Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis

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Background: A growing proportion of patients on antiretroviral therapy in resource-limited settings have switched to second-line regimens. We carried out a systematic review in order to summarize reported rates and reasons for virological failure among people on second-line therapy in resource-limited settings.

Methods: Two reviewers independently searched four databases and three conference websites. Full text articles were screened and data extracted using a standardized data extraction form.

Results: We retrieved 5812 citations, of which 19 studies reporting second-line failure rates in 2035 patients across low-income and middle-income countries were eligible for inclusion. The cumulative pooled proportion of adult patients failing virologically was 21.8, 23.1, 26.7 and 38.0% at 6, 12, 24 and 36 months, respectively. Most studies did not report adequate information to allow discrimination between drug resistance and poor adherence as reasons for virological failure, but for those that did poor adherence appeared to be the main driver of virological failure. Mortality on second-line was low across all time points.

Conclusion: Rates of virological failure on second-line therapy are high in resource-limited settings and associated with duration of exposure to previous drug regimens and poor adherence. The main concern appears to be poor adherence, rather than drug resistance, from the limited number of studies accessing both factors. Access to treatment options beyond second-line remains limited and, therefore, a cause for a concern for those patients in whom drug resistance is the identified cause of virological failure.
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Introduction

The rapid scale-up of antiretroviral therapy (ART) in resource-limited settings over the past decade has resulted in substantial reductions in morbidity and mortality [1,2] and increased life expectancy [3] for people living with HIV/AIDS. Employing a simplified, standardized package of care has allowed large numbers of patients to access life-saving ART in highly under-resourced settings [4]. Particularly, the use of simple, affordable, fixed-dose

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combination therapies has supported rates of adherence to treatment comparable to that seen in developed countries [5].

A number of patients can be expected to develop drug resistance to first-line regimens, and a growing number of patients on ART in developing countries have switched to second-line therapy [6–8]. Limited access to viral load monitoring and genotyping, and poor availability of second-line treatment options [9], has meant that failure is likely underdiagnosed [10], with the consequence that some patients eligible for second-line therapy are not switched and many die as a result [11].

For patients failing second-line therapy, treatment options are largely nonexistent. Current WHO guidelines provide some guidance for treatment in the case of second-line failure, but these are prefaced with the caveat that many countries have financial constraints that will limit the adoption of third-line options. For example South Africa, the best resourced high HIV burden country in Africa, makes no provision for ART beyond second-line in its national guidelines [12].

Thus, there is a need to understand the rates and reasons for virological failure on second-line regimens in resource-limited settings in order to both limit its occurrence and forecast the need for treatment options beyond second-line. In this systematic review, we assess the frequency and determinants of second-line failure in resource-limited settings.

Methods

Data sources and searches

We developed a compound search strategy combining terms for second-line regimens and treatment failure according to a predefined protocol (http://tinyurl.com/ctr9rau). The following databases were searched from inception to July 2011: *PubMed*, *EMBASE*, *Cochrane Library* and *Science Direct*. We also searched the websites of the following conferences: the International AIDS society (IAS), Conference on Retroviruses and Opportunistic Infections (CROI) and the AIDS Education Global Information Systems (AEGIS). We additionally searched the bibliographies of relevant articles and contacted experts in the field to locate additional resources on ongoing or completed studies. No language or geographical restriction was applied.

Study selection

We included any study that reported rates of failure among patients on second-line therapy within clearly defined cohorts from low-income and middle-income countries as defined by the World Bank classification. Studies limited to cohorts of only patients failing second-line treatment were excluded from the main review, as they could not be used to calculate incidence estimates. We included randomized trials, nonrandomized trials and observational studies, but excluded nonsystematic observations (case reports or case series <10 patients). Virological failure was defined according to the definitions used in each study, allowing for the inclusion of studies that performed a single viral load and studies in which virological failure was confirmed through two consecutive viral loads. Two reviewers (O.A., S.M.) independently screened articles by title and abstract. In case of disagreement or uncertainty, a third reviewer (N.F.) was consulted. Full text articles were screened and data extracted using a standardized data extraction form.

Data extraction and quality assessment

The following data were abstracted: publication status, year of publication, study design, study location, type of analysis, age, sample size, type of second-line drugs, treatment failure definition, follow-up duration on first-line, follow-up requirements for second-line, follow-up duration on second-line, baseline genotyping, viral load monitoring, baseline CD4 cell count, treatment failure rates (of any kind), genetic mutation, mortality and lost-to-follow-up at second-line therapy and other failure-associated factors such as adherence. Where there was uncertainty about the data, study authors were contacted for clarification.

The methodological quality of each study was assessed independently and in duplicate using a checklist that assessed the risk of bias across five different categories (selection bias, performance bias, detection bias, reporting bias and attrition bias) according to the *Cochrane* handbook for systematic reviews [13].

Data synthesis and analysis

Point estimates and 95% confidence intervals (95% CIs) were calculated for the proportion of patients failing second-line therapy. Where studies reported rates at different timepoints, results are reported cumulatively. The variance of the raw proportions was stabilized using a Freeman–Tukey-type arcsine square-root transformation [14] and estimates were pooled using a DerSimonian–Laird random effects model. As pooled proportions yield high rates of heterogeneity irrespective of the magnitude of heterogeneity [15], we estimated the magnitude of heterogeneity using the τ^2-statistic. We explored the potential influence of clinical and programmatic covariates identified through univariate subgroup analyses to assess the potential influence of baseline genotyping and whether the definition of virological failure was based on a single test or two consecutive tests. All P values are two-sided, and a P value of 0.05 or less was considered to be significant. All analyses were conducted using Stata (version 11; StataCorp LP, College Station, Texas, USA).

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Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search strategy identified a total of 5812 journal articles and conference papers, of which 5121 were excluded based on the title either because it was a subject matter not relevant to our research question; the study was done in a high-income country; or it was a discussion paper. After screening full text of published articles and conference papers with our eligibility criteria, an additional 496 were excluded (Fig. 1). Of the 195 full text articles retained, 178 were excluded because they did not meet the inclusion criteria: 43 were discussion papers; 20 included patients on nonprotease-inhibitor based regimens; 47 studies did not report the outcomes of interest; 35 did not include data on second-line failure; and 33 conducted in developed countries. Of five additional studies identified through bibliographic searches, three were excluded as they reported outcomes only within a cohort of patients failing treatment. In total, 19 studies (2035 patients), comprising 13 journal articles [16–28] and six conference abstracts [29–34], were taken through for analysis.

The characteristics of studies included in the review are summarized in Table 1 [16–34]. Studies were published between 2007 and 2011 and carried out in Botswana [29], South Africa [17,21,23,24,28], Malawi [18], Uganda [26], Tanzania [31], Cambodia [19,33], Thailand [20,22,25,32,34] and China [27]. Two studies were multicentric analyses [16,30].

Most studies (13 studies) defined virological failure using the WHO definition of RNA viral load more than 400 copies/ml, but only around half of these reported two consecutive measures [17,20,22,26,27,29,30]. Lopinavir-based second-line regimens were the preferred option in most studies. The majority (13 studies) performed baseline genotype testing, but only four studies reported genotyping among virologically failing patients. Pre-second-line CD4 cell counts were consistently low, at around 200 cells/μl.

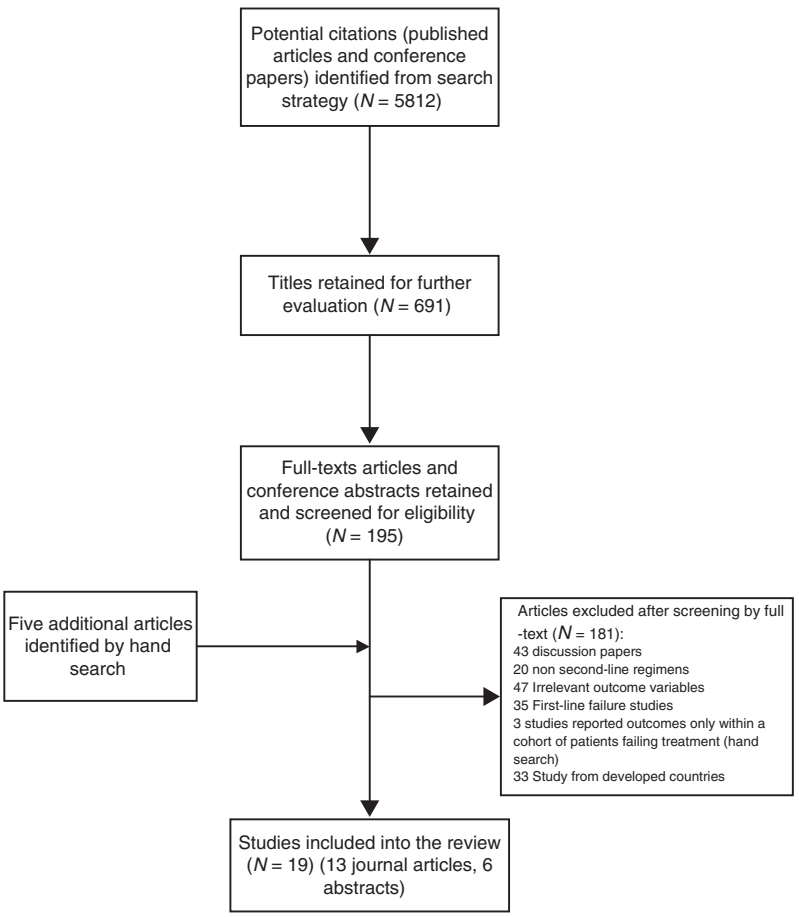

Fig. 1. Flow diagram of study selection process.

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Table 1. Characteristics of included studies.

References	Country	Median age, years	Treatment regimen(s)	Second-line failure definition(s)	Duration on first-line (months)	Baseline genotyping	Presecond-line baseline CD4 cell count (cells/μl)	Presecond-line baseline viral load (copies/ml)	Mean follow-up, months
Pujades-Rodriguez *et al.* [16]	Africa and Asia[a]	35 (30–42)	LPV/r -based; NFV-based	WHO guideline (2006)	24.1 (16.1–31.1)	No	122 (53–220)	4.5 (4.0–5.0)	16.6 (10.1–27.0)
Fox *et al.* [17]	South Africa	35.8 (27.7–43.9)[b]	ZDV/ddl/LPV/r	Two consecutive VL ≥1000 copies/ml	15.6 (9.6–22.8)	Yes	203.3 (75–331.6)	N/A	N/A
Hosseinipour *et al.* [18]	Malawi	38.0 (32.0–46.0)	ZDV/TDF/3TC/LPV/r	One VL >400 copies/ml	35.2 (25.4–49.0)	Yes	65 (22–173)	52939 (15739–148149)	N/A
Ferradini *et al.* [19]	Cambodia	40 (37–46)	ddl/3TC/LPV/r; TDF/3TC/LPV/r; TDF/ddl/LPV/r; ZDV/ddl/LPV/r; ZDV/3TC/LPV/r	One VL >250 copies/ml	26.6 (15.2–29.4)	Yes	106 (42–168)	4.7 (3.1–5.4)	27.4 (25.3–29.7)
Bunupuradah *et al.* [20]	Thailand	9.3	SQV/LPV/r-based	Two consecutive VL >400 copies/ml	N/A	Yes	160 (44–287)	4.8 (4.5–5.1)	9.8 (8.4–14)
van Zyl *et al.* [21]	South Africa	30–46[c]	LPV/r-based	One VL >500 copies/ml	N/A	Yes	N/A	N/A	11.5 (9–21.5)
Siripassorn *et al.* [22]	Thailand	39.7 (18–60)	Single and double-boosted PI	Two consecutive VL >400 copies/ml	29 (18–39)	Yes	159 (92–269)	N/A	19 (13–29)
Boulle *et al.* [23]	South Africa	N/A[d]	ZDV/ddl/ LPV/r	One VL >400 copies/ml	N/A	No	N/A	N/A	N/A
El-Khatib *et al.* [24]	South Africa	N/A[d]	LPV/r-based; ATV-based	One VL >400 copies/ml	N/A	Yes	N/A	N/A	24–>36
May Myat *et al.* [25]	Thailand	38.9 (30.9–46.9)	LPV/r -based; IDV/r-based	One VL >400 copies/ml	29 (13–50)	Yes	158 (75–260)	4.1 (3.6–4.5)	24 (11–42)
Castelnuovo *et al.* [26]	Uganda	39 (36–43)	ZDV/ddl/LPV/r; d4t/ddl/LPV/r	Two consecutive VL >400 copies/ml	22 (19–29)	Yes[e]	108 (43–205)	4.8 (4.0–5.4)	Varies
Zhao *et al.* [27]	Rural China	13.9 (11.1–16.0)	LPV/r-based	Two consecutive VL ≥1000 copies/ml	33.1 (24.2–40.8)	Yes	143 (61–255)	4.6	12
Levison *et al.* [28]	South Africa	34 (27–41)	LPV/r-based	One VL >400 copies/ml	11 (7–18)	No	212 (133–289)	3.97 (3.63–4.38)	6
Avalos *et al.* [29]	Botswana	14–67	d4t/ddl/NFV; d4t/ddl/LPV/r	Two consecutive VL >400 copies/ml	N/A	No	90.4 (81.0–99.8)	5.3 (5.2–5.4)	11.2 (9.1–13.5)
Bartlett *et al.* [30]	Africa and Asia[a]	39 (22–60)	TDF/FTC/ LPV/r	Two consecutive VL >400 copies/ml	≥6	Yes	164	4.34	5.6
Reddy *et al.* [31]	Tanzania	N/A[f]	PI-based therapy[g]	One VL >400 copies/ml after 180 days; HIV RNA < 1 log10 after 70 days	27.6 (6–63.6)	Yes	N/A	N/A	5.6 (2.3–9.3)
Treebupachatsakul [32]	Thailand	N/A[d]	IDV/r-based	One VL >50 copies/ml	N/A	Yes	N/A	N/A	5.1 (3.7–14)
Sophan *et al.* [33]	Cambodia	N/A[d]	ABC/ddl/ LPV/r; 3TC/TDF/ LPV/r	One VL >2.4 copies/ml	31 (6–75)	Yes	N/A	5.1 (4.7–5.4)	18 (1–56)
Manosuthi *et al.* [34]	Thailand	37.4	ATV/SQV/r	One VL >400 copies/ml	30 (20–41)	Yes	179 (47–311)	41 600 (10 600–112 250)	14

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; d4t, stavudine; ddl, didanosine; FTC, emtricitabine; IDV, indinavir; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NS, not stated; PI, Protease Inhibitor; SQV, saquinavir; TDF, tenofovir; VL, viral load; ZDV, zidovudine.

[a]Cohort originates from different antiretroviral therapy programs across Africa and Asia.

[b]Data expressed in means; N/A means information was not reported or could not be determined from report.

[c]Information representative of only a subset of the samples.

[d]Age not defined but population group made up of adults.

[e]Genotyping available in only 16 cases.

[f]Age not defined but population group consisting of children.

[g]PI drug name not stated.

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The assessment of methodological quality of included studies is presented in Table 2 [16–34]. The main limitations of the studies related to the ascertainment of causes of treatment failure.

Proportion of patients with virological failure on second-line therapy

Seven studies reported virological failure at 6 months, with proportions ranging from 8.59 (95% CI 0.36–26.01%) [32] to 37.34% (95% CI 31.30–43.59%) [29]; the pooled proportion was 21.79% (95% CI 13.25–30.32%, τ^2 105.8) (Fig. 2). Virological failure at 12 months was reported by seven studies and ranged from 11.35 (95% CI 4.89–29.97%) [27] to 39.89% (95% CI 30.27–49.93%) [21], with a pooled proportion of 23.06% (95% CI 16.14–29.97%, τ^2 69.07). Failure at 24 months was reported by five studies in adults and one study in children. For adults, failure ranged from 8.32 (95% CI 2.93–16.12%) [19] to 41.15% (95% CI 31.54–51.10) [25], with a pooled proportion of 26.65% (95% CI 14.28–39.02%, τ^2 176.9). For children, the proportion failing second-line was 20.58% (95% CI 10.72–32.64%) [20]. Finally, three studies reported failure at 36 months which ranged from 6.4 (95% CI 3.18–10.64%) [16] to 57.32% (42.07–71.88%) [26] with an overall pooled proportion of 38.02% (95% CI 1.04–74.99%, τ^2 100.3).

In subgroup analysis comparing the proportion of patients failing second-line at 6 months, there was no statistically significant difference according to whether baseline genotyping was assessed or not ($P=0.22$), or whether the definition of virological failure was based on a single test or two consecutive tests ($P=0.34$). However, the number of patients contributing to each analysis and the effect size was small.

Mortality and loss to follow-up

Mortality on second-line regimens was reported by nine studies. As data were provided for varying treatment durations, pooled estimates were not calculated. Two studies reported mortality at 6 months, with mortality ranging from 2.0 (95% CI 0.5–5.0%) [28] to 6.45% (95% CI 1.52–14.46%) [31]. Mortality at 12 months was reported by four studies and ranged from 5.27 (95% CI 3.31–8.38%) [17] to 10.49% (95% CI 6.68–15.04%) [22]. Twenty-four-month mortality was reported by two studies, one among adults (4.91%, 95% CI 1.14–11.10%) [19] and the other in children (6.83%, 95% CI 1.61–15.28%) [20]. Loss to follow-up of patients on second-line therapy was reported inconsistently. Two studies reported losses at six months, ranging from 3.71 (95% CI 2.38–5.32%) [16] to 12.07% (95% CI 7.96–16.89%) [28]. Three studies reported losses at 12 months [17,18,22], ranging from 3.41 (95% CI 0.79–7.79%) to 17.04% (95% CI 13.09–21.39%). Two studies reported losses at 24 months, ranging from 3.49 (95% CI 0.51–8.97%) to 8.50% (95% CI 2.02–18.83%) [19,26]. Finally, one study reported that 12.03% of patients on second-line

Table 2. Assessment of methodological quality.

	Selection bias			Performance bias			Detection bias			Attrition bias	Reporting bias
References	Patients PI-naive at baseline	All eligible patients included	Patients with toxicities/ abnormalities excluded	PI-based second-line	Objective criteria for defining treatment failure	Viral load monitoring performed at baseline	Genotyping performed at baseline	Adherence taken into account	All patients included in analysis	Follow-up ≥6 months	Selective reporting
Pujades-Rodriguez *et al.* [16]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Fox *et al.* [17]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Hosseinipour *et al.* [18]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Ferradini *et al.* [19]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	Yes	No
Bunupuradah *et al.* [20]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
van Zyl *et al.* [21]	NR	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	No	No
Siripassorn *et al.* [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Boulle *et al.* [23]	NR	NR	No	Yes	Yes	No	No	No	No	No	Yes
El-Khatib *et al.* [24]	NR	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
May Myat *et al.* [25]	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No
Castelnuovo *et al.* [26]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Zhao *et al.* [27]	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Levison *et al.* [28]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Avalos *et al.* [29]	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes
Bartlett *et al.* [30]	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Reddy *et al.* [31]	Yes	No	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Treebupachatsakul [32]	NR	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Sophan *et al.* [33]	NR	NR	NR	No	Yes	NR	No	No	No	NR	Yes
Manosuthi *et al.* [34]	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	No

NR, not reported; PI, protease inhibitor.

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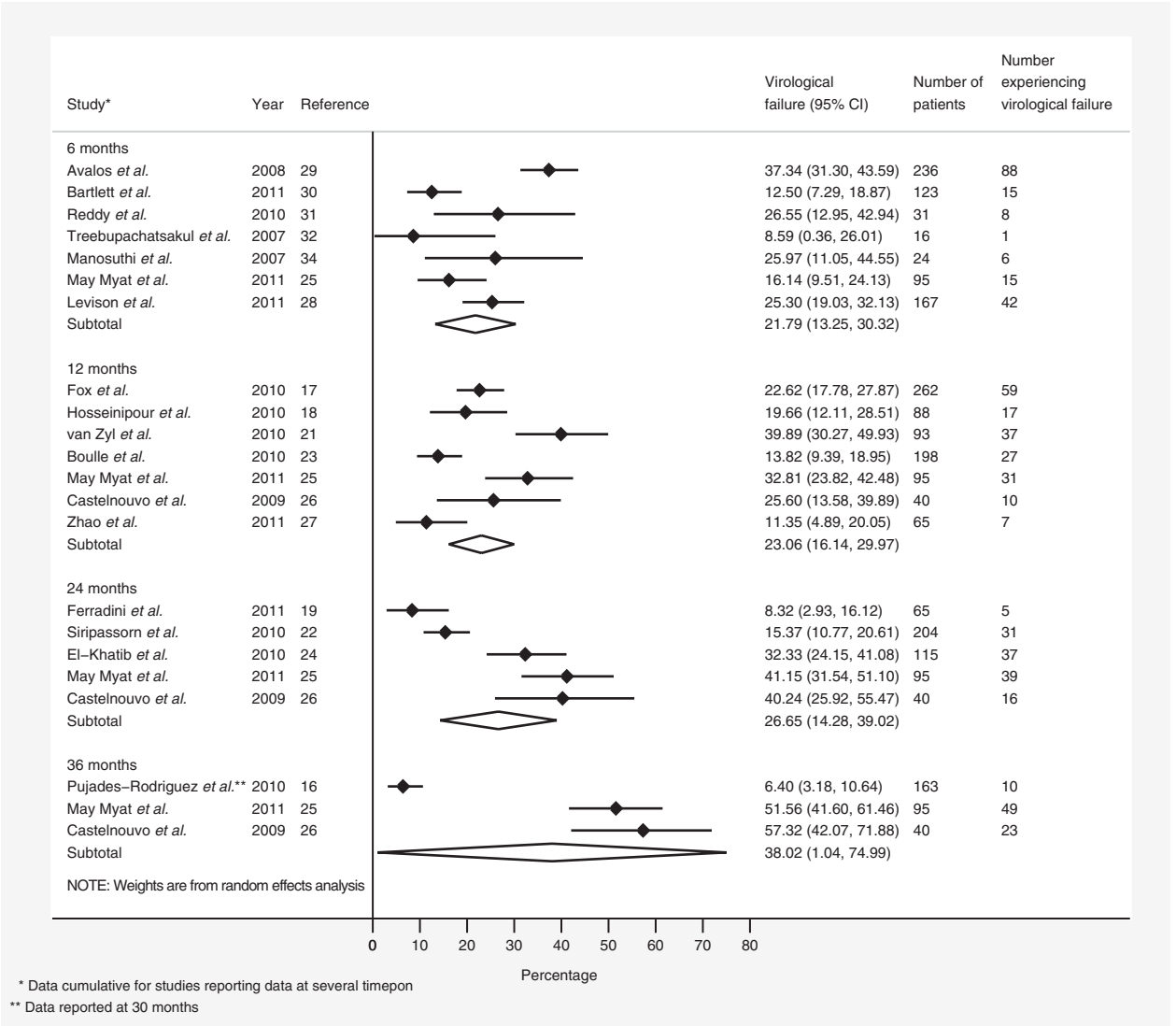

Fig. 2. Proportion of patients experiencing virological failure.

were lost to follow-up at 60 months (95% CI 8.20–16.46%) [29].

Determinants of treatment failure

Adherence

Five studies assessed the association between adherence and second-line failure. A multicentre analysis [16] found that patients with an adherence index of less than 80% reported significantly higher treatment failure rates (383.5 per 1000 person-years) compared with those with an adherence index of at least 95% (176 per 1000 person years; adjusted incidence rate ratio 3.14; 95% CI 1.67–5.90; $P<0.001$). A study from Malawi [18] that defined poor adherence as 'ever missing a dose' was reported to be significantly associated with failure to achieve HIV-RNA less than 400 copies/ml: after adjusting for potential confounders, patients rated as poorly adherent were five times less likely to achieve viral suppression (adjusted odds ratio 5.70; 95% CI 1.16–27.93). A study from Thailand [25] reported that virological success was greater among patients who had no documentation of poor adherence compared with those with documented poor adherence (hazard ratio 2.94; 95% CI 1.60–5.39; $P<0.001$). A study, from South Africa [17], reported that patients switched to second-line therapy for reasons other than noncompliance were more likely to achieve second-line virological success than those shifted for noncompliance reasons (adjusted hazard ratio 1.83; 95% CI 1.14–2.93); a second study from South Africa [24] found a non-significant tendency toward a greater risk of viraemia associated with reported incomplete adherence to second-line therapy (odds ratio 2.8; 95% CI 0.4–19.6; $P=0.29$).

Drug resistance

Four studies assessed drug resistance patterns among patients who experienced virological failure [19–21,24]. The most commonly reported resistance mutations were

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for nucleoside reverse transcriptase inhibitors (NRTIs) (26%, 20 of 78 patients) and non-NRTIs (NNRTIs) (27%, 21 of 78 patients), as would be expected for patients on second-line therapy. Protease inhibitor resistance mutations were found in only 18% of patients (14 of 78) where genotyping was performed. Resistance mutation associated with M184V was the most prevalent form of nucleoside reverse transcriptase inhibitor mutation (16.9%), followed by thymidine analogues (11.7%): M41L, D67N, K70R, T215F and K219Q. Of the two studies that detected NNRTI resistance mutations [19,24], only one reported the specific mutation. In that study, K103N was the most common form of nonnucleoside reverse transcriptase inhibitor mutation, observed in 15 patients (19.2%) [24]. Nineteen different mutations associated with protease inhibitors were also reported across three studies [20,21,24], with mutations at M36I and I54V being the most common.

The association between second-line failure and drug resistance at first-line failure was assessed by three studies. Two of these studies compared resistance mutations at first-line failure in patients who did and did not achieve virological suppression on second-line therapy [25,27]; these studies found no statistically significant difference between the two groups. In the third study from Uganda, all 16 patients who underwent resistance testing prior to second-line ART had at least one mutation conferring resistance to NNRTI (and 87% of those also had M184V mutation); virological success (HIV-RNA <400 copies/ml) was achieved at 12 months [26] by all 16 patients.

Discussion

Our analysis found a high proportion of patients on second-line ART were reported to be failing virologically in resource-limited settings, with most failures occurring within the first 6 months after initiation of second-line therapy. Failure rates are higher than reported rates of failure to first-line therapy [35] in resource-limited settings, and reported rates of second-line failure from developed country settings [36]. The cumulative pooled proportions reported in this review should be considered with caution, as there was considerable between-study variation in the reported estimates and substantial statistical heterogeneity. Importantly, studies used different definitions of virological failure with over half of studies included in this review performing a single viral load. Although we were unable to detect any clear programme determinants of study heterogeneity, these sensitivity analyses were limited by the small sample size.

Virological failure on ART can be due to a number of factors, including baseline drug resistance among patients prior to starting treatment [37], the evolution of drug resistance during treatment, duration of time on treatment and poor adherence to medication. From a programme perspective, the most important distinction is between patients who have failed due to drug resistance (and, therefore, need to switch to a third-line regimen) and patients who are nonadherent but have not yet developed drug resistance mutations (and who, therefore, require adherence support). The majority of studies included in this review did not provide adequate information to be able to discriminate between these two issues. Nevertheless, the fact that for all studies that measured adherence, poor adherence was a risk factor for second-line failure, together with the low frequency of resistance mutations overall, and to protease inhibitors in particular, suggests that virological failure for the majority of patients is due to suboptimal adherence rather than resistance development. Protease inhibitors generally have a high genetic barrier to resistance [38], and studies that have examined genotypes of patients who had developed virological failure on second-line therapy found resistance to lopinavir in only 5.9–11.1% of patients [39–41].

Adherence to first-line therapy was not reported by the majority of studies, but it is likely that a proportion of patients failing virologically due to poor adherence to second-line therapy may also have been poorly adherent to their initial first-line regimen. The higher rate of failure to second-line therapy compared with first-line therapy may, thus, be partly explained by the fact that a higher proportion of patients on second-line therapy are generally poorly adherent. Side-effects are an important factor associated with poor adherence [42], and cumulative toxicity associated with nucleosides used in both first-line and second-line regimens may drive poor adherence in some patients. A number of trials are underway to improve the evidence base for second-line therapy and assess the potential for nucleoside-sparing regimens in treatment-experienced patients that will help inform the evidence base for future second-line regimens [43,44]. Another challenge to adherence in resource-limited settings is the occurrence of antiretroviral drug shortages. Stock-outs have been reported in several African countries in recent years and have been associated with increased treatment interruption and mortality [45].

There are several limitations to note. First, the reporting of patient and programme variables was inconsistent, limiting the possibility to conclusively determine factors driving virological failure. Second, the overall sample size was small and data were derived from observational studies which resulted in low statistical precision and a moderate degree of heterogeneity. We used a random-effects model which is more appropriate for meta-analyses in which heterogeneity is anticipated and explored potential sources of heterogeneity in a series of subgroup analyses. Third, there may be other explanations to second-line failures, including drug–drug interaction (particularly with anti-tuberculosis

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drugs) [46] and drug toxicities that may not have been adequately considered. Finally, observational studies are subject to a range of potential biases, as outlined in our assessment of the methodological quality of studies.

Our study indicates several directions for future research. Current WHO guidelines recommend that patients failing virologically be subject to an adherence support intervention, after which a second viral load test should be performed prior to deciding on a regimen change. Future studies should be encouraged to follow these recommendations and report the results of both the first and second viral load, and the type of adherence intervention carried out, in order to better quantify the proportion of virological failures due to nonadherence and assess the effectiveness of adherence interventions. At the same time, we should not lose sight of the fact that not all second-line virological failures are due to poor adherence, and access to third-line regimens will likely become a growing concern for those patients who fail second-line therapy.

This study, therefore, underscores the need for greater access to routine virological monitoring in order to detect virological failure and implement more intensive adherence counselling prior to the development of resistance mutations. The cost-effectiveness of viral load in resource-limited settings is still debated [47], but the benefit of avoiding unnecessary treatment switches and accumulation of HIV-resistance is increasingly being acknowledged [48]. Recent costing studies have concluded that when the benefits of guided regimen-switches are considered, viral load monitoring is found to be cost-effective and life-saving [49]. Improving the feasibility and reducing the cost of viral load are important policy objectives [50], and a number of strategies have been proposed to target the use of viral load to help target its use pending price reductions [51,52].

A number of studies among patients on first-line ART have found that in the majority of cases, viraemia on first-line therapy can be reversed with adequate adherence support [53,54]. This, together with algorithms for using genotyping to confirm drug resistance for cases in which viraemia is detected on second-line, will help to preserve the use of second-line drugs which is an important objective given that therapeutic options beyond second-line are very expensive and poorly available in resource-limited settings.

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Conflicts of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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