Title: Adult antiretroviral therapy in resource limited settings: a systematic review of first-line failure and attrition rates

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Abstract

Background

To forecast demand for antiretroviral therapy (ART), data on the treatment failure and attrition rates in treatment cohorts are needed.

Methods

We conducted a systematic review of the treatment failure and attrition rates reported by cohorts using WHO-recommended first-line antiretroviral regimens in resource-limited settings.

Findings

For studies using clinical/immunological definitions of treatment failure, the failure rate per 100 patient years of follow-up (PYFU) was 1.9 (95%CI 1.48-2.38). By region, this rate was 2.64 (95%CI 1.73-3.56) in Africa, 2.57 (95%CI 1.80-6.94) in Latin America, and 1.11 (95%CI 0.11-2.1) in Asia. For studies using virological criteria to define failure, the failure rate was 6.08 (95%CI 4.51-7.66) overall, 7.10 (95%CI 5.11-9.09) in Africa, and 2.55 (95%CI 1.14-3.96) in Asia. The attrition rates were 20.17 (95%CI 17.35-22.98) overall, 23.47 (95%CI 18.73-28.21) in Africa, 9.75 (95%CI 8.59-22.98) in Latin America and 9.95 (95% CI 7.47-16.97) in Asia. Failure rates were comparable when adjusted for attrition; for studies using clinical/immunological definitions 2.13 (95%CI 1.61-2.64), and 5.88 (95%CI 4.37-7.39) for those using virological definitions of failure.

Interpretation

While the heterogeneity between studies and regions, and study methodologies require cautious interpretation, the reported first-line treatment failure rates in resource-limited settings were low when clinical/immunological failure definitions were used, but approximately three times higher when viral load was used to define failure. The ability to retain people in treatment remains limited. African programmes reported, on average, higher failure and attrition rates than Latin American and Asian programmes.

INTRODUCTION

The United Nations General Assembly High-Level Meeting on AIDS (UNGASS) has committed to reaching as close to the goal of universal access to HIV prevention, treatment, care and support by 2010.(1) Key to achieving this goal is increased production, sustainable supply of antiretroviral treatment (ART), and accurate demand forecasting. The latter requires data on cohort attrition and the rate of switching from first-line to second-line ART within treatment programmes.

In previous forecasts of demand for antiretroviral medicines, the Secretariat of AIDS Medicines and Diagnostics Services (AMDS) of the World Health Organization (WHO), and the Joint United Nations Programme on HIV/AIDS (UNAIDS), in collaboration with Mexico's National Institute of Public Health, and the Clinton Foundation HIV/AIDS Initiative used a survival curve derived from empirical data from Senegal, Brazil and the USA and assumptions on loss to follow up (LTFU) reported by the Antiretroviral Therapy in Lower Income Countries (ART-LINC) initiative, but also identified the need to develop more generalisable assumptions.(2) This led to the present systematic review of rates of first line ART failure and attrition in low and middle income countries.

METHODS

Definitions

In this review, first-line ART is the initial regimen prescribed for an ART-naïve patient. (3) Second-line ART is the next regimen used in sequence immediately after first-line ART has failed. (3) Switching is defined as a change to second-line ART due to failure of first-line ART.

Treatment failure is defined by one of the three WHO criteria: clinical (new or recurrent WHO stage 4 or certain stage 3 conditions); immunological (CD4 decrease to pre-therapy baseline or below, 50% fall from the on-treatment peak value, or persistent CD4 levels <100 cell/mm^3); or virological (plasma viral load > 10,000 copies/ml). (3) As the WHO-recommended definition of virological failure was used in only one study, the viral load cut-off for failure reported by each individual study was used in this analysis. If virological failure cut offs were reported at both 1000 copies/mL and 400 copies/mL, we used 400 copies/mL. We also accepted a decline in CD4 cell count of 30% from the peak on-treatment level as this was used in two of the studies. (4-5) In our analysis, we combined clinical and immunological definitions of failure, as most studies did not report these separately.

Retention is defined as alive and still on any ART. That is, 1 – ((proportion of patients LTFU) + (proportion of patients who die) + (proportion of patients who stop ART))

Attrition (1-retention) is defined as loss to follow-up, death, transferred out (censored after transfer) or discontinuation of ART for any other reason. Loss to follow up is defined as not showing up for more than 3 months for a scheduled clinic or pharmacy pick-up visit. Transferred out is relocation to another treatment facility. Adult is defined as over 13 years old.

Search Strategy

A search of publications and conference presentations was conducted for the period from 2003 to 2008. Online databases (MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews) were searched.

A controlled vocabulary of key words was used in the search. We combined the key words of resistance, failure or treatment failure, switching, second-line or salvage with antiretroviral or antiretroviral therapy or antiretroviral agents and highly active (adult or adolescent). For attrition, we combined the key words of survival, attrition, retention, mortality or lost to follow up with antiretroviral therapy, highly active or antiretroviral agents or antiretroviral therapy or antiretroviral (adult or adolescent) with the same publication year limits.

To reduce the chances of missed data caused by indexing lags in electronic database and to reduce publication bias, presentations (plenary sessions, oral and poster sessions) from the Conference on Retroviruses and Opportunistic Infections (CROI), International AIDS Conference (IAC), International AIDS Society (IAS) conference and HIV/AIDS implementers meetings were searched from 2003 to 2008. The QUORUM guidelines were followed for the meta-analysis except that no assessment of report quality was undertaken. Two reviewers worked independently to appraise and abstract data using an EXCEL data collection instrument designed for this purpose, and agreed criteria for inclusion/exclusion. Studies were reviewed for relevance, based on the inclusion/exclusion criteria. Irrelevant reports were discarded, and the fully published articles obtained for potentially relevant reports. For conference reports, abstracts were reviewed. Disagreements between reviewers were resolved by consensus.

Inclusion and Exclusion Criteria

Reports were included if they presented data from clinical trials or cohort studies (2003-2008) on ART-naive adult subjects receiving WHO-recommended first-line ART, with a minimum of six months follow-up, presented data on switching from first-line to second-line ART, or treatment failure based on WHO definitions of ART failure in resource-limited settings (or CD4 decline of 30% from on–treatment peak or the viral load cut-off for failure used in the study), and/or presented data on cohort

attrition or retention. If data were reported at a conference and subsequently published, only the published data were included. If data from the same cohort were presented more than once at different conferences or by different authors, the most recent data were included. If data were reported individually and also as part of larger collaboration, the latter were included.

Statistical analysis

Statistical analysis was conducted with Stata version 10 (Statacorp, College Station, TX, USA). The primary outcome of interest was treatment failure on first-line ART, and the secondary outcome was the retention rate of cohorts in resource-limited settings. If switch was not reported in a paper, we used virological failure as a surrogate endpoint. If both switch and virological failure were reported, we used virological failure as it is possible that some patients with virological failure may not have switched due to unavailability of second-line antiretroviral drugs. As this study was motivated by the need to determine when switching to second-line treatment occurs, we also introduced our operational definition of treatment failure: the time when switch to second-line treatment occurred If a paper did not report a failure rate per/100 patient years of follow-up (PYFU), or the number of PYFU in the study, we estimated these rates in the following way. Failure percentage at the latest time point in the study was used and PYFU was estimated by multiplying the median study time by the number of study participants. If median study time was not reported, we multiplied the latest time where the rate was reported, and assumed a linear fall-off in patient numbers from the start of the study to calculate the retention rate at the point failure was reported. If it was not possible to adjust for retention, we calculated PYFU by the latest time point where failure was reported, and excluded these studies in a sensitivity analysis. Attrition rates per 100 PYFU were calculated in the same way for our secondary endpoint. Where retention or attrition rates or proportions were not reported in a paper, we used the probability of retention assessed by a Kaplan Meier estimator instead. Confidence intervals around the failure and retention rate estimates were calculated according to a Poisson distribution. Thereafter, we used the metan command with Stata to calculate the overall effect estimate and confidence intervals using a random effects analysis, as effect estimates for individual studies are assumed to vary (to have some degree of heterogeneity) around the overall effect estimate. Effect size was calculated separately for studies assessing switch by virological criteria as opposed to clinical and immunological criteria, and by region. In a separate sensitivity analysis, we examined the clinical/immunological and virological failure rate adjusted for attrition. We assumed a linear drop-off in patient numbers from the start of the study to achieve the retention rate at the time point that switch was reported. Thereafter, we adjusted the total patient years of follow-up and recalculated the failure

rates and standard errors based on the adjusted, and probably more realistic total patient years of follow-up.

RESULTS

Of 804 potentially relevant citations identified, 42 were included in the final analysis. Inclusion and exclusion criteria are reported in figure 1. Studies were divided into two groups; those which reported on failure, and those which reported on attrition. Some studies reported both.

Cohorts in this analysis contributed data on 124,491 antiretroviral naive subjects initiating WHO-recommended first-line therapy. Five studies were cross sectional in design, and the remainder were cohort studies. 66% of the studies were from Africa. Table 1 shows the baseline characteristics of the study populations for Africa, and for all regions. Other studies characteristics are summarised in tables 2a, 2b and 2c.

Failure studies

Of studies which reported on failure, 15 used virological criteria to define failure, and 12 used clinical and/or immunological definitions. Two studies (6-7) reported failure rates by clinical/immunological, and virological criteria and were included in analyses using rates from both failure estimates.

For virological failure, studies more commonly used either a plasma viral load cut off >400 copies/ml or >1,000 copies/ml. One study defined failure as >5,000 copies/ml (8) , another as >250 copies/ml (9), and only one used the WHO definition of >10,000 copies/ml. (7)

Figure 2 shows the individual effects sizes and the weighting for each study in a random effects model. For studies reporting clinical/immunological failure definitions (fig. 2a), the overall failure rate per 100 person years of follow up (PYFU) was 1.9 (95%CI 1.48 to 2.32). By region, this rate was 2.64 (95%CI 1.73-3.56) in Africa, 2.57 (95%CI -1.80-6.94) in Latin America and 1.11 (95%CI 0.11-2.1) in Asia. For the global study, the failure rate estimate was 0.55 (95%CI 0.53-0.65).

For studies employing a virological endpoint, (fig. 2b) the failure rate (per 100 PYFU) was 6.08 (95%CI 4.51-7.66). Comparative regional data were: Africa 7.10 (95%CI 5.11-9.09), and Asia 2.55 (95%CI 1.14-3.96).

Attrition studies

Attrition rates are presented in figure 3. Overall attrition rate (per 100 PYFU) was 20.17 (95%CI 17.35-22.98), with similar rates for Africa (23.47; 95%CI 18.73-28.21), and the global studies

(20.20; (95%CI 7.47-32.93). By comparison, the estimated attrition rate in Latin America was 9.75 (95%CI 8.59-22.98), and in Asia was 9.95 (95% CI 7.47-16.97).

We conducted sensitivity analyses with the objective of improving ART demand forecasting by adjusting failure rates for attrition. For clinical/immunological endpoints adjusted for retention, the failure rate (per 100 PYFU) was 2.13 (95%CI 1.61-2.64). For virological endpoints adjusted for retention, the failure rate was 5.88 (95%CI 4.37-7.39).

DISCUSSION

The slow uptake of second line antiretroviral therapy has been a growing concern in organizations providing treatment to PLWH and civil society organizations, including those of PLWH, in recent times. (10) Over time, the proportion of PLWH receiving ART in low and lower middle income countries who accessed second line treatment, has been fairly constant, at about 3% whereas in middle income countries 25-40% were accessing it. (11) Various explanations have been proposed such as the tolerability of first-line regimens, limited capacity to diagnose treatment failure and limited second line treatment options due to unavailability of drugs and high cost . (12) While it is important to address the causes of to the perceived slow uptake of second line ART in some settings, it is equally important to characterize cohort behavior for the purposes of forecasting demand for both first and second line medicines and avoiding global stock outs, The capacity of treatment programs and clnincs to retain people in care, and the rate at which they switch them from first to second line, are important assumptions in such forecasting and need to have as strong as possible evidence base.

Our study found that rates of first-line failure in resource-limited settings were low and comparable to previous WHO estimates.. These rates were 6% (of those patient still on first line therapy) each year for Brazil, 4% for other Latin America countries, and 2% for all other countries.The 6% rate of failure used for Brazil is consistent with that reported from cohorts that used virological criteria to define failure in our meta-analysis 6.08 (95%CI 4.51-7.66) (per 100 PYFU). That of 2% for "all other countries" is consistent with 1.90 (95%CI 1.48-2.32) for a combined clinical/immunological endpoint in our meta-analysis. The difference is explained by the fact that clinical/immunological criteria are known to be relatively insensitive markers of failure when compared to virological failure. (6) (13) However, the low 2% switching rate from cohorts in which clinical/immunological criteria were used to define treatment failure found in our meta-analysis might represent a over-estimate of what is happening in real life. As only 3% of people in low income countries are on second line ART (11), Employing a simple Markov model (available on request) the switching rate in real life is more likely

about 1%. On the other hand, a switching rate at 6% lead to about 20% of people on ART to be using such treatment. It illustrates that in developing forecasts on future ART use, it will be important to include explicit assumptions on the use of virological testing. However, improving the quality of clinical follow up and reducing loss to follow up rates would also be important to increase the up-take of second line ART.

Failure rates by any criteria were higher in Africa compared to Latin America or Asia. The studies which reported globally presented similar failure rates for Africa. The representation of African cohorts in these global studies was 75-79%. (14-16) As shown in table 1, the baseline characteristics were similar in the African cohorts when compared to all cohorts. The only regional differences in baseline characteristics were for gender representation, with more males in Asia and Latin America studies (62.6% and 64.5% respectively) compare to Africa (35.5%) and all studies (38.3%).

Large studies have reported variable rates of retention within treatment cohorts. Rosen et al. performed a systematic review of patient retention in 32 cohorts in sub-Saharan Africa 2000-07. (14-16) Weighted mean retention rates were 79.1%, 75% and 61.6 % at 6, 12, and 24 months. The most successful program retained 85% of patients and the least successful program retained 46% at 24 months. Our data are consistent with these findings with attrition rates ranging from 4.95/100 PYFU in Cambodia to 48.70/100 PYFU in Zambia.

Attrition rates in African cohort were higher [23.47 (18.73-28.21)] than in cohorts from Asian [9.95 (2.92-16.97)] and Latin America [9.75 (17.35-22.98)]. Reasons for the different outcomes likely include severe resource constraints in African health systems, which are much less funded, and which often face severe human resource problems. For example of 46 countries on the continent, WHO estimates that 36 face a severe human resource crisis in the health sector (14-16) In addition, opportunistic infections such as tuberculosis, frequently occurring in the first three months (17-18), are more difficult to diagnose and treat in poorly developed health systems and a likely explanation for the higher attrition reported by African cohorts.

. It was expected that adjustment for attrition would improve the accuracy of failure estimates, and most probably increase these estimates, as adjustment accounts for not only those who had a failure diagnosis but also those who died or were lost to follow up. However, adjusted and unadjusted rates were similar. This most likely reflects the fact that the studies which could not be adjusted were smaller and contributed limited patient time in the unadjusted analyses, or the inability to anticipate or

prevent the excess mortality or the effect of adherence associated in treatment failure when it manifest itself clinically.

There are several limitations to this study including selection bias. Time points for reporting failure and attrition vary. To overcome this difficultly and create a data set for analyses, we calculated a rate of failure or attrition/100 PYFU. For attrition, we, as have other authors, assumed a linear decline in patient numbers from the start of the study to calculate the retention rate (19) In practice, it is unlikely that the attrition will be linear as several studies have reported higher LTF rates in the first six months following ART initiation (20-21), or in the period of 6-12 months (50) compared to later during follow-up.

The large heterogeneity in failure and attrition rates between studies and regions further raise questions regarding the interpretation and generalization of our results. While the statistical analysis using random effects models accounts for this heterogeneity to some extent. Simply adopting our best estimates of switch rates may underestimate or overestimate the need for second line ARV in particular countries. One advantage of a meta-analysis like the one presented here is that it does show this heterogeneity which enables upper and lower limits to assess the likely effect of failure rates on the need for second-line ARV, and the adoption of a risk benefit analysis failure.

Rates of failure within WHO-recommended first-line antiretroviral regimens in resource-limited settings depend on the definition of failure and the region in which the treatment programme is operating. If programmes employ virological criteria, the rate of failure and switching is consistently higher across all countries and regions compared to programmes which employ immunological/clinic failure criteria. Knowledge of expected switch rates based on the monitoring strategy of a programme will assist in accurate demand forecasting for second-line antiretrovirals. It is expected that programmes will move towards viral load monitoring as they seek to quantify failure more precisely, to effectively manage those who have failed, and to optimize the use of expensive second drugs. While this strategy can be expected to improve the efficacy of second line regimens by reducing the “resistance penalty” of continued non-suppressive first-line therapy, it is expected to result in increased demand for second-line antiretroviral drugs. This finding is significant because it adds complexity to decisions that programme managers need to make. The pursuit of better treatment outcomes by increased use of viral load and a more rapid move to expensive second-line treatment will need to be balanced against the goal of universal access to HIV prevention, treatment, care and support.

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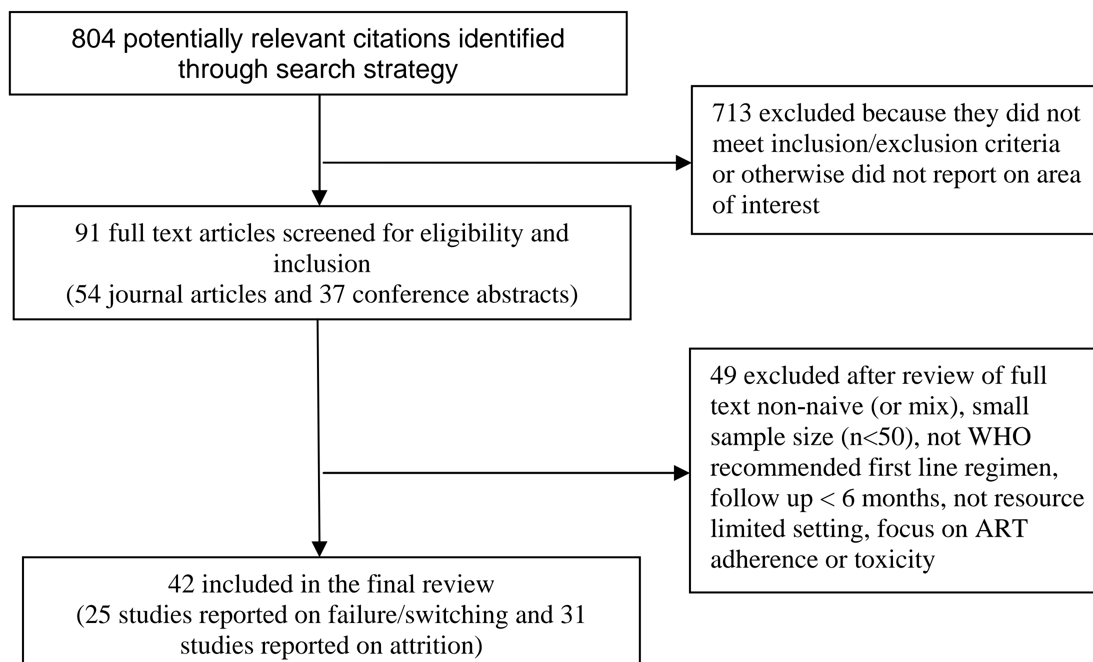


Figure1: Study flow chart

Baseline Characteristic	Africa		All regions	
	Failure studies	Attrition studies	Failure studies	Attrition studies
Median study sample size	1416	1297	1416	1308
Median age (years)	35	34.9	35.5	36
Male gender	31	35.5	37	38.3
Median CD4 cell count (cells/mm^3)	121	123	114	115.5
WHO stage 3 or 4 (%)	81.1	81	81.6	81.2

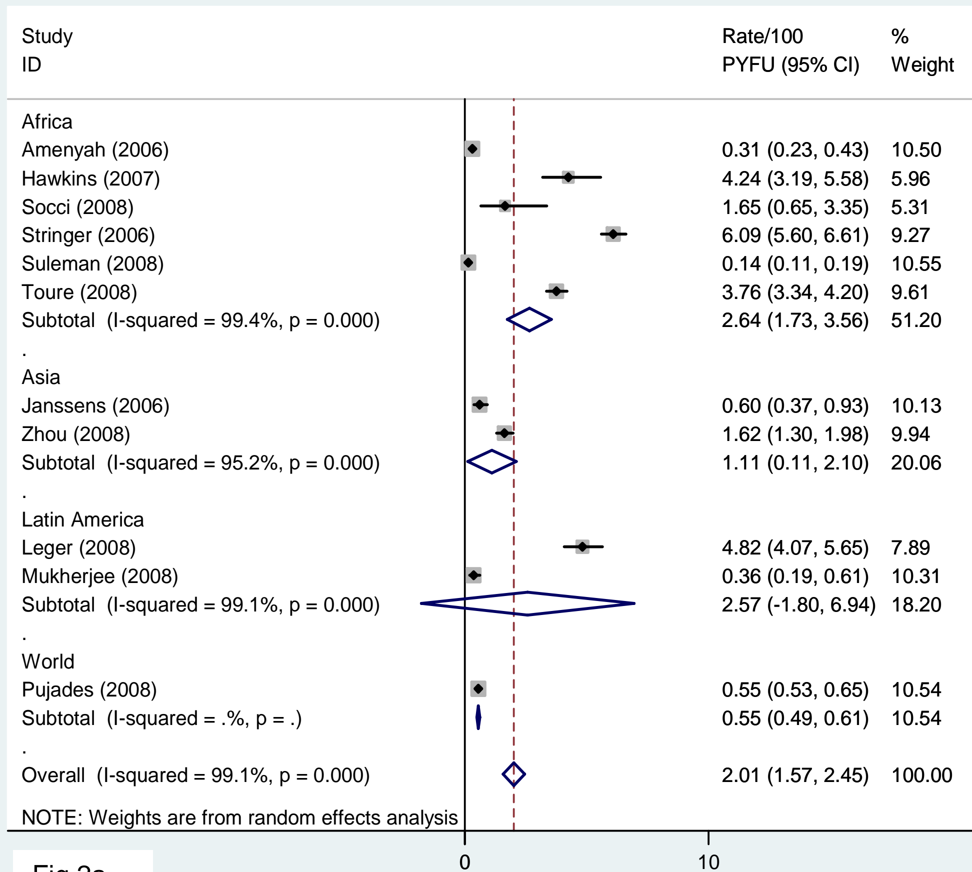
Table 1: Baseline characteristics of the study populations in cohorts from African and for all regions

Major author	Ref	Countries	Report type	N	Time point for analysis (Months)	Definition of failure
Table 2a Studies reporting clinical/immunological definitions of failure						
Amenyah	(4)	Ghana	IAC 2006	3806	42	CD4 drop >30% from peak
Hawkins	(9)	Kenya	AIDS 2007	1286	11.6	WHO
Janssens	(5)	Cambodia	IAC 2006	2857	14	CD4 drop >30% from peak
Leger	(10)	Haiti	IAC 2008	910	48	WHO
Mukherjee	(11)	Haiti	IAC 2008	1826	24	WHO
Pujades	(8)	Global	AIDS 2008	48,338	17.5	WHO
Socci	(12)	Africa	IAC 2008	215	24	WHO
Stringer	(13)	Zambia	JAMA 2006	16,198	6.9	WHO
Suleman	(14)	South Africa	IAC 2008	8,640	23	WHO
Toure	(15)	Cote d'Ivoire	AIDS 2008	10,211	7.7	WHO
Zhou	(16)	Asia	IAC 2008	2,246		WHO
Table 2b Studies reporting virological definitions of failure						
Avalos	(17)	Botswana	15th CROI	13,879	60	VL>400 copies/ml
Barth	(18)	South Africa	Eur J Clin microbiol inf dis	609	12	VL>1,000 copies/ml
Boulle	(19)	South Africa	13th CROI	1,700	36	VL> 5,000 copies/ml
Bussmann	(20)	Botswana	IAC 2008	633	41	VL>400 copies/ml
Ferradini	(21)	Malawi	Lancet 2006	398	8	VL>400 copies/ml
Ferradini	(22)	Cambodia	AIDS 2007	346	24	VL>400 copies/ml
Innes	(23)	South Africa	IAC 2008	1,416	36	VL>1,000 copies
Kamya	(24)	Uganda	14th CROI	526	12	2nd line switch or detectable VL
Kouanfack	(25)	Cameroon	IAC 2008	178	24	VL >1,000 copies/ml
Marazzi	(26)	Mozam-bique	15th CROI	3,749	36	WHO & in-country guidelines
Nachega	(27)	Africa	AIDS 2008	2,591	24	VL>400 copies/ml or switch to second line
Orrell	(28)	South Africa	Antiviral therapy 2007	929	6.3	VL.1,000 copies/ml
Schramm	(29)	Cambodia	IAC 2008	349	48	VL>250 copies/ml
Socci	(12)	Africa	IAC 2008	215	24	VL>400 copies/ml
Zhou	(16)	Asia	IAC 2008	2,246		WHO virological

Major author	Ref	Countries	Report type	N	Time point for analysis (Months)
Table 2c: Studies reporting retention and attrition					
Alamo	(30)	Uganda	IAC 2008	360	24.8

Talisuna					
Banda	(31)	Malawi	Plos One 2008	547	11.1
Barth	(18)	South Africa	Eur J Clin microbiol inf dis 2008	609	12
Bisson	(32)	Botswana	Plos One 2008	410	10.2
Boulle	(33)	South Africa	Bulletin WHO	12.587	48
Braitstein	(7)	Africa Latin America	Lancet 2006	4.810	12
Bussmann	(34)	Botswana	IAC 2008	633	41.9
Cortes	(35)	Chile	IAC 2008	3321	24
Ferradini	(21)	Malawi	Lancet 2006	1308	8.3
Ferradini	(22)	Cambodia	AIDS 2007	416	23.8
Hawkins	(9)	Kenya	JAIDS 2007	1,286	11.6
Innes	(36)	South Africa	IAC 2008	1,416	36
Jahn	(37)	Malawi	IAC 2008	114,375	36
Johanessen	(38)	Tanzania	BMC Inf Dis 2008	320	10.9
Kamya	(24)	Uganda	JAIDS 2007	526	12
Karcher	(39)	Kenya	Trop Med Int Health 2007	124	9
Leger	(10)	Haiti	IAC 2008	910	48
Makombe	(40)	Malawi	BULL WHO 2007	57,366	12
Marazzi	(41)	Mozambique	Aids research and human retroviruses 2008	3,456	12
Moh	(42)	Côte d'Ivoire	AIDS 2007	792	8
Mukherjee	(11)	Haiti	IAC 2008	1,826	24
Nachega	(43)	Africa	AIDS 2008	2,591	24
Ndamage	(44)	Rwanda	CROI 2008	3,196	12
Orrell	(28)	South Africa	Antivir Therapy 2007	929	6.3
Pujades	(8)	Africa, Asia, Latin America, Eastern Europe	AIDS 2008	48.338	17.5
Rewari	(45)	India	IAC 2008	972	24
Schramm	(46)	Cambodia	IAC 2008	349	48
Stringer	(13)	Zambia	JAMA 2006	16,198	6.9
Toure	(15)	Cote d'Ivoire	AIDS 2008	10,211	7.7
Zannou	(47)	Benin Côte d'Ivoire Gambia Mali Senegal	IAC 2008	14,830	12

Table 2: Characteristics of studies



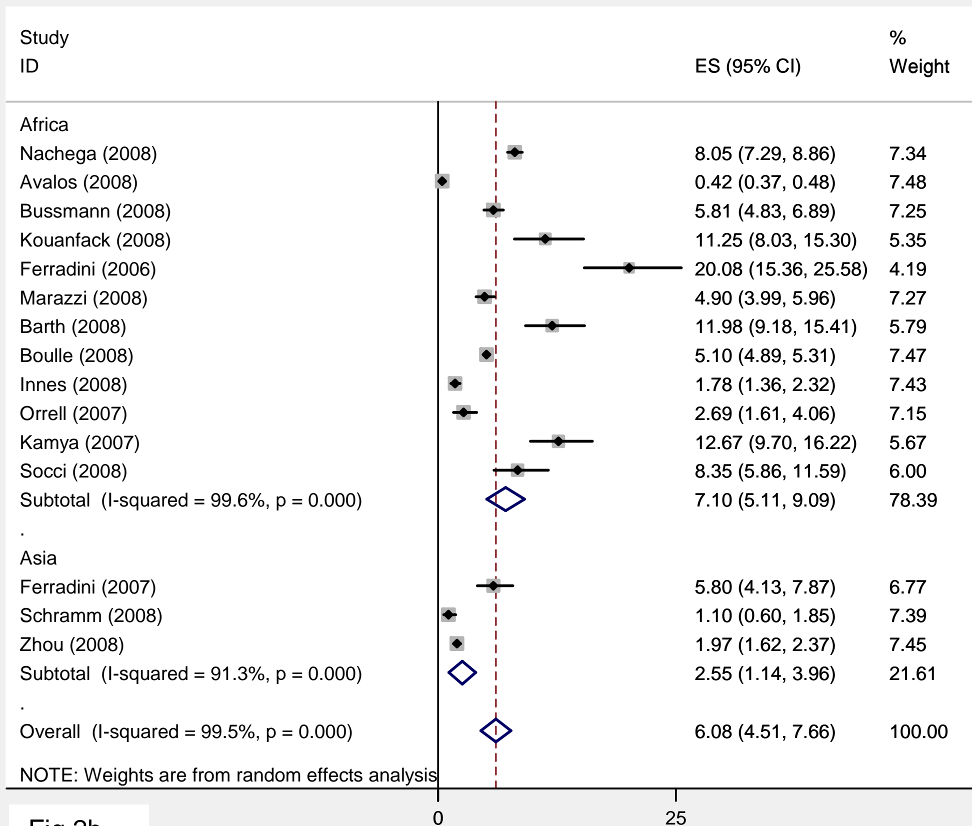


Figure 2: Random effects meta-analysis of switch rates/100 PYFU in studies using clinical/immunological failure definitions (a) and virological failure definitions (b), overall and by region.

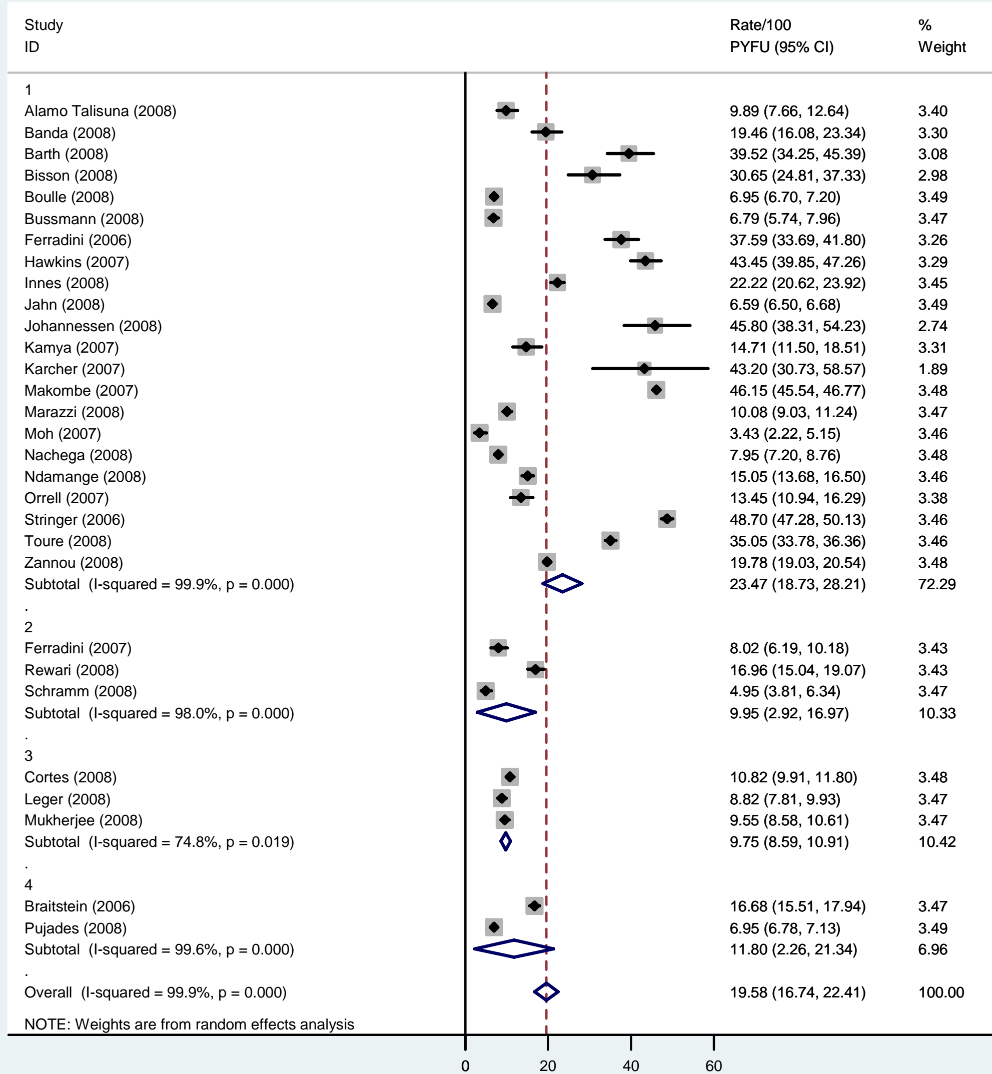


Figure 3: Random effects meta-analysis showing attrition rates/100 PYFU by region

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