted. In 3381 (70%) cases the patient's outcome was verified through tracing

(see **Table S3, Section 1.1, Supplemental Digital Content**, http://links.lww.com/QAI/A493). We estimated time from start of ART to the first instance of death, official transfer, self-transfer, discontinuation of ART, irregular ART or LTFU. We used a competing risk analysis to calculate the cause-specific hazard and corrected these hazards for events that could not be verified by assuming that the proportion of events was the same among unverified cases as among verified cases (see **Section 1.2-1.3, Supplemental Digital Content**, http://links.lww.com/QAI/A493Sections 1.2-1.3). We estimated expected non-HIV-related background mortality from the Global Burden of Disease study[13,14] and subtracted it from observed mortality. Parametric distributions were fitted to the corrected hazards. We then investigated the probability of finding patients LTFU by tracing, and the rate of their return back to care. We fitted a Weibull distribution to the observed distribution of return times.

Mathematical model

We used the R package 'gems', a general framework for individual-based multistate models to simulate patients under different scenarios of LTFU and tracing[15]. The model simulates the progression of individual patients from a chosen starting time until a fixed censoring time. The possible paths of progression are presented as states and transitions. Transition times are sampled for each patient from transition-specific time-to-event distributions, which are allowed to take an arbitrary form. The output of the model is a matrix of the entry times of each simulated patient into each state, which we then convert into rates of outcomes of interest.

Figure 1 illustrates the possible transition paths. The simulation begins at start of ART, after which point the patient is at risk of official transfer, self-transfer, change to irregular ART, discontinuation, and death (Table 1). A proportion of official transfers, deaths and discontinuations remain unregistered. These unregistered events, as well as self-transfers and changes to irregular ART, are initially observed as LTFU. Patients who discontinued ART or are on irregular ART can return to care spontaneously or after tracing. Time spent on ART is further divided into first-line and second-line

ART, and into successful ART, virologically failing ART (viral load permanently above 1000 copies/ml) or immunologically failing ART (CD4 count meeting the WHO immunological failure criteria[16]). We assumed that 6-monthly CD4 count (but not viral load) monitoring is available, and that patients switch to second-line ART after two consecutive measurements that meet WHO immunologic failure criteria[16]. The full model includes 113 states (see **Table S4, Section 2.1, Supplemental Digital Content**, http://links.lww.com/QAI/A493). We simulated cohorts of 1000 patients followed-up for five years after starting ART.

Based on the transition times, we assigned each simulated patient a viral load trajectory to determine their risk of HIV transmission over time (see **Section 2.2, Supplemental Digital Content**, http://links.lww.com/QAI/A493). We assumed that patients on virologically successful ART, including patients on irregular ART, had undetectable viral load. Two measures of transmission were estimated: cohort viral load (the sum of mean viral loads of each patient during a particular year[6], applying the concept of community viral load[17] to a cohort of treated patients); and, the expected number of transmissions, calculated from the individual viral load trajectories using a functional formula[5,6]. We assumed that all patients were in consecutive one-year partnerships and had 100 unprotected sex acts per year[5]. HIV prevalence among partners at the beginning of the partnership was assumed to be 15%[18].

Whenever possible, we used the results of our statistical analyses to estimate the parameters related to the patient's progression through different retention states (Table 2; see **Table S5, Section 3, Supplemental Digital Content**, http://links.lww.com/QAI/A493). Parameters related to virological and immunological progression were based on the findings of a previous study of two South African township cohorts[6].

Simulated strategies

We simulated four scenarios. In the first scenario, "No LTFU", we assumed all patients stay in care and on ART until death, and events (death, transfer) are correctly recorded. In the remaining three

scenarios, we included all types of LTFU (unregistered deaths and transfers, irregular ART and discontinuation of ART). A patient was considered LTFU if he or she missed a visit at the clinic (scheduled once a month) by 3 weeks. In the "No tracing" scenario, patients could return spontaneously to care, not as a result of tracing efforts. In the "Delayed tracing" scenario, patients were traced six months after LTFU. In the "Immediate tracing" scenario, patients were traced as soon as they were LTFU (3 weeks after the missed appointment).

We first describe the model's estimation of LTFU. To estimate the impact of retention in care on the preventive effect of ART, we then compare cohort viral load and transmission in scenarios with and without LTFU. Finally, we compare cohort viral load and transmission across the three scenarios in which patients LTFU are traced. Model outputs are presented as mean values over 100 model runs, with 95% prediction intervals (PrI). We conducted two sensitivity analyses to account for uncertainty in selected parameters. In the first analysis, we modified the rates of discontinued and irregular ART. About one-third of the patients in the dataset who were on irregular ART had gaps in ART intake and may therefore have had detectable viral load. We reduced the hazard of irregular ART by one-third and increased the hazard of ART discontinuation by the corresponding amount. In the second analysis, we decreased the rate of spontaneous return to one-third of the assumed rate we had assumed in the main analysis.

Results

Table 3 shows model estimates for the number of patients LTFU for different reasons, number of patients traced, number of patients returning to care, total cohort viral load, and number of expected transmissions for the three strategies that included LTFU per 1000 patients over five years.

Rates of loss to follow-up

The model estimated that about 440 out of 1000 simulated patients were LTFU in the first five years of ART (Table 3). About 160 patients were lost in the first year of ART, and between 50 and 90 in each of the following years. According to the model outputs, 23% of the patients LTFU had died. Discontinued treatment accounted for 37% of LTFU, changes to irregular ART for 26%, unregistered official transfers out for 8%, and self-transfers for 5%.

Effect of loss to follow-up on transmission

In the absence of tracing, LTFU more than doubled cohort viral load over that of a cohort fully retained in care (Figure 2A). The number of expected transmissions over five years increased from 33 to 54 per 1000 patients (Figure 2B). In the first year of ART, the number of expected transmissions per 1000 patients was about 9 in the scenario without LTFU, and 11 in the scenario with LTFU. Annual transmissions in subsequent years decreased in the scenario without LTFU, and stayed close to 6 from the second year on. In the scenario with LTFU and no tracing, transmissions per year were between 10 and 11.

Tracing and prevention of transmission

Without tracing, 50% of the patients who discontinued or changed to irregular ART spontaneously returned to care within five years. Immediate tracing increased the probability of return to 68%. With delayed tracing after 6 months, 59% of the patients who were expected to return did so within the 5-

year follow-up time. Tracing reduced transmission moderately from the second year onwards. Cohort viral load in the cohort of 1000 patients was about 9 million copies/ml during the first year for all three strategies (Figure 2A). Cohort viral load remained on the same level without tracing over the following years, but declined gradually to 6–7 million copies/ml with tracing. The pattern for expected transmissions was similar (Figure 2B). During the first year, the 1000 treated patients transmitted on average 11 new infections in all scenarios. Over the subsequent years, the number of expected transmissions remained close to 11 without tracing, and decreased gradually to about nine per 1000 with tracing. Over the five first years of ART, immediate tracing prevented 3.6 (95% PrI - 3.3–12.8) new infections for each 1000 patients. Tracing after six months prevented 2.5 (95% PrI - 5.8–11.1) new infections. Immediate tracing was more efficient than delayed tracing: 116 patients had to be traced to prevent one infection when tracing was immediate; 142 patients had to be traced to prevent one infection when tracing was delayed.

Sensitivity analyses

In the first sensitivity analysis, we increased the rate of discontinuation and decreased the rate of changing to irregular ART. Among all LTFU cases, the proportion of patients who discontinued ART increased from 37% to 51%. The increase in the number of patients alive and not on ART also increased the cohort viral load and moderately raised expected transmissions above the number from the main analysis in the absence of tracing. However, immediate tracing was more efficient than in the main analysis, and prevented 5.1 (95% PrI -3.6–13.4) infections. The number of patients who needed to be traced to prevent one infection decreased to 86, with immediate tracing (see **Table S6, Supplemental Digital Content**, http://links.lww.com/QAI/A493).

In the second sensitivity analysis, we decreased the rate of spontaneous return from 0.33 to 0.10, so that about 10% (instead of almost 30%) of patients outside care spontaneously returned to the clinic within a year. If tracing was not available, during the five years of follow-up, only 58 of the 138 patients expected back actually returned. In the main analysis, immediate tracing increased the

proportion of patients returning to care by 37%. In this sensitivity analysis, the immediate tracing more than doubled the proportion of patients who returned. The higher return from tracing reduced HIV transmission: tracing with a six-month delay prevented 3.7 infections, and immediate tracing prevented 5.5 infections. About 78 immediate tracing efforts were needed to prevent one new infection (see **Table S7, Supplemental Digital Content**, http://links.lww.com/QAI/A493).

Discussion

This mathematical modelling study based on two ART programmes in Malawi found that tracing patients LTFU can slightly reduce transmission from patients who started ART. If 1000 patients are in one-year partnerships and engage in 100 sex acts per year, active tracing can prevent one to five infections in this cohort over the first five years of ART. This is only a fraction of the >20 infections transmitted by patients who discontinued or interrupted ART. The effect depends on the delay between missed visit and tracing and on assumptions about both the rate of spontaneous return and the virological suppression of patients on irregular treatment.

In our main analysis, we found that 120 patients needed to be traced to prevent one new infection. If one tracing clerk can trace 4-5 missing patients per day, preventing a single transmission would require a 1.5 month workload. We judge this a reasonable investment since a newly infected patient will need life-long treatment and care costing thousands of dollars, and HIV infection can cut short a patient's life. We made some conservative assumptions (a relatively high spontaneous return rate and a complete viral suppression for patients with irregular ART) in our main analysis, and so may have underestimated the efficacy of tracing as prevention. We used sensitivity analyses to test on these assumptions the dependency of the efficacy of tracing as prevention, and found that the number of patients who needed to be traced decreased to about 70 if we used assumptions more favourable to tracing.

Immediate tracing of patients LTFU compared to delayed tracing after six months increased the efficacy of the intervention. The rationale for delayed tracing is that it reduces the burden of tracing by giving the patient time to spontaneously return. The delay slightly decreased the number of necessary tracings, but did not prevent as many transmissions as immediate tracing, and was thus less efficient. When tracing was delayed, the number of tracing efforts needed to prevent one

infection increased about 26%. Our results underline the necessity of tracing patients LTFU as soon as possible.

Patients who interrupted ART contributed almost 40% of transmissions from treated patients, but tracing prevented less than a fifth of these infections. Interventions to improve retention and prevent LTFU may be more effective in reducing transmissions although no dedicated modelling studies have been conducted. Studies from Malawi show LTFU rates are lower in health centres than in large referral hospitals, so decentralized ART care in smaller health care units is a promising strategy[19,20]. Retention may also be improved by introducing rapid point-of-care diagnostic tests[21] and increasing community support[22]. Patients in care also contribute to transmission through poor adherence and treatment failure. Viral load monitoring can help identify patients with detectable viral load and minimise the transmission from these patients. Viral load monitoring can prevent about 30% of transmissions from patients retained in care[6] and is likely to prevent more infections than tracing.

Strengths and limitations

Our model was parameterised with routine data from two typical African public-sector ART programmes in Lilongwe, Malawi, where patients present with low CD4 counts and symptoms of advanced disease, and the majority of patients are women (see **Table S2, Supplemental Digital Content**, http://links.lww.com/QAI/A493). Our results should be applicable to many African settings, but are affected by our assumptions and we must acknowledge several limitations. We found that the rate of LTFU remained high even after tracing. We assumed the same proportion of different outcomes among patients who remained LTFU after tracing as among patients who were found. This might not be accurate because the outcome can influence the probability of finding the patient: for example, a patient who has moved to another region is probably harder to trace and also more likely to have transferred to another ART clinic than a patient who stays at the same address. Moreover,

we could not estimate some parameters, like the rate of spontaneous return and the infectiousness of patients who dropped out of care, from the data.

One advantage of cohort viral load is that it does not depend on assumptions about the sexual behaviour of patients. The disadvantage is that it cannot estimate the reduction in the absolute number of infections, and can only approximate relative benefit. On the other hand, the expected number of transmissions is easily understood, but also sensitive to the frequency of sex acts and changes of partners. In our model, all patients had 100 unprotected acts per year and changed partners each year. The absolute numbers of new infections that we present are therefore specific to this scenario. Due to the low per-act probability of transmission, the number of transmissions is approximately proportional to the frequency of acts, and the effect of partner change rate is negligible[6]. Therefore, the relative reduction in transmissions due to tracing will remain stable across the different risk behaviour scenarios. If we however assume, for example, 25 sex acts per year, then it would take 400-500 tracings to prevent one infection.

Mathematical modelling has been widely used to compare management strategies for HIV-infected patients and to identify the optimal strategy[3,6,23-25], but most modelling studies have not compared model outputs to observed data. One reason for this is that the outputs of models are not necessarily directly comparable to observed data. The proportions of true outcomes among patients LTFU in our model did not exactly match the corresponding proportions in the source data. This is mainly due to differences in censoring between the data and model: in the model everyone is followed up for exactly 5 years, whereas in the dataset the follow-up time varied considerably, ranging from no follow-up to 10 years. Some of the difference can be attributed to the model: patients cannot return to earlier states and the number of events per patient is restricted in the model. In the real world, the same patient can become LTFU and return several times within a given follow-up period. This means that although the number of LTFU episodes predicted by the model is close to reality, the number of patients who survive the entire follow-up time is higher in the data than in the model. This makes it harder to compare the model with data, but it should not affect new infections, the

main outcome of interest. Our model is also not a dynamic transmission model: we can estimate the potential transmission from the cohort but not evaluate the long-term effect on the transmission at the population level. The model we used has some important advantages. For example, time-to-event distributions are flexible and the model allows for time- and history-dependent hazards.

Some of the differences we observed may also be due to chance. We investigated the possibility of stochastic error by splitting the total cohorts into 10 subcohorts of 10,000 patients and compared the results. Consistent results from the subcohorts confirmed that cohorts of 100,000 simulated patients are large enough to provide reliable estimates of the true effect.

Conclusions

Until now, the focus of tracing has been on improving the patient's own health, on preventing mother-to-child transmission and on providing reliable estimates of cohort outcomes[7,26,27]. Our analysis shows that tracing offers an additional benefit. Tracing patients LTFU may efficiently reduce HIV transmission in Malawi and similar settings. Although the number of prevented transmissions may be small, the associated workload is reasonable in light of the cost of each infection averted. Our findings support the inclusion of active tracing in guidelines of ART provision in low-income settings. However, most transmissions from patients who dropped out of care cannot be prevented by tracing alone. Interventions to keep patients in care and monitoring of adherence and treatment response accurately are likely to be of greater importance than tracing patients lost to follow-up.

Acknowledgements

We thank Kali Tal for commenting on and editing the paper.

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Figure Legends

Figure 1. Schematic representation of the mathematical model. The full model consists of 113 states, which are grouped here into 13 groups to simplify the graph (for a description of the full model, see **Table S4, Supplemental Digital Content**, http://links.lww.com/QAI/A493). Each patient starts in the group of states "alive and on ART (antiretroviral therapy)" and can proceed through the different paths. White boxes represent states where the patient's outcome is known to the original ART clinic. Grey boxes represent states observed as loss to follow-up, and patterned boxes states where the patient is being traced. Tracing is represented by dashed arrows.

Figure 2. Cohort viral load and expected transmissions in the four modelled scenarios: no loss to follow-up (LTFU), realistic LTFU without tracing, realistic LTFU with tracing after 6 months and realistic LTFU with immediate tracing. Panel A shows the cohort viral load and panel B the expected number of transmissions from 1000 patients during the first five years after ART initiation.

Table 1. Interpretation of events in the mathematical model.

Event	Interpretation
Official transfer out, recorded	Patient transfers to another clinic, and transfer is recorded in the health passport and the clinic records.
Official transfer out, unrecorded	Patient transfers to another clinic, and transfer is recorded in patient's health passport but not in the clinic records.
Self-transfer out	Patient transfers to another clinic without informing the original clinic.
Irregular ART	Patient takes ART (with or without gaps) but does not receive antiretroviral drugs from official clinics.
ART discontinuation, recorded	Patient discontinues ART by clinician's recommendation, and this is recorded in the clinic's records.
ART discontinuation, unrecorded	Patient discontinues ART without informing the clinic.
Death, recorded	Patient dies and the clinic is informed about the death.
Death, unrecorded	Patient dies, but the clinic is not informed about the death.

The events listed in this table correspond to the events presented in Figure 1. See Table S1 (Supplemental Digital Content) for the corresponding list of events in the dataset.

Table 2. Selected key model parameters.

	Distribution and value	Source
HIV-related mortality	Double Weibull	B2C
Shape 1	1.340	
Scale 1	0.199	
Shape 2	0.719	
Scale 2	40.557	
Weight of 1st component	0.031	
Official transfer out	Weibull	B2C
Shape	1.015	
Scale	8.196	
Self-transfer out	Weibull	B2C
Shape	1.637	
Scale	32.813	
Changing to alternative ART sources	Weibull	B2C
Shape	1.207	
Scale	21.785	
ART discontinuation	Weibull	B2C
Shape	0.666	
Scale	43.102	
Probabilities of missing an event		B2C
Death	0.583	
Official transfer out	0.140	
ART discontinuation	0.900	
Spontaneous return	Exponential	assumption
Rate	0.333	
Probability to be found by tracing		B2C
If discontinued ART or on irregular ART	0.700	
Return after tracing if discontinued ART	Weibull	B2C
Shape	0.476	
Scale	2.74	
Return after tracing if on irregular ART	Weibull	B2C
Shape	0.574	
Scale	0.599	
Partner change		assumption
Rate	1	
Frequency of sex acts		assumption
Acts per year	100	
Per-act probability of transmission		From Wilson et al.[5]
Male to female, viral load 10 copies/ml	$4.3*10^{-5}$	
Female to male, viral load 10 copies/ml	$2.2*10^{-5}$	
Risk ratio per 1 $\log_{10}$ increase in viral load	2.45	

ART, antiretroviral therapy; LH, Lighthouse Clinic (longitudinal data from IeDEA Southern Africa database); B2C, Back-to-Care tracing programme[7]. Weibull distribution is parameterised using the following formula for cumulative incidence (*CI*): $CI(t) = 1 - e^{-\left(\frac{t}{\lambda}\right)^{k}}$, where *k* is the shape parameter and λ the scale parameter. Double Weibull distribution is a mixture of two Weibull distributions.

Table 3. Outcomes and potential transmission from simulated cohorts of 1000 patients during the first 5 years since antiretroviral therapy start with either no tracing, tracing after 6 months (delayed tracing) or immediate tracing.

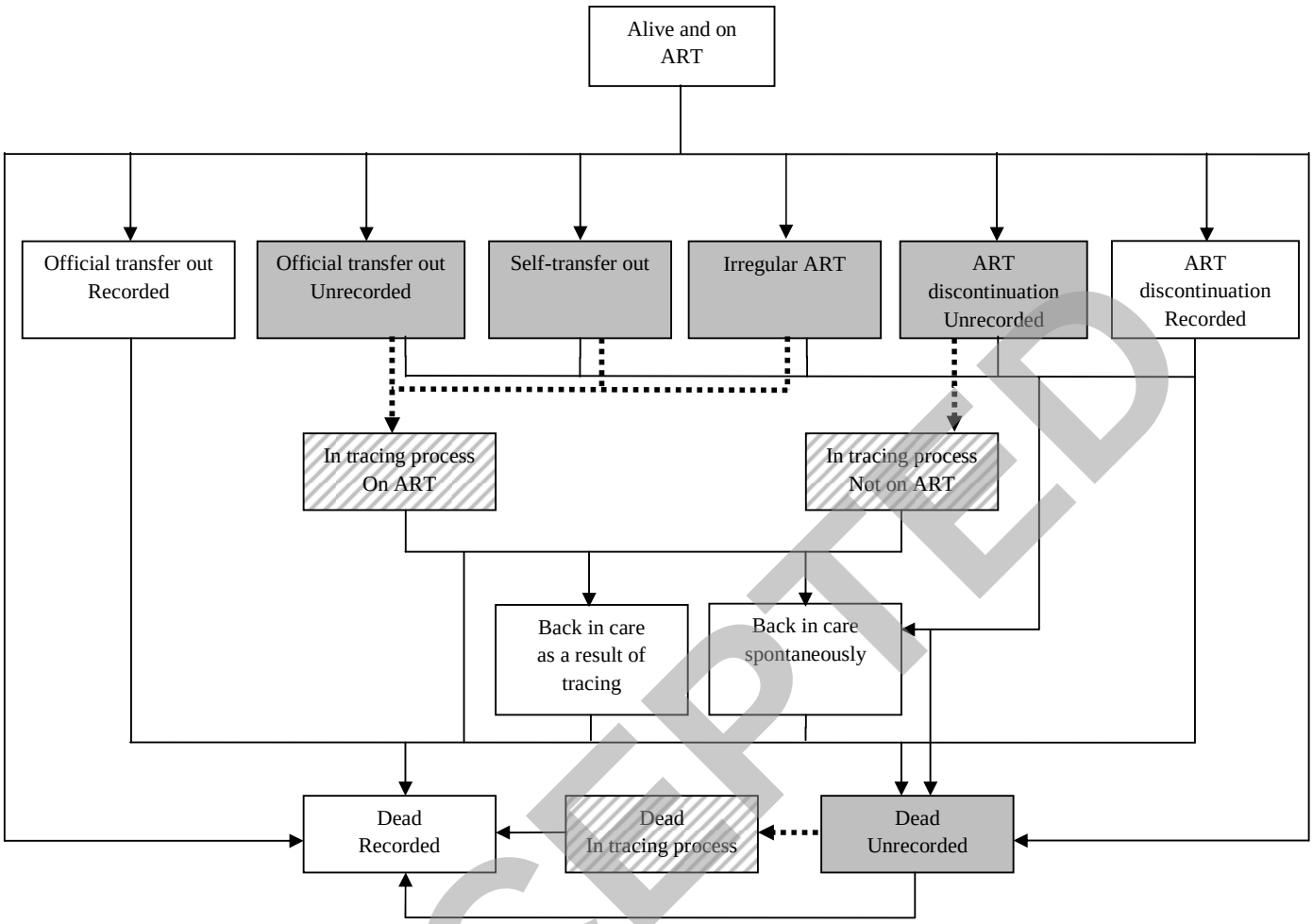
Outcomes	Immediate tracing	Delayed tracing	No tracing
Loss to follow-up			
Unrecorded deaths	158 (134-180)	168 (142-194)	181 (158-205)
Unrecorded official transfers out	36 (26-47)	37 (27-47)	36 (23-51)
Self-transfers out	21 (13-31)	20 (13-29)	21 (12-31)
Irregular ART	110 (91-130)	109 (93-128)	114 (96-140)
Discontinuation of ART	152 (136-174)	155 (130-175)	162 (138-189)
Total*	440 (409-474)	438 (405-471)	437 (403-468)
No. of tracings attempted	420 (385-453)	360 (334-391)	0
Returned to care	179 (156-200)	157 (132-184)	138 (120-155)
HIV transmission			
Cohort viral load (10^6 copies/ml)**	7.7 (6.2-9.1)	8.0 (6.7-9.5)	8.6 (7.3-10.0)
No. of new infections	50.1 (43.7-56.4)	51.2 (45.8-56.4)	53.7 (47.4-60.4)

ART, antiretroviral therapy

Results are given as total number of events over the 5 years of follow-up unless otherwise mentioned. We present the mean values over 100 model runs with 95% prediction intervals.

*Number of patients lost to follow-up at least once; patients were allowed to have at maximum one of the following events: unrecorded official transfer-out, self-transfer out, irregular ART, discontinuation of ART; and in addition to this, unrecorded death.

**Cohort viral load is defined as the sum of mean viral loads of all patients across the 5 years of follow-up.



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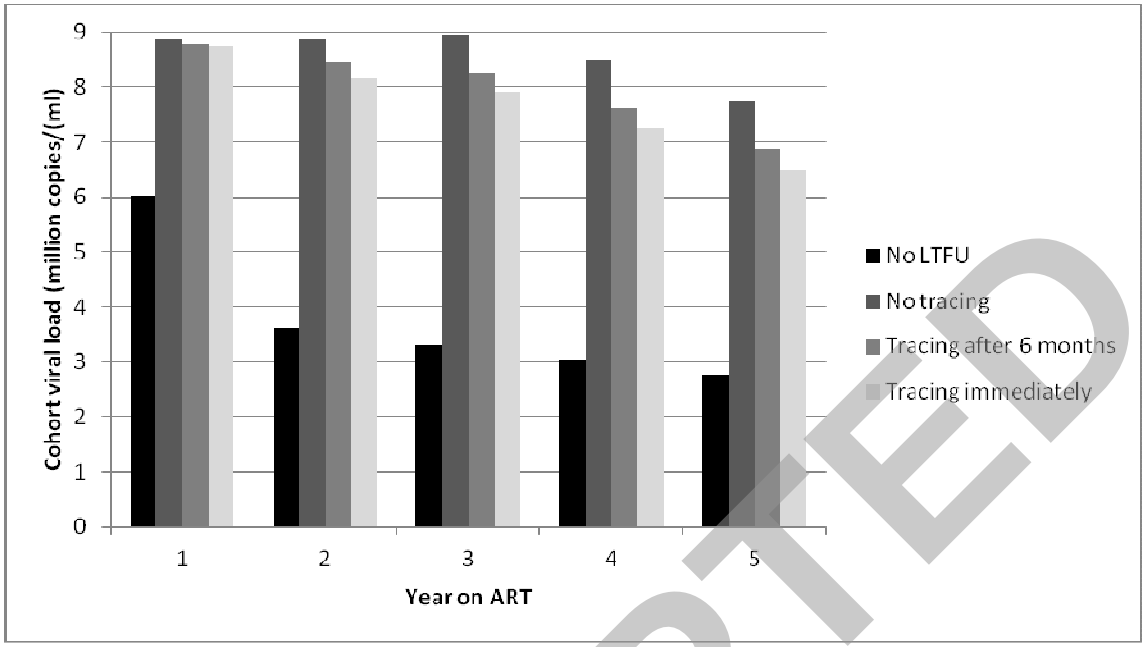

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