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Review

Immunological Treatment Failure Among Adult Patients Receiving Highly Active Antiretroviral Therapy in East Africa: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Minimizing antiretroviral treatment failure is crucial for improving patient health and for maintaining long-term access to care in low-income settings such as eastern Africa. To develop interventions to support adherence, policymakers must understand the extent and scope of treatment failure in their programs. However, estimates of treatment failure in eastern Africa have been variable and inconclusive.

Objective: This systematic review and meta-analysis sought to determine the pooled prevalence of immunological failure among adults receiving antiretroviral therapy in eastern Africa.

Methods: We performed a systematic search of the PubMed, Google Scholar, Excerpta Medica Database, and the World Health Organization's Hinari portal (which includes the Scopus, African Index Medicus, and African Journals Online databases) databases. Unpublished studies were also accessed from conference websites and university repositories. We used Stata version 14 for data analysis. The Cochrane Q test and I^2 test statistic were used to test for heterogeneity across the studies. Due to high levels of heterogeneity, a random effects model was used to estimate the pooled prevalence of immunological failure. Begg and Egger tests of the intercept in the random effects model were used to check for publication bias.

Results: After removing duplicates, 25 articles remained for assessment and screening. After quality screening, 15 articles were deemed eligible and incorporated into the final analysis. The average pooled estimate of immunological treatment failure prevalence was found to be 21.89% (95% CI, 15.14–28.64). In the subgroup analysis conducted by geographic region, the pooled prevalence of immunological treatment failure in Ethiopia was 15.2% (95% CI, 12.27–18.13) while in Tanzania it was 53.93% (95% CI, 48.14–59.73). Neither the results of Egger test or Begg tests suggested publication bias; however, on visual examination, the funnel plot appeared asymmetric. The large heterogeneity across the studies could be explained by study country.

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Conclusion: Immunological treatment failure among patients receiving antiretroviral therapy in eastern Africa was high, and greater than previously reported. The relatively low rates of treatment failure found in Ethiopia suggest that its health extension program should be studied as a model for improving adherence in the region. (*Curr Ther Res Clin Exp.* 2021; 82:XXX–XXX) © 2021 Elsevier HS Journals, Inc.

Introduction

This systematic review and meta-analysis estimates the pooled prevalence of immunological failure among adults who are receiving antiretroviral therapy (ART) in eastern Africa and Ethiopia. Since the Joint United Nations Program on HIV and AIDS and the World Health Organization (WHO) set the first global AIDS treatment target in 2003, annual AIDS-related deaths have decreased by 43%.[1] In the regions most affected by HIV—eastern and southern Africa—the number of people receiving ART has more than doubled since 2010, reaching nearly 10.3 million people, and AIDS-related deaths in the region have decreased by 36% since 2010.[2] Despite these dramatic advances, several serious challenges remain for halting the spread of HIV/AIDS and ensuring continued access to treatment for those already infected.[3] In particular, declines in the growth of HIV/AIDS donor funding due to donor fatigue and competing global health priorities threaten the quality and sustainability of national treatment and prevention programs.[4] Current donor funding is estimated to be insufficient to meet the targets set by the Joint United Nations Program on HIV and AIDS during 2011, let alone to meet newer targets that are as high as $35 billion annually.[5,6] In this climate of financial austerity and growing numbers of patients, it is imperative that national HIV/AIDS programs are vigilant about minimizing treatment failure among patients receiving first-line antiretroviral regimens, because second-line regimens can be extremely expensive; are limited in number; and can be difficult to administer and to keep in stock in low-income settings.[7] In sum, minimizing treatment failure is crucial both for maintaining patient health and for ensuring overall long-term access to HIV treatment.

To develop interventions to minimize treatment failure, policymakers must understand the extent and scope of treatment failure in their programs. Such estimates are particularly important for HIV/AIDS programs in eastern African countries that have the largest numbers of people living with HIV/AIDS. Establishing good estimates of treatment failure is complicated by the lack of viral load monitoring, which is largely unavailable in low-income countries.[8] WHO recommends viral load monitoring (copies of HIV RNA per milliliter) to assess treatment effectiveness because this method provides the most timely and accurate indications of treatment failure.[9] But because viral load testing is so rarely available in low-income settings, it cannot serve as a routine monitoring and patient support tool, and cannot be widely used to assess treatment failure.[8,10,11] In the absence of viral load testing, clinicians in these settings often base the decision to switch to second-line drug regimens on clinical criteria such as the presence of opportunistic infections; or on immunological criteria, such as patient cells of differentiation (CD) 4 T-cell count.[12–14]

Several studies have used this immunological measure to assess the extent of treatment failure in low-income country programs. They suggest that that failure levels in sub-Saharan African countries are high compared with those in Latin America and Asia, and compared with global averages.[15,16] In addition, a cross-national review of pretreatment drug resistance found that the pooled prevalence of pretreatment resistance to first-line medications was 11% in southern Africa, 10.1% in eastern Africa, and 9.4% in Latin America and the Caribbean.[15]

Our study is interested in examining levels of immunological treatment failure in Ethiopia and countries in the east of Africa (ie, Kenya, Uganda, Tanzania, Rwanda, Burundi, South Sudan, Djibouti, Eritrea, and Somalia) because this region has among the highest HIV/AIDS burdens worldwide and is heavily donor dependent for the financing of its HIV/AIDS programs. Estimates of the prevalence of immunological treatment failure in eastern African countries are often inconsistent and there are wide prevalence ranges. For example, the prevalence of immunological failure in Tanzania is estimated to range from 48% to 57%,[17–19] studies estimate a 5.7% prevalence in Kenya[20] and a 41.8% prevalence in Uganda,[21] and in Ethiopia, estimated prevalence ranges from 6.8% to 21%.[22–27] To establish a more precise estimate of treatment failure levels in this region, we conduct a systematic review and meta-analysis to determine the pooled prevalence of immunological failure among adults who are receiving ART in eastern Africa.

Methods

Search approach and appraisal of studies

We conducted this study according to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis Protocols checklist guidelines.[28] This systematic review and meta-analysis has been registered in Prospero with registration number CRD42020209448. Studies for this meta-analysis and systemic review were retrieved via a systematic web-based database search and by accessing abstracts and studies from international conferences and university library archives. The databases searched were PubMed/Medline, Google Scholar, the Cochrane Library, and Hinari (a WHO portal for low- and middle-income countries that includes Web of Science, Scopus, African Index Medicus, WHO's Institutional Repository for Information Sharing, and African Journals Online databases).

For the database searches, the following key terms were used: *antiretroviral* [MeSH terms] OR *antiretroviral agents* [MeSH terms] OR *highly active antiretroviral therapy* [MeSH terms] AND *Treatment* [MeSH terms] OR *Therapy* [MeSH terms] AND *Immunological* [MeSH terms] AND *Failure* [MeSH terms] AND *Uganda*) AND *Kenya* AND *Tanzania* AND *Rwanda* AND *Burundi* AND *Ethiopia* AND *South Sudan*) AND *Djibouti* AND *Eritrea* AND *Somalia* and combinations of those words using the Boolean operator. We conducted our search from December 30, 2018, to February 18, 2020. After identifying relevant articles, their reference lists were used to retrieve other related articles.

Inclusion and exclusion criteria

All articles that were conducted in Kenya, Uganda, Tanzania, Rwanda, Burundi, Ethiopia, South Sudan, Djibouti, Eritrea, and Somalia, written in English, published in peer-reviewed journals, published between the years 2009 and 2019, designed as an observational study (cross-sectional, prospective, or retrospective cohort), and that reported the proportion of adult patients on antiretroviral treatment experiencing immunological failure were

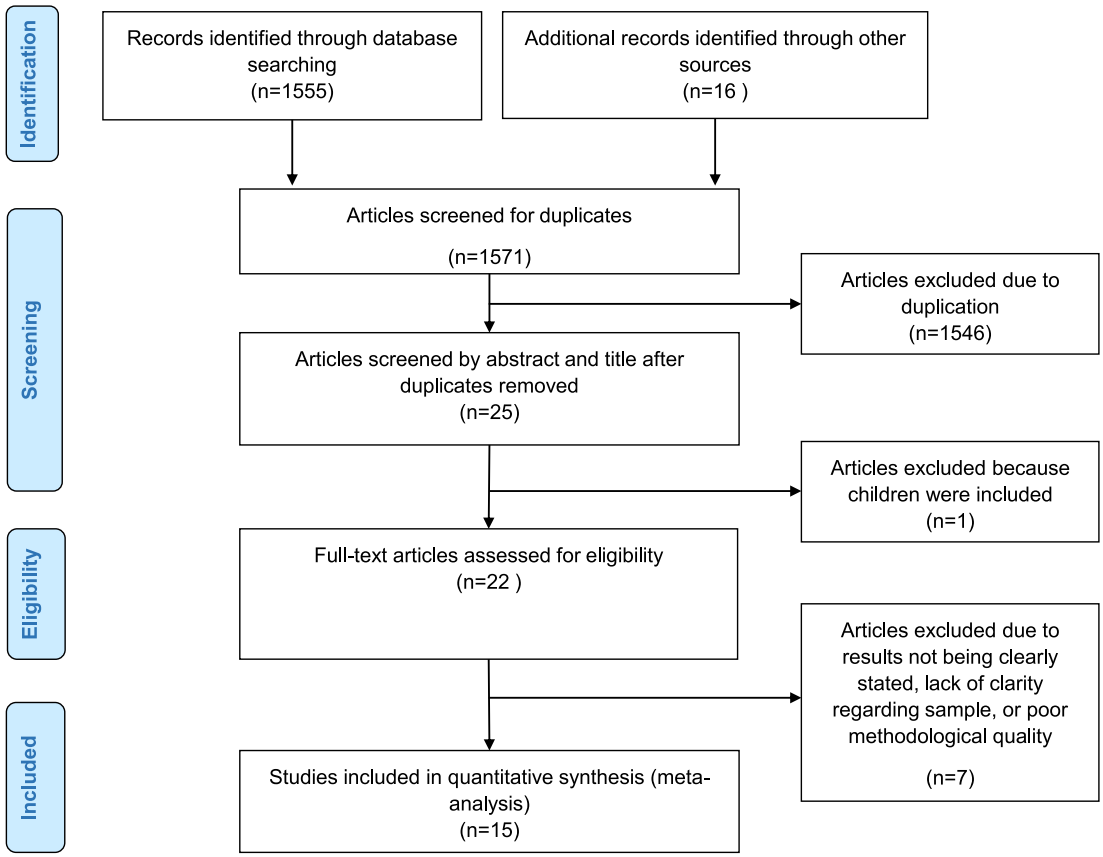

Figure 1. Preferred Reporting Items of Systematic Reviews and Meta-Analysis flow diagram showing the procedure of selecting studies for meta-analysis on the prevalence of immunological treatment failure among adult patients taking antiretroviral therapy, in eastern Africa during 2009 to 2019.

eligible for inclusion in this study. We excluded studies that did not have full text available that that did not report quantitative adult immunological failure outcomes or that did not pass our quality screening, described below.

Data abstraction and quality assessment

Six reviewers (A.N., A.Z., D.K., F.W., G.D., and H.M.) reviewed article titles generated by our search, removing duplicates and articles whose title indicated that they did not concern immunological treatment failure. The remaining abstracts were critically reviewed by each of the 6 reviewers against both the inclusion and exclusion criteria. After reading the full abstract, studies were excluded if they had methodological flaws, if they did not have clearly set immunological failure outcomes or measurements, or if no full text of the article was available. If the study was deemed relevant for our review, the full text of the article was reviewed for relevance based on topic, objectives, and methodology and assessed for quality by 2 reviewers using the Newcastle-Ottawa Scale criteria.[29] The average of 2 independent reviewers' Newcastle-Ottawa Scale score was used to determine article quality. Discrepancies regarding quality were resolved by a third reviewer.

Outcome measurements

The outcome measure of interest was immunological treatment failure, using WHO definition of a "fall of CD4 counts to pre-therapy baseline (or below), or 50% fall from the on-treatment peak value (if known), or persistent CD4 levels below 100 cells/mm^3 6 months after ART initiation."[30]

Data analysis

The necessary information was extracted from each original article using a Microsoft Excel (Redmond, Washington) spreadsheet template. Extracted data were transferred to Stata software version 14 (Stata Corp, College Station, Texas) for further analysis. Heterogeneity was assessed using I^2 test statistic.[31] Funnel plot asymmetry and Egger test of the intercept were used to assess publication bias.[32] Two researchers independently conducted the statistical analysis and confirmed consistency of results. The effect size estimates were reported in the form of pooled prevalence.

Results

Explanation of original studies

The original search resulted in a total of 1571 articles, of which 1555 abstracts were found in PubMed, Hinari, and Google Scholar. The remaining 16 were found in conference websites and university repositories (see Figure 1). We excluded 1546 articles due to duplication and lack of relevance. For the remaining 25 records, abstracts were accessed and screened. Seven articles were excluded because their results did not clearly state the prevalence of immunological treatment failure.[33–39] One article was excluded because children were included in the sample.[40] The other 2 articles were also excluded due to low methodological quality.[41,42] After this review, 15 studies fulfilled the eligibility criteria and were included in the final analysis.

Table 1
Characteristics of included studies for meta-analysis on the prevalence of immunological treatment failure among adult patients receiving antiretroviral therapy (ART) in East Africa during 2009 to 2019.

Author	Publication year	Country	Study design	Sample size	Prevalence (%)	Definition criteria
Bayou, et al[22]	2015	Ethiopia	Retrospective cohort	828	6.8	Fall of CD4 count to pretherapy base line, 50% fall from the on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Yimer, et al[26]	2015	Ethiopia	Retrospective cohort	525	15	Fall of CD4 count to baseline (or below), or 50% fall from on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Sisay, et al[23]	2017	Ethiopia	Retrospective cohort	595	15.3	Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value or persistent CD4 levels below 100 cells/mm^3
Brhane, et al[27]	2017	Ethiopia	Cross-sectional	421	15.9	CD4+ T cell count below the baseline or persistent CD4+ T-cell levels below 100 cells/mm^3
Teshome and Tefera[45]	2015	Ethiopia	Retrospective cohort	293	15.7	Fall of CD4 count to baseline (or below), or 50% fall from on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Yirdaw and Hattingh[24]	2015	Ethiopia	Retrospective cohort	1304	11.5	Fall of CD4 count to baseline (or below) or 50% fall from on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Melsew, et al[25]	2013	Ethiopia	Retrospective cohort	509	21	Fall of CD4 count to baseline (or below), or 50% fall from on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Lenjiso, et al[46]	2019	Ethiopia	Cross-sectional	949	19.3	Fall of CD4 counts to baseline (or below), or 50% fall from the on-treatment peak value (if known), or persistent CD4 levels below 100 cells/mm^3 6 month after ART initiation
Gesesew, et al[47]	2015	Ethiopia	Retrospective cohort	4900	19.7	Fall of CD4 counts baseline (or below), or persistent CD4 levels below 100 cells/mm^3 after 6 mo of ART treatment
Ayele, et al[48]	2018	Ethiopia	Cross-sectional	423	14.7	Fall of follow-up CD4 count to baseline (or CD4 falls below baseline), or CD4 levels persisting below 100 cells/mm^3, or 50% fall from on-treatment peak value
Ferreyra, et al[20]	2012	Kenya	Cross-sectional	926	5.7	CD4 count below the patient's baseline measurement at 6 mo of therapy, CD4 count <50% of peak measurement at any time after 6 mo of therapy, or 100 cells/mm^3 after 12 mo of therapy
Mpondo, et al[17]	2015	Tanzania	Cross-sectional	274	57	Fall of follow-up CD4 cell count to baseline (or below), or CD4 levels persisting below 100 cells/mm^3, or 50% fall from on-treatment peak value; in the absence of concurrent infection(s)
Gunda, et al[18]	2017	Tanzania	Cross-sectional	274	56.9	Fall of CD4 count to pretherapy baseline or below, or ≥50% fall of absolute CD4 count from the on-treatment peak value, or persistent CD4 levels below 100 cells/mm^3
Kamugisha, et al[19]	2018	Tanzania	Retrospective cohort	2565	48.2	Not stated
Reynolds, et al[21]	2009	Uganda	Prospective cohort	1133	11	Persistent CD4 below 100 cells/mm^3, or a drop of CD4 cell count below baseline pretreatment level, or a drop of CD4 cell count of 50% from peak on-treatment value all in the absence of an ongoing coinfection

CD = cluster of differentiation.

Characteristics of included studies

The search strategy yielded a total of 15 studies with a total sample of 17,203 adult patients. Of the 15 articles, 10 were from Ethiopia,[22,23,25,26,43–48] 3 were from Tanzania,[18,19,42] and the remaining 2 were from Kenya[20] and Uganda.[21]

Eight of the studies were retrospective cohort studies,[19,22–26,45,47] Six were cross-sectional[17,18,20,27,46,48] and 1 was prospective cohort study[21] (see Table 1). A study conducted in Ethiopia had the largest sample size,[47] and the smallest sample size was observed in the studies conducted in Tanzania. All but 1 study used the WHO definition for immunological treatment failure of a CD4 count "at or below 250 cells/mm^3 following clinical failure, or persistent CD4 levels below 100 cells/mm^3,"[30] and some also evaluated clinical and/or virologic treatment failure.

Pooled effect size

In the random effects model, each study was weighted based on individual study effect size and sample size.[49] Because the I^2 test for heterogeneity showed significant difference between studies ($I^2 = 96\%$; $P < 0.05$), the DerSimonian and Laird random effect model was fitted to determine the pooled effect size.[49,50]

The average pooled estimate of immunological treatment failure prevalence was found to be 21.89% (95% CI, 15.14–28.64) (see Figure 2). In the subgroup analysis conducted by geographic region, the pooled prevalence of immunological treatment failure was 15.2% (95% CI, 12.27–18.13) in Ethiopia, 53.93% (95% CI, 48.14–59.73) in Tanzania, and 8.09% (95% CI, 2.92–13.26) in other eastern African countries.

We found no evidence of publication bias in our statistical tests: The Egger test had an intercept (B0) of 0.35 (95% CI, −0.40 to 1.10; $P > 0.05$) and the Begg Test had a P value > 0.05. However, on visual examination, the funnel plot appears asymmetric suggesting either some level of publication bias or the presence of small study effects (Figure 3).

Meta-regression

There was a great deal of heterogeneity across the studies, which we explored by conducting a meta-regression analysis on study publication year, sample size, study design, and country. The results of the meta-regression suggest that the country variable

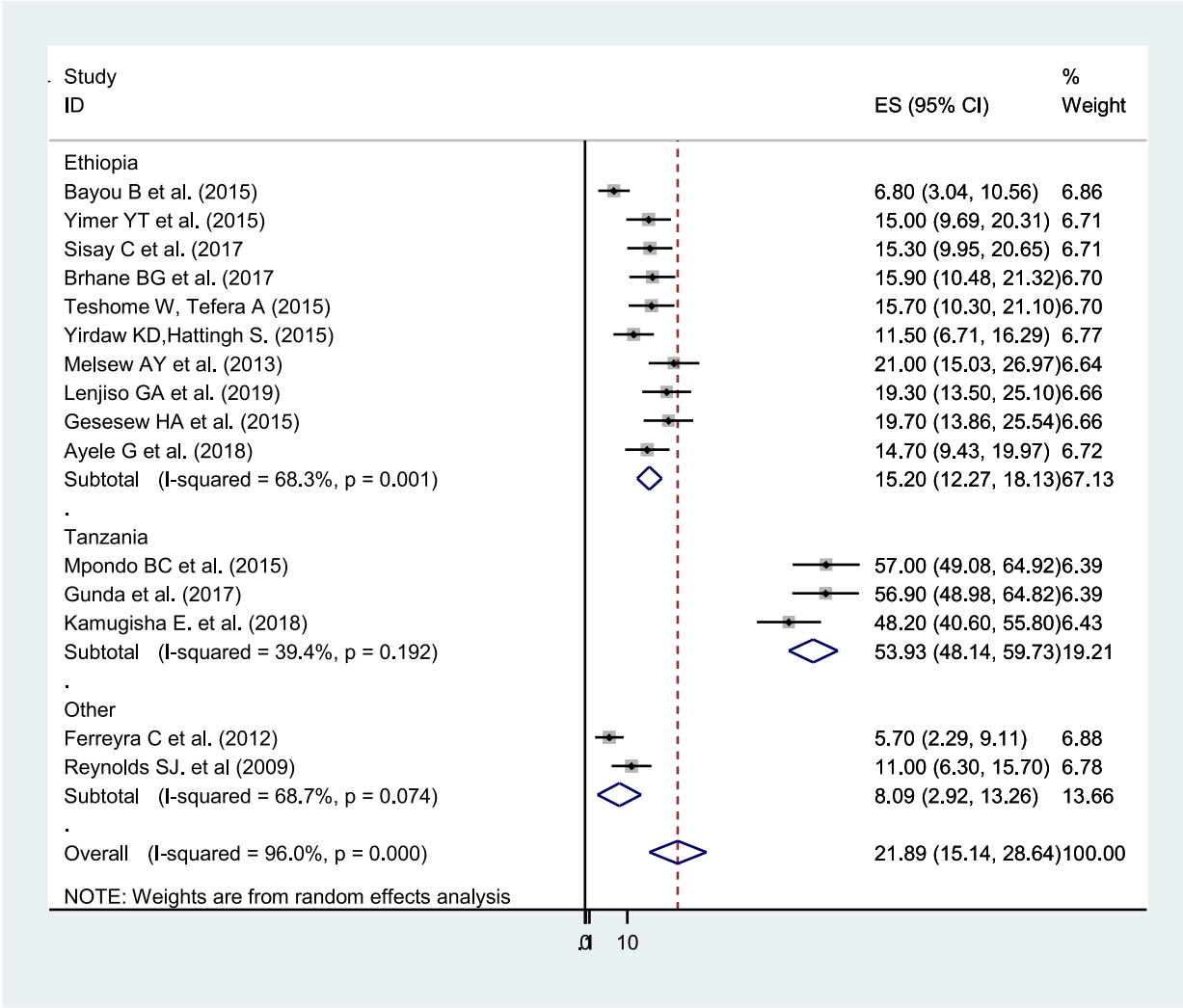

Figure 2. Forest plot of 15 studies on the prevalence of immunological treatment failure among adult patients taking antiretroviral therapy, in eastern Africa during 2009 to 2019.

Table 2
Meta-regression results on selected variables in studies conducted in East Africa from 2009 to 2019.

Variable	Coefficient	*P* value
Publication year	1.15	0.39
Sample size	0.01	0.823
Study design		
Retrospective cohort	−3.41	0.228
Prospective cohort	5.3	0.392
Country		
Ethiopia	−36.88	0.001
Other	−49.01	0.001

had a significant impact on the level of heterogeneity in study outcomes (see Table 2). Therefore, we fitted subgroup analysis based on country to minimize heterogeneity.

Discussion

This systemic review and meta-analysis attempted to assess the pooled estimate of immunological treatment failure among adult patients receiving ART in eastern Africa. Our findings suggest that a significant proportion, 21.89% (95% CI, 15.14–28.64), of adult patients receiving ART experience immunological treatment failure.

Our estimated 21.89% prevalence of treatment failure is far higher than those found in other cross-national studies and meta-analyses. For example, a 2010 cross-national meta-analysis of treatment failure found a 1.9% prevalence worldwide, and 2.57% (95% CI, 1.80–6.94) prevalence for sub-Saharan African countries, when using CD4 cell count or clinical definitions as an outcome measure.[16] However, a 2018 major review and meta-analysis on HIV drug resistance before initiation or reinitiation of first-line ART in low- and middle-income countries found pretreatment resistance prevalence to be 11.0% in southern Africa, 10.1% in eastern Africa, and 7.2% in western and central Africa,[15] suggesting higher and perhaps growing rates of treatment failure than previously believed.

The relatively high failure rates found in our meta-analysis may reflect the growing number of people on the continent who have been receiving ART over long time periods. The studies in the previous meta-analysis reporting very low rates of treatment failure in sub-Saharan were conducted more than 10 years before the studies in our meta-analysis, during which time the average duration of treatment for the populations under study, has most likely increased. Patient monitoring standards may also have become more rigorous during this time period, with more frequent CD4 monitoring conducted as treatment programs matured. We must also note that the 2018 study,[15] reported the presence of virological resistance in patients who were starting or restarting treatment,

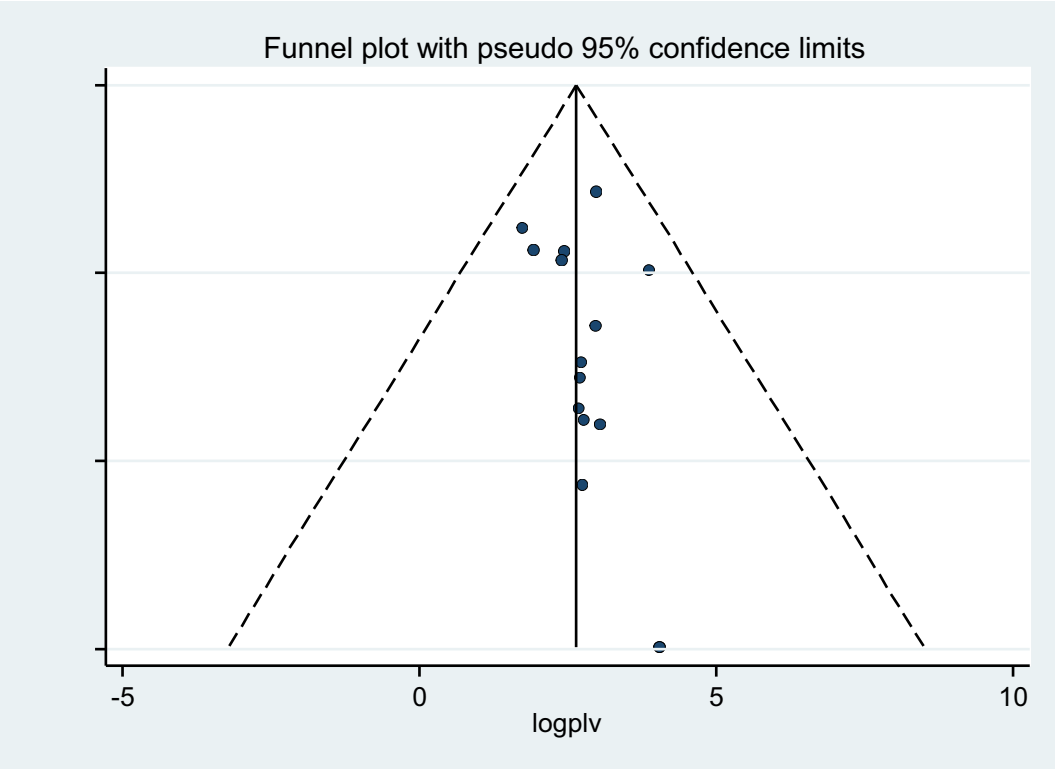

Figure 3. Meta funnel presentation of the prevalence of immunological treatment failure among adult patients taking antiretroviral therapy, in eastern Africa during 2009 to 2019.

not immunological treatment failure for those currently receiving treatment; this makes their outcomes difficult to compare with our estimates. In addition, we note that our immunological failure estimate is in line with the 16% to 25% estimated prevalence of virological failure reported in several studies of ART program effectiveness in eastern African countries.[51,52]

Overall our findings suggest that antiretroviral treatment failure remains an important public health concern in eastern Africa warranting continued vigilance and program re-evaluation by governmental and nongovernmental organizations in the region. With increased adherence support and easier treatment regimens, failure rates could be further decreased, preventing the use of less-accessible second-line therapies and potentially reducing overall HIV-related morbidity and mortality.

Our second main finding was the significantly lower immunological failure levels in Ethiopia compared with its neighbors in eastern Africa. This discrepancy may be due to health systems differences that shape the quantity and quality of adherence support available to patients, particularly at the community level. Ethiopia has trained, remunerated health extension workers who are a formal part of the health system and who are able to follow-up patients at the village/*kebele* level even in fairly remote rural areas.[53] These workers are, in turn, supported by volunteer community health workers who are also able to provide education, support, and information at the household level.[54,55] Ethiopian health extension workers and volunteers provide education and support across a range of health issues, not just HIV, which might make their HIV/AIDS adherence work less stigmatizing to community members than standalone services. Although many countries in east Africa use community health workers and community members to support patients living with HIV, none have as institutionalized and comprehensive a structure as Ethiopia.

Another potential reason for Ethiopia's relatively low prevalence is that although HIV/AIDS treatment standards and protocols are centralized in the Ethiopian Federal Ministry of Health, whose public facilities provide most HIV/AIDS treatment in the country, ART service delivery has rapidly decentralized in Ethiopia with a significant proportion of treatment being delivered at primary care facilities.[55] This may facilitate continued access to care, and therefore better adherence, in rural areas. In addition, Ethiopia's epidemic is not as generalized or as severe in terms of prevalence as it is in many of the other countries in the region. Lower HIV prevalence and a more concentrated epidemic may create less stress on Ethiopia's health system than occurs in neighboring countries, allowing the country to provide a relatively high quality of care. The few Ugandan and Kenyan studies in our sample also reported lower treatment failure rates than Tanzania. Kenya's relatively low treatment costs[56] and Uganda's extensive use of treatment support groups and adherence buddies[57] might explain these figures. Health systems in countries like Tanzania that seem to have high levels of treatment failure may want to borrow practices from Ethiopia, Kenya, and Uganda that facilitate adherence. Finally, we must note that factors other than adherence such as malnutrition, the prevalence of coinfections, the ART regimens used, ART efficacy and clinical factors such as a delayed initiation of ART may influence adherence and treatment failure rates and that the prevalence of these factors may vary significantly by country.[43,58,59]

Limitations of the review

This study has several limitations. First, the countries that make up the region of eastern Africa are defined differently by different actors and it may be that the countries we chose for our analysis will not be relevant to other researchers or program managers. Moreover, only a small number of studies meeting our criteria were published outside of Ethiopia, limiting our ability to calculate a precise estimate of treatment failure prevalence in these countries. The CIs around our estimates are very wide,

indicating that larger regional studies may be warranted. A second limitation of this study was that we only included articles that were written in English, which may have caused us to overlook relevant articles written in Arabic, Swahili, French, or Portuguese. A third limitation is that due to the small number of east African studies outside of Ethiopia and variation in their study design, we were not able to conduct subgroup analysis on sociodemographic, study setting, or clinical factors that might have explained the large heterogeneity that we found in the study outcomes. Fourth, we have not included compliance or adherence data but instead confined our discussion of immunological treatment failure in low-income countries to other factors, such as malnutrition, the prevalence of coinfections, the ART regimens used, ART efficacy, and clinical factors such as a delayed initiation of ART. And fifth, because the criteria for children differs from that of adults, we have tried to use only articles conducted among adults to avoid introducing bias. Our study findings would be best if interpreted in the context of these limitations.

Our findings suggest that the prevalence of immunological treatment failure may be lower in Ethiopia than in other East African countries. This suggests that that good patient adherence and retention can be achieved even in relatively low-resourced settings. It also suggests that the incorporation of institutionalized, formally trained, and remunerated health extension workers into HIV/AIDS care programs may play a crucial role in improving access to care and supporting adherence.[53,60–63] In order to maintain the efficiency of current treatment programs and to improve the quality of care, other countries in the region may want to consider expanding and formalizing structural interventions that improve community-level access to care such as health extension workers and studying their impact.

Conclusions

The systematic review and meta-analysis revealed that immunological treatment failure among adult patients receiving ART in East Africa may be significantly higher than previously estimated. Ministries of Health, health professionals, and program managers in each country should consider conducting additional research on this topic and developing interventions to strengthen adherence support and CD4 monitoring.

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G. Dessie developed the protocol and involved in the design, selection of study, data extraction, statistical analysis, and developing the initial drafts of the manuscript. G. Dessie, F. Wagnew, H. Mulugeta, A. Negesse, A. Zegeye, and D. Kiross were involved in data extraction, quality assessment, statistical analysis. G. Dessie, F. Wagnew, H. Mulugeta, A. Negesse, A. Zegeye, T. Getaneh, D. Kiross, and A. Ohringer prepared and revised subsequent drafts. G. Dessie and A. Ohringer prepared the final draft of the manuscript. All authors read and approved the final draft of the manuscript.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2020.100621.

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