Efficacy of Antiretroviral Therapy Programs in Resource-Poor Settings: A Meta-analysis of the Published Literature

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(See the editorial commentary by del Rio and Priddy on pages 225–6)

Background. Despite the advent of effective combination antiretroviral drug therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection, many doubt the feasibility of ART treatment programs in resource-poor settings. We performed a meta-analysis of the efficacy of ART programs in the developing world. We searched the Medline database with the index terms "HIV," "antiretroviral therapy," "CD4 count," "viral load," "experience," and "outcomes." A total of 201 abstracts were reviewed, and 25 articles were selected for detailed review. Ten observational studies with details on patient outcomes were ultimately included in the analysis.

Methods. Three readers independently extracted data from the articles. The details recorded included patient demographic characteristics, baseline CD4 cell counts, baseline HIV RNA viral loads, ART histories, outcomes, and timing of the outcome measure.

Results. The proportion of subjects with an undetectable HIV viral load provided the measure of treatment efficacy. A random-effects model weighted the proportion of patients with undetectable viral load at various time points during ART. The proportion was 0.697 (95% CI, 0.582–0.812) at month 6 and 0.573 (95% CI, 0.432–0.715) at month 12 of ART. The provision of medications free of charge to the patient was associated with a 29%–31% higher probability of having an undetectable viral load at months 6 and 12 than was the requirement that patients pay part or all of the cost of therapy.

Conclusions. ART treatment programs in resource-poor settings have efficacy rates similar to those reported for developed countries. The provision of medications free of charge to the patient is associated with a significantly increased probability of virologic suppression at months 6 and 12 of ART.

The life-saving benefits of antiretroviral therapy (ART) for the treatment of HIV infection have been well documented [1]. Despite this fact, access to treatment is severely limited in the poorest countries of the world, where the HIV epidemic continues to have its most devastating impact [2]. This results in the alarming fact that >95% of people infected with HIV worldwide do not have access to ART simply because they live in resource-poor countries [3–5].

Despite the advent of effective therapy, there have been many obstacles to the implementation of comprehensive HIV treatment programs in the developing world. Not least of these has been the cost of medications, although the recent decreases in prices and the availability of funding have increased the possibilities for expanding access to treatment [6–9]. With this opportunity has come much discussion regarding the best programmatic approach to implementing such a complex health intervention in developing countries. Many people have voiced doubts about the feasibility of HIV treatment programs in areas of the world where health care capacity is very limited [10, 11]. Despite a lack of corroborating evidence, specific concerns have been raised regarding the ability of Africans and other groups in the developing world to adhere to ART regimens [12].

In many countries, nonprofit organizations have led the way in successfully implementing HIV prevention

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and treatment programs in settings with limited public infrastructure and minimal health care [13, 14]. In concert with new funding for treatment, the World Health Organization (WHO) set a target in 2003 of having 3 million HIV-infected persons receive therapy by 2005 [15].

At this time, the data on the outcomes of a number of small- to moderate-sized treatment programs have been published. We sought to determine the efficacy of ART programs in the developing world by performing a meta-analysis of the published literature and to compare the outcomes with typical outcomes in the developed world.

METHODS

We reviewed the medical literature to find published articles related to HIV treatment programs in the developing world. We initially considered any observational study or clinical trial in which patients received ART and in which outcomes were reported in either defined clinical or laboratory terms. We excluded studies that exclusively dealt with pediatric populations, HIV-2 infection, or prevention of maternal-to-child transmission of HIV infection. We originally intended to exclude studies in which some patients had received monotherapy or dual ART (as opposed to triple-drug therapy) and to exclude studies in which some patients were ART experienced; however, in most cases, it was possible to specifically retrieve data on effect measures for the triple-drug therapy and the ART-naive groups, so these studies were ultimately included in the analysis.

Search strategy. We searched the Medline database, using both PubMed and OVID, with the following search criteria: ("antiretroviral therapy" OR ART OR HAART) AND ("developing country" OR "resource poor" OR "resource-poor" OR Africa) AND ("viral load" OR "CD4" OR outcome OR mortality OR result OR experience). We reviewed article references and searched WHO literature for references and bibliographies.

Data extraction. Three observers independently reviewed and extracted data from the studies, using a customized form developed for this purpose. The data collected were the number of patients who received ART; patient demographic characteristics, such as age and sex; markers of disease status at initiation of therapy (i.e., baseline median CD4 cell count and viral load, and previous ART experience); and outcomes (i.e., change in median CD4 cell count, change in median viral load, proportion of patients with an undetectable viral load, and mortality), as well as the timing of the outcome measure. Data were also gathered on programmatic and study design elements, including the proportion of the study population that received triple-drug therapy, whether medications were provided free of charge to participants, whether loss to follow-up and treatment adherence were discussed in the analyses, whether outcomes were stratified by CD4 cell count or other potential confounders, whether information for at least 48 weeks of follow-up was available, and whether data on effect measures were available specifically for the patients in each cohort who received triple-drug therapy.

Disagreements about data extraction were settled by conversation among the 3 reviewers and were resolved with a majority vote. In the case of missing key information, the study authors were contacted for further details.

Methodological quality. A method of scoring methodological quality was devised and then applied independently by the 3 raters. Disagreement among raters was addressed through conversation, which ultimately resulted in consensus on all scores. The quality score assigned equal weight to the following objective characteristics for each study: (1) discussion of adherence to treatment regimens; (2) stratification of outcome by initial CD4 cell count; (3) stratification of outcome by any other potential confounder; (4) availability of effect measures, specifically for patients who received triple-drug ART; (5) follow-up of at least 48 weeks; and (6) report of a <10% loss to follow-up. Each of these categories was scored as a binary, and the scores were summed to produce the quality score for each study.

Sources of potential bias in our analysis included the exclusion of articles on the basis of our inability to locate them, specifically if the articles held systematically different results from the articles we did find. One article written in French and published in the *Tunisian Medical Journal* described the investigator's experience with ART treatment of HIV infection in 139 infected patients [100]. Insufficient data were available in the abstract to include it in the analysis, and we were unable to retrieve the article. A second missing article was a duplicate publication that involved a cohort that was considered for inclusion in the analysis. The third article had insufficient data in the abstract for it to be included.

The studies ultimately included in our analysis are observational and have no control groups. There is no real ethical equipoise for the use of control groups in this instance (i.e., a "no therapy" group). As a result, our analysis summarizes efficacy in terms that are comparable to reported treatment outcomes in wealthier countries. Although this can be considered an informal analysis, it is a reasonable comparison.

Statistical analysis. Data on efficacy of ART from the studies were categorized according to 5 time points (described below). Summary effect measures and heterogeneity were assessed at each time point by use of random effects models. For proportions presented without an estimation of error, a 95% CI was calculated using the binomial distribution based on sample size and the effect measure. This 95% CI was then used to calculate the standard error for the effect measure.

A random-effects regression model was used to explore sources of heterogeneity, and we focused on 3 key variables of interest: quality score, provision of medications free of charge

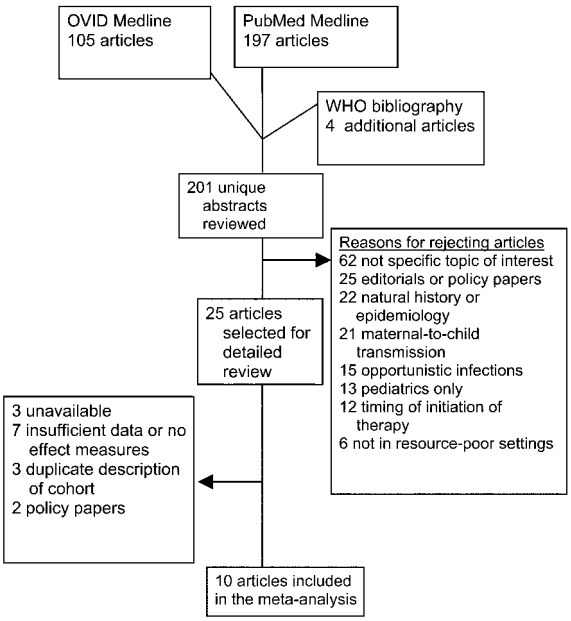

Figure 1. Flowchart summarizing the literature search of Medline. WHO, World Health Organization.

to the patient, and initial CD4 cell count. These regression models were generated for data in the categories of 6 months and 12 months, because these categories contained data from the greatest number of studies. All analyses were performed using Stata statistical software (Stata) and Excel spreadsheet software (Microsoft).

RESULTS

The PubMed search of Medline yielded 197 titles and abstracts. The OVID search yielded 105 titles, all of which had also been retrieved by the PubMed search. Review of the WHO literature and bibliography resulted in an additional 4 articles for review (see figure 1).

A total of 201 abstracts were reviewed. Of those abstracts, 62 did not relate specifically to the topic of interest, 13 were directly related to pediatric topics, 25 were editorials or policy articles, 22 were related to the natural history or epidemiology of HIV infection, 12 were concerned with methods for determining when to initiate ART, 6 were not programs in resource-poor settings, 15 were related to opportunistic infections, and 21 were specifically related to prevention of maternal-to-child transmission of HIV. Attempts were made to review the remaining 25 articles in detail.

Of 25 articles meeting our criteria, 3 were unavailable and 7 had insufficient detail regarding outcomes or had no data reported on effect measures. Included in the analysis were 3 duplicate publications describing the same patient cohorts—in these cases, the version of the article with the most complete details regarding patient outcomes was included. Also excluded were 2 policy articles. Data from the remaining 10 articles were included in the meta-analysis [14, 16–24].

Study features and data pooling. Since most studies reported outcomes at several time points, we grouped the available outcome data according to the following times after initiation of ART: months 3–4, month 6, month 12, month 18, and month 24. Some studies reported outcomes in terms of weeks, and others in terms of months or days. When necessary, we calculated the approximate number of months of therapy on the basis of a 30-day, 4-week calendar month. One study reported results at months 7 and 13, and these findings were included in the categories of 6 months and 12 months, respectively [20]. One study reported outcomes in a format that grouped results for months 2–5, months 10–13, months 18–21, and months 22–25 [24]. We included these data with the data for time points months 3–4, month 12, month 18, and month 24, respectively.

When results were represented in a graphic format in an article, proportions for analysis were determined by personal communication with the author [16, 20]. No study reported outcomes at both month 3 and month 4, and, because only a small number of studies had data for either of those 2 time points, we collapsed the data to a single group. The fewest data points were reported for the time points of month 18 ($n = 4$) and month 24 ($n = 3$). The 10 studies included in the analysis contained a total of 28 data points for the time points of interest. These are given in table 1.

Summary effect measures. The mean proportions of patients with an undetectable viral load was 0.697 (95% CI, 0.582–0.812) at month 6, 0.573 at month 12 (95% CI, 0.432–0.715), and 0.634 at month 18 (95% CI, 0.506–0.762). Table 2 displays pooled estimates, 95% CIs, and heterogeneity scores for each of the time points considered. Figures 2 and 3 display the outcomes for month 6 and month 12 in the form of Forest plots.

Analysis of heterogeneity. Random effects regression models were developed to identify potential sources of heterogeneity in the effect measure. Metaregression, with the month of follow-up as a predictor of outcome, was not found to be significant. In further analyses, we focused on the groups of data for the 2 time points for which the largest number of studies reported findings: month 6 (8 studies) and month 12 (7 studies). Regression was performed on 3 variables: quality score (ordinal), availability of medications free of charge to the patient (binary), and initial CD4 cell count (continuous), for both groups.

The availability of free medication had a significant impact on the mean proportion of subjects who had undetectable viral loads. On the basis of this model, the proportion of patients with an undetectable viral load at month 6 was 29.4% higher

Table 1. Studies included in meta-analysis of antiretroviral therapy (ART) programs in resource-poor settings.

Reference	Location	No. of patients	Baseline value, median (IQR)			Change in value at end of study, median (IQR)[a]		Proportion of patients with an undetectable viral load (95% CI) at time point
			Age, years	CD4 cell count, cells/mm^3	HIV load, copies/mL	CD4 cell count, cells/mm^3	HIV load, copies/mL	Months 3–4
[17]	South Africa	287	31	43 (13–94)	5.18	288 (181–470)	…	0.881 (0.832–0.920)
[20]	Cote d'Ivoire	276	37	182 (55–372)	…	>100	−1.9	0.545 (0.477–0.611)
[18]	Senegal	58	41.5	108.5 (34–17)	…	179	−2.8 (−1.1 to −3.2)	…
[19]	Cameroon	60	34.5	118 (78–167)	5.02	83 (40–178)	−3.1 (−2.5 to −3.6)	0.75 (0.62–0.85)
[21]	South Africa	289	33.4	268[d]	5.49[d]	…	…	…
[22]	Uganda	34	35	63.5	5.3	…	…	0.765 (0.585–0.886)
[14][e]	Multinational[f]	743	33	48 (11–120)	5.12	104 (47–163)	…	…
[16]	Uganda	399	38	73	5.29	…	…	0.45 (0.33–0.576)
[24][g]	Cote d'Ivoire	101	36	135	5.3	115	…	0.50 (0.341–0.659)
[23]	Kenya	217	…	80	5.13	74	−1.9	…

[a] At the latest time point reported for that study, except for [23], for which the change was reported at 12 months.
[b] Defined in Methods, subsection "Methodological quality."
[c] Personal communication with author.
[d] Mean value.
[e] In this study, 21.5% of the subjects were ART experienced, but data could not be extracted separately for those who were ART naive.
[f] Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand, and Guatemala.
[g] In this study, 10.9% of the patients received only 2-drug therapy, and data could not be extracted separately for those who received 3-drug therapy.

among those who did not have to pay for medication than among those who did ($P < .0001$). At month 12, the estimated mean proportion of patients with an undetectable viral load was 30.5% higher among those who did not pay than among those who did ($P = .006$).

In the regression model, the effect of initial CD4 cell count on variability was not significant at month 6 or month 12 ($P = .147$ and $P = .761$, respectively). Quality score had no effect on variability.

Sensitivity analysis. Sensitivity analysis was performed on the aggregated data by removing 2 specific studies whose evidence could have impacted the effect measure. In one study [14], 21.5% of the patients whose data was included in the effect measure were not ART naive. In the other study [24], 10.9% of the patients whose data was included in the effect measure had received dual-nucleoside therapy. However, removing these 2 studies from the analysis had no significant impact on the pooled estimate of the random effects model. The quality score was recalculated using as the threshold value a <20% loss to follow-up; this had no effect on the pooled estimates in regression analysis.

DISCUSSION

This meta-analysis of 10 observational studies demonstrates that ART is effective for HIV-infected individuals in resource-poor settings. ART resulted in an HIV RNA viral load suppression in ~60%–70% of individuals at time points up to month 18. This proportion of individuals who had viral suppression is similar to that observed in developed countries, even in clinical trials [25–28]. The pooled estimate of the proportion at month 24 (0.496) included effect-measure data from only 3 studies, which resulted in an unstable estimate with a wide confidence interval (95% CI, 0.252–0.740).

There were significant differences in the observed efficacy of ART across the 10 studies. Much of the heterogeneity in these studies may be due to bias introduced within each study. One source of bias is the settings in which these observational studies were conducted. Nine of the studies were conducted in urban health centers specializing in HIV/AIDS care, whereas the study by Coetzee et al. [17] was conducted in an urban primary health care community clinic. It is possible that there were baseline differences in the populations who attended these clinics. These studies also used different types of assays to measure HIV RNA viral load. However, all studies used an HIV RNA viral load of <400 or <500 copies/mL to define viral load suppression; therefore, this measurement is unlikely to be a significant contributor to heterogeneity.

It is likely that additional variability was introduced by the fact that these studies were performed in different countries. Differences in population genetics or HIV clades could result in some of the observed heterogeneity. Furthermore, if clinically unwell patients were more likely to have their viral load monitored than those who were clinically well, then the studies may have underestimated the efficacy of ART programs. Conversely,

Proportion of patients with an undetectable viral load (95% CI) at time point						
Month 6	Month 12	Month 18	Month 24	Probability of survival or AIDS-free event	ART free of charge to patient	Quality score[b]
0.892 (0.844–0.929)	0.842 (0.775–0.895)	0.750 (0.630–0.847)	0.697 (0.513–0.844)	0.863 (at 24 months)	Yes	6
0.592 (0.496–0.682)	0.543 (0.369–0.708)	…	…	0.84 (at 12 months)	No	4
0.712 (0.568–0.825)	0.514 (0.347–0.678)	0.593 (0.391–0.770)	…	0.823 (at 18 months)	No	4
0.80 (0.68–0.89)	…	…	…	0.85 (at 6 months)	Yes[c]	3
…	0.709 (0.641–0.769)	…	…	…	Yes	5
…	…	…	…	…	No	4
0.898 (0.825–0.944)	…	…	…	0.895 (at 6 months)	Yes	4
0.48 (0.358–0.605)	0.37 (0.258–0.497)	…	…	…	No	5
0.55 (0.382–0.708)	0.51 (0.323–0.695)	0.68 (0.449–0.851)	0.46 (0.218–0.720)	…	No	4
0.592 (0.473–0.702)	0.473 (0.339–0.611)	0.488 (0.332–0.647)	0.323 (0.174–0.515)	…	No	2

if the monitoring tests were performed preferentially for healthier patients, then the studies may have overestimated the efficacy of therapy. It is also not possible to assess the contribution of selection bias to the observed differences between studies in the effectiveness of ART, because none reported the rate of refusal of ART. Through metaregression, however, we were able to more formally explore several additional potential sources of heterogeneity.

Payment for laboratory monitoring was considered a factor that possibly influenced patient outcomes; however, laboratory tests were provided to subjects free of charge in 8 of the 10 studies, including 4 of the 6 studies that required payment for ART. In metaregression analysis, the availability of free laboratory testing at months 6 or 12 did not account for significant variability in the outcome ($P = .513$ and $P = .543$, respectively), although only a single study (which evaluated ART in the private sector in Kenya [23]) was in the "laboratory payment required" group in the analysis.

All these studies were observational and were conducted in resource-poor settings, which raises the potential for variability due to differences in study quality. Metaregression using the quality score revealed no evidence that quality accounted for variability in the observed proportion of patients who had an undetectable viral load. This likely represents a true lack of association; however, it may be the result of an inability to effectively capture study quality with the scoring scheme. We acknowledge that the use of quality scores in a meta-analysis of observational studies is controversial, because scores constructed for these purposes are not validated and ultimately may be not truly associated with quality [29]. However, given the diverse designs of the studies included, we preferred to attempt to reflect design factors that might influence the outcome in some way.

It is important that metaregression revealed that provision of ART free of charge accounted for the largest amount of variability in the rates of viral load suppression among the studies. A mean of 29%–31% more patients who received therapy free of charge had viral load suppression at months 6 and 12 of ART than did patients who had to pay for therapy. This finding is not entirely unexpected, since inconsistent ability to pay for medications may lead to treatment interruptions that cannot be controlled by either patients or physicians. It is well documented that such treatment interruptions must be avoided to maintain viral load suppression [15]. Financial constraints may also play a role in adherence and treatment success in developed countries [30].

Overall, ART programs in the developing world were successful and had outcomes similar to those in the developed world, regardless of whether therapy was free of charge or was paid for, in whole or in part, by patients. For example, in an

Table 2. Summary of pooled estimates and heterogeneity in studies of antiretroviral therapy (ART) programs in resource-poor settings.

Time point after start of ART	No. of patients	Proportion of patients with undetectable HIV load (95% CI)	Heterogeneity score or Q value
Months 3–4	6	0.651 (0.483–0.819)	102.207
Month 6	8	0.697 (0.582–0.812)	96.920
Month 12	7	0.573 (0.432–0.715)	73.069
Month 18	4	0.634 (0.506–0.762)	7.734
Month 24	3	0.496 (0.252–0.740)	9.671

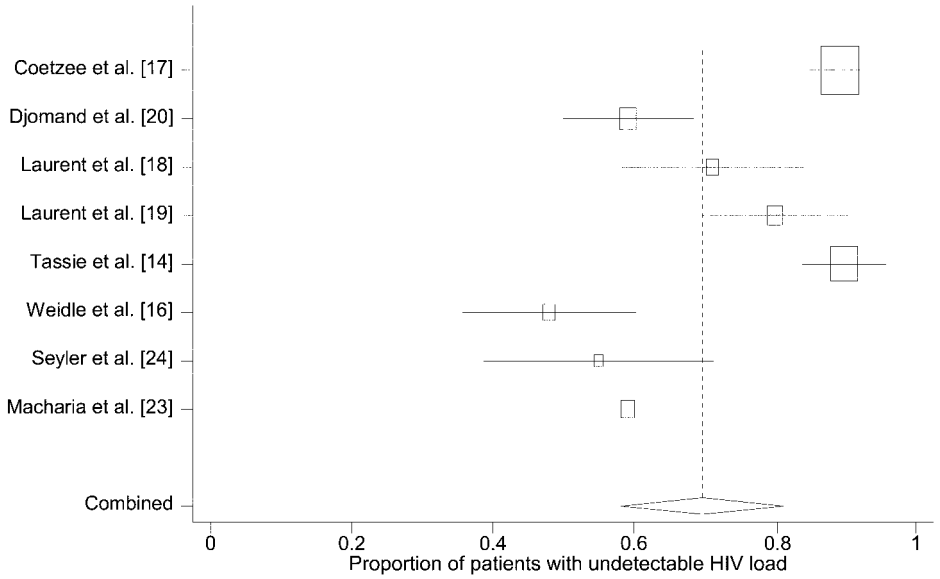

Figure 2. Forest plot displaying the proportions of patients in 8 studies with an undetectable HIV load at month 6 of antiretroviral therapy

analysis of 23 clinical trials in Europe, Australia, and North America [28], the average rate of virologic response (i.e., achievement of an HIV RNA load of <400 copies/mL) was 64% (95% CI, 60%–67%) at week 24 and 55% (95% CI, 51%–58%) at week 48. When a threshold value of <50 copies/mL of HIV RNA was used, the percentage of patients who had undetectable viral loads was 54% (95% CI, 50%–57%) at week 24 and 47% (95% CI, 43%–51%) at week 48 [28]. Observational studies have generally found virologic response rates that are lower than those found in clinical trials [31–33].

The positive impact of the availability of free drugs is notable. Whether it is an independent predictor of improved rates of treatment response or simply a marker of another factor related to health care delivery or infrastructure cannot be ascertained from the current analysis. Regardless, this finding has significant implications for the planning and implementing of HIV treatment programs in resource-poor settings.

As ART becomes increasingly available in resource-poor areas, and as treatment programs in those areas are shown to have efficacy rates equivalent to the rates in wealthier countries,

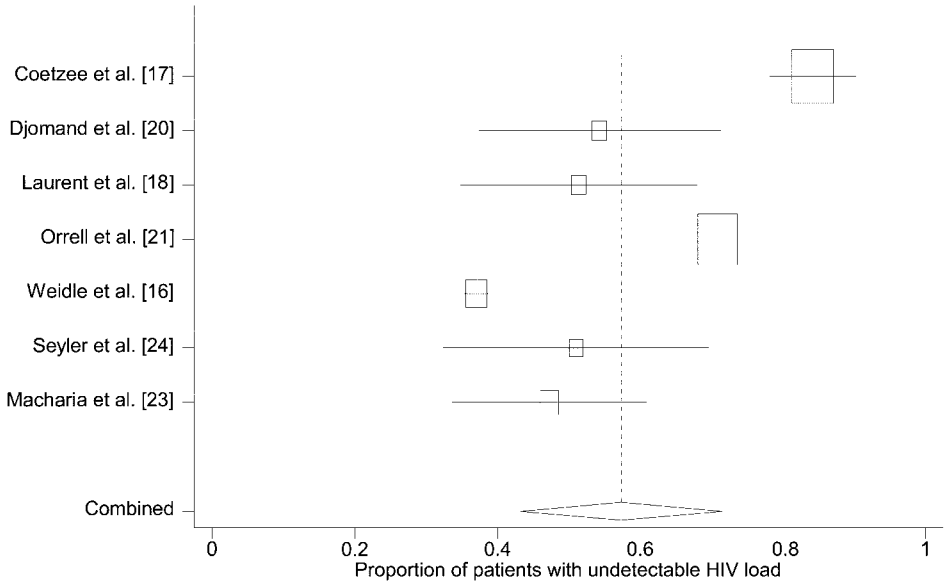

Figure 3. Forest plot displaying the proportions of patients in 7 studies with an undetectable HIV load at month 12 of antiretroviral therapy

further research should focus on identifying the program components that are most effective in delivering this complex health care intervention to areas with limited infrastructure. Identifying the most effective ways to deliver such health care will be crucial in the scaling up of HIV treatment programs in a variety of rural and urban resource-poor settings. Additional data on longer-term follow-up of patients in such clinical cohorts will also be highly valuable.

CONCLUSIONS

In this meta-analysis, we found that ART results in HIV viral load suppression in ~57% of patients at month 12 of therapy in resource-poor settings—a rate of viral suppression similar to that observed in developed countries. This supports the argument that ART programs in the developing world are effective. Provision of free medication is associated with a significantly greater proportion of patients who had viral load suppression than is the requirement of partial or full payment for therapy. These findings should be considered in the planning and development of HIV treatment programs worldwide.

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Potential conflicts of interest. All authors: no conflicts.

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