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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A B S T R A C T

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 Unpublished studies were also accessed from conference websites and university repositories.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 I² 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 23.93% (95% CI, 18.41–29.73). 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.

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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%. 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. 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. 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. 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. In this climate of financial austerity and growing numbers of patients, it is imperative that national HIV/AIDS programs be 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. 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. 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. 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. 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.

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. In addition, a cross-national review of pretreatment drug resistance found that the pooled prevalence of pretreatment resistance to first-line medica-

ions was 11% in southern Africa, 10.1% in eastern Africa, and 9.4% in Latin America and the Caribbean.

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%, and studies estimate a 5.7% prevalence in Kenya and a 41.8% prevalence in Uganda, and in Ethiopia, estimated prevalence ranges from 6.8% to 21%. 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. This systematic review and meta-analysis has been registered in Prospero with registration number CRD42020209448. Studies for this meta-analysis and systematic 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
eligible for inclusion in this study. We excluded studies that did not have full text available 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. 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<sup>3</sup> 6 months after ART initiation.”

**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<sup>2</sup> test statistic. Funnel plot asymmetry and Egger test of the intercept were used to assess publication bias. 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. One article was excluded because children were included in the sample. The other 2 articles were also excluded due to low methodological quality. After this review, 15 studies fulfilled the eligibility criteria and were included in the final analysis.
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, 22–26, 28, 29, 31, 32, 33, 34, 35, 36, 37, 38 and the remaining 2 were from Kenya and Uganda.

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 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/mm³ following clinical failure, or persistent CD4 levels below 100 cells/mm³,”49 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 I² test for heterogeneity showed significant difference between studies (I² = 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 (80) 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...
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. 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, 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 Africa 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 reported the presence of virological resistance in patients who were starting or restarting treatment,

### Table 2

| 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   |

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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.  

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 regimes, 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. 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. 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. 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 and Uganda’s extensive use of treatment support groups and adherence buddies 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.

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 good patient adherence and retention can be achieved even in relatively low-resource 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.\(^{5,6,60-63}\) 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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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.

References

1. The 3 by 5 Initiative [https://www.who.int/3by5/en/14035.en.html].
2. Joint United Nations Programme on HA: Global AIDS Update 2016. In: Geneva: UNAIDS, 2016: 16.
3. Parker R. The Global HIV/AIDS Pandemic. Structural Inequalities, and the Politics of International Health. American Journal of Public Health. 2002;92(3):343–347.
4. Grimp KA. Efficiency considerations of donor fatigue, universal access to ARTs and health systems. Sex Transm Infect. 2012;88(2):75–78.
5. Schwartzländner B, Stover J, Hallett T, Atun R, Avila C, Gouws E, Bartos M, Ghys PD, Opunji M, Barr D, et al. Towards an improved investment approach for HIV/AIDS. Lancet. 2011;377(9782):2031–2041.
6. Joint United Nations Programme on HA: Fast-track—ending the AIDS epidemic by 2030. Geneva, Switzerland: UNAIDS; 2014.
7. Long L, Fox M, Sanne I, Rosen S. The high cost of second-line antiretroviral therapy for HIV/AIDS in South Africa. AIDS (London, England). 2010;24(6):915–919.
8. Médecins Sans F: Undetectable: How Viral Load Monitoring Can Improve HIV Treatment in Developing Countries. Geneva, Switzerland: MSF Access Campaign; 2012.
9. Concluded guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva, Switzerland: World Health Organization; 2013;272.
10. Ford N, Meinjes G, Pozniak A, Bygrave H, Hill A, Peter T, Davies M-A, Grinsztejn B, Calmy A, Kumarasamy N, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. Lancet Infect Dis. 2015;15(2):241–247.
11. Phillips AN, Pillay D, Miners AH, Bennett DE, Gilks CF, Lundgren JD. Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model. Lancet. 2008;371(9622):1443–1451.
12. Mermim J, Ekwaru JP, Were W, Degirmen R, Bunnell R, Karahara F, Downing R, Coutinho A, Solberg P, Alexander LJ, et al. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults and children on antiretroviral therapy in Uganda: randomised trial. BMJ (Clinical research ed). 2011;343:d6792.
13. Danitie D, Yismaw G, Woldeyohannes D, Anagaw B. Common opportunistic infections and their CD4 cell correlates among HIV-infected patients attending antiretroviral therapy clinic of Gondar University Hospital, Northwest Ethiopia. BMC research notes. 2013;6:5334.
14. Muri L, Gamell A, Ntamarungiro AJ, Glass TR, Luwanda LB, Battegay M, Furrer H, Hatz C, Tanner M, Felger I, et al. Development of HIV drug resistance and therapeu­tic failure in children and adolescents in rural Tanzania: an emerging public health concern. AIDS (London, England). 2017;31(1):61–70.
15. Gupta BK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Forero LA, Kaleebu P, Watiera C, Akgolak A, Mutenda N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. The Lancet Infectious Diseases. 2018;18(3):346–355.
16. Renaud-Théry F, Duncombe C, Kerr S, Thierry S, Perrasien J. Adult antiretroviral therapy in resource limited settings: a systematic review of first-line failure and attrition rates. In: Geneva, Switzerland; 2010.
17. Mpondo BCT, Kilonzo SB, Gunda DW. Prevalence and predictors of immunological failure among HIV-infected adults on HAART in Northwestern Tanzania: A cross sectional study. Tanzania Medical Journal. 2015;27(1).
18. Gunda DW, Kidenya BR, Mshana SE, Kilonzo SB, Mpondo BCT. Accuracy of WHO immunological criteria in identifying virological failure among HIV-infected adults on First-line antiretroviral therapy in Mwanza, North-western Tanzania. BMC Research Notes. 2017;10(1):45.
19. Kamugisha E, Chomboko B, Kyabemera R, Kidenya B. Prevalence and Predictors of Immuno­logical Treatment Failure among HIV Infected Adults on the First-line Antiretroviral Therapy in Mbeya Region, Tanzania. Mj HIV. 2018;3(1):017.
20. Ferreyra C, Yun O, Eisenberg N, Alonso E, Khamadi AS, Mwau M, Mugendi MK, Alvarez A, Vehila E, Flevaud I, et al. Evaluation of Clinical and Immunological Markers for Predicting Virological Failure in a HIV/AIDS Treatment cohort in Russia. PloS one. 2012;7(11):e049834.
21. Reynolds SJ, Nikagzo G, Newell K, Ndyabanu A, Galiwongo R, Boaz I, Quinn TC, Gray R, Wawer M, Serwadda D. Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. AIDS (London, England). 2009;23(6):697–700.
22. Bayou B, Bisay A, Kumie A. Assessment of the magnitude and associated factors of immunological failure among adult and adolescent HIV-infected patients in St. Luke and Tulubolo Hospital, Oromia Region, Ethiopia. The Pan African Medical Journal. 2015;21.
23. Bisay C, Bekele A, Bisay A, Mekonen H, Terfa K, Melese D, Dufera B. Incidence and Predictors of Anti-Retroviral Treatment (ART) Failure among Adults Receiving HIV Care at Zewdu Memorial Hospital, Addis Ababa, Ethiopia. Journal of AIDS & Clinical Research. 2017;8(12).
24. Yirdaw KD, Hattingh S. Prevalence and Predictors of Immunological Failure among HIV Patients on HAART in Southern Ethiopia. PloS one. 2015;10(5).
25. Alemu Metewel Y, Terefe MW, Tessema GA, Ayele TA. Rate of immunological Failure and its predictors among Patients on Highly Active Antiretroviral Therapy at Debremarkos Hospital, Northwest Ethiopia: A Retrospective Follow up Study. Journal of AIDS & Clinical Research. 2013(05):04.
26. Tesfahuneman Yimer Y, Ayele WH. Magnitude and Predictors of Anti-Retroviral Treatment (ART) Failure in Private Health Facilities in Addis Ababa, Ethiopia. PloS one. 2015;10(5).

G. Dessie, H. Mulugeta, F. Wagnew et al. Current Therapeutic Research 94 (2021) 100621.
27. Gidey Brhane B, Nibret E, Kahsu Abay G: HIV/AIDS Treatment Failure and its Determinant Factors among First Line HAART Patients at Felege-Hiwot Refer-ral Hospital, Bahar Dar, Northwest Ethiopia. Journal of AIDS & Clinical Research. 2017;8(11).

28. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine. 2009;151(4):264-269, W264.

29. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology. 2010;25(9):603–605.

30. World Health Organization: What's new in treatment monitoring: viral load and CD4 testing. Geneva, Switzerland: World Health Organization; 2017:2.

31. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychological Methods. 2006;11(2):193–206.

32. Rendina-Gholff G. Detecting publication bias in random effects meta-analysis: An empirical comparison of statistical methods. Graduate Theses and Dissertations. 2006.

33. Teshome W, Asea A, Assefa A. Predictors of immunological failure of antiretroviral therapy among HIV infected patients in Ethiopia: a matched case-control study. PLoS one. 2014;9(12).

34. Niemeyer K, King A, Mengistu S, Hennig N. Predictors of antiretroviral therapy failure in an urban HIV/AIDS clinic in Addis Ababa, Ethiopia. The Lancet Global Health. 2016;4:56.

35. Mulisa D, Tesfa M, Mullu Kassa G, Tolossa T. Determinants of first line antiretro- viral therapy treatment failure among adult patients on ART at central Ethiopia: un-matched case control study. BMC Infectious Diseases. 2019;19(1):1024.

36. Bezbash YM, Bejene F, Bezabhe WM. Factors associated with first-line antiretroviral therapy failure in adult HIV-positive patients: a case-control study from Ethiopia. BMC Infectious Diseases. 2019;19(1):537.

37. Kapesa A, Magesa D, William A, Kaswija J, Seni J, Makwaya C. Determinants of immunological failure among clients on the first line treatment with highly active antiretroviral drugs in Dar es Salaam, Tanzania. Asian Pacific J ournal of Tropical Biomedicine. 2014;4:5520–5524.

38. Ayalew MB, Kumilachew D, Belay A, Getu S, Teju D, Endale D, Tesgaye Y, Wale Z. First-line antiretroviral treatment failure and associated factors in HIV patients in the University of Gondar Teaching Hospital, Gondar, Northwest Ethiopia. HIV AIDS (Auckl). 2016;8:141–146.

39. Babo YD, Aleme GA, Festaye FW. Predictors of first-line antiretroviral ther-apy failure among HIV-positive adult clients at Woldia Hospital, Northeast Ethiopia. PLoS one. 2017;12(11).

40. Yirdaw KD, Hattingh S. Prevalence and predictors of immunological failure among HIV patients on HAART in southern Ethiopia. PLoS one. 2015;10(5).

41. Waruru A, Mustai H, Ng’ang’a L, Ackers M, Kim A, Miruka F, Erck O, Okoni J, Ayuuya T, Schwarz S. Positive Predictive Value of the WHO Clinical and Immuno- logical Criteria to Predict Viral Load Failure among Adults on First, or Sec- ond-Line Antiretroviral Therapy in Kenya. PLoS one. 2016;11(7).

42. Vanobbergen FM, Kilama B, Wringe A, Madamani A, Zaba B, Mmbando D, Todd J. Immunological failure of first-line and switch to second-line antiretrovi-ral therapy among HIV-infected persons in Tanzania: analysis of routinely col-lected national data. Trop Med Int Health. 2015;20(7):830–832.

43. Solomon SS, Hawcroft DM, Narasimhan P, Subbaraman R, Srikrishnan AK, Cc-celia AJ, Suresh Kumar M, Solomon S, Gallant JE, Celentano DD. Comorbidities among HIV-infected injection drug users in Chennai, India. Indian J Med Res. 2008;127(5):447–452.

44. Brennan AT, Maskew M, Sanne I, Fox MP. The interplay between CD4 cell count, viral load suppression and duration of antiretroviral therapy on mortality in a resource-limited setting. Trop Med Int Health. 2013;18(5):619–631.

45. Teshome W, Tefera A. Detection of immunological treatment failure among HIV infected patients in Ethiopia: a retrospective cohort study. BMC immunology. 2015;16:55.

46. Lenjisa GO, Endale BS, Bacha YD. Clinical and immunological failure among HIV-positive adults taking first-line antiretroviral therapy in Dire Dawa, eastern Ethiopia. BMC public health. 2019;19(1):771.

47. Gesesse HA, Ward P, Woldemichael K, Mwanri L. Immunological failure in HIV-infected adults from 2003 to 2015 in Southwest Ethiopia: a retrospective cohort study. BMJ open. 2018;8(8).

48. Ayele C, Tesemma A, Amsalu A, Ferede G, Yismaw G. Prevalence and associ- ated factors of treatment failure among HIV/AIDS patients on HAART attend- ing University of Gondar Referral Hospital Northwest Ethiopia. BMC immunol- ogy. 2018;19(1):37.

49. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. British Medical Journal. 2003;327(7441):557–560.

50. Kelley GA, Kelley KS. Statistical models for meta-analysis: A brief tutorial. World Journal of Methodology. 2012;2(4):27–32.

51. Harries AD, Zachariah R, van Oosterhout JJ, Reid SD, Hosseinipour MC, Arndt V, Chiuwa Z, Jahn A, Schouten EJ, Kamoto K. Diagnosis and management of antiretroviral-therapy failure in resource-limited settings in sub-Saharan Africa: challenges and perspectives. The Lancet Infectious Diseases. 2010;10(1):60–65.

52. Akilawasan C, Lurie MN, Flanagan TP, Mayer KH. Lessons Learned from Use of Highly Active Antiretroviral Therapy in Africa. Clinical Infectious Diseases. 2005;41(3):376–385.

53. Wang H, Tesfaye R, Ramana GN, Chekagn CT. Ethiopia Health Extension Pro- gram.I.2.

54. Mwa CI, Mburu G, Torpey K, Frost P, Ford N, Seeley J. Role and outcomes of community health workers in HIV care in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2013;16(1).

55. Assefa Y, Jereme D, Luigseg O, Ooms C, Damme WV. Rapid Scale-Up of Antiretroviral Treatment in Ethiopia: Successes and System-Wide Effects. PLOS Medicine. 2009;6(4).

56. Ambia J, Benju J, Wringe A, Todd J, Geubbels E, Nakinying-Miro J, Urasa M, Lutalo T, Crampin AC, Kwaro D. From policy to practice: exploring the imple-mentation of antiretroviral therapy access and retention policies between 2013 and 2016 in six sub-Saharan African countries. BMC health services research. 2017;17(1):758.

57. Nakamanya S, Mayanja BN, Muhumuza R, Bukenya D, Seeley J. Are treat- ment supporters relevant in long-term Antiretroviral Therapy (ART) adherence? Experiences from a long-term ART cohort in Uganda. Global public health. 2019;14(3):469–480.

58. Levison JL, Orell C, Losina E, Lu Z, Freedberg KA, Wood R. Early outcomes and the virological effect of delayed treatment switching to second-line ther-apy in an antiretroviral treatment-outcome programme in South Africa. Antivir Ther (Lond). 2011;16(6):853–861.

59. Scanlon ML, Veenman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV/AIDS (Auckland, NZ). 2013:5:1.

60. Assefa Y, Gilks CF, Lynen L, Williams O, Hill PS, Tolver A, Malva A, Van Damme W. Performance of the Antiretroviral Treatment Program in Ethiopia, 2005–2015: strengths and weaknesses toward ending AIDS. Int J Infect Dis. 2017;60:70–76.

61. Hermann K, Van Damme W, Pariyo GW, Schouten E, Assefa Y, Cirea A, Mas- savon W. Community health workers for ART in sub-Saharan Africa: learning from experience – capitalizing on new opportunities. Hum Resour Health. 2009;7:31.

62. Ejjugu Y, Tadesse B. HIV testing during pregnancy for prevention of mother- to-child transmission of HIV in Ethiopia. PLoS one. 2018;13(8).

63. Celletti F, Wright A, Palen J, Freyhoof S, Markus A, Greenberg A, de Aquar RAT, Campos F, Buch E, Samb B. Can the deployment of community health workers for the delivery of HIV services represent an effective and sustainable re- sponse to health workforce shortages? Results of a multicountry study. AIDS. 2010;24:545.