Factors associated with antiretroviral treatment failure among people living with HIV on antiretroviral therapy in resource-poor settings: a systematic review and metaanalysis

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Abstract

Background: Despite the increase in the number of people accessing antiretroviral therapy (ART), there is limited data regarding treatment failure and its related factors among HIV-positive individuals enrolled in HIV care in resource-poor settings. This review aimed to identify factors associated with antiretroviral treatment failure among individuals living with HIV on ART in resource-poor settings.

Methods: We conducted a comprehensive search on MEDLINE (PubMed), Excerpta Medica Database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization’s (WHO’s) library database, and Latin American and Caribbean Health Sciences Literature (LILACS). We included observational studies (cohort, case-control, and cross-sectional studies) where adolescents and adults living with HIV were on antiretroviral treatment regardless of the ART regimen. The primary outcomes of interest were immunological, virological, and clinical failure. Some of the secondary outcomes were mm³ opportunistic infections, WHO clinical stage, and socio-demographic factors. We screened titles, abstracts, and the full texts of relevant articles in duplicate. Disagreements were resolved by consensus. We analyzed the data by doing a meta-analysis to pool the results for each outcome of interest.

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Background

Human immunodeficiency virus (HIV) infections are a major global public health concern. In 2019, an estimated 38 million people were living with HIV infection (PLWH) [1]. With new infections, an estimated 1.7 million people became newly infected with HIV in 2019. Sub-Saharan Africa (SSA) remains the most affected region in the world, with about 20.7 million prevalent cases and 730,000 new infections were recorded in 2019, seconded by Asia and the Pacific region with 5.8 million prevalent cases [1]. Although Southern Africa is home to less than 1% of the global population, the region has more than a fourth of all HIV infection in the world, with 300,000 acquired immune deficiency syndrome (AIDS)-related deaths registered in the same year in SSA [1].

Although anti-retroviral therapy (ART) coverage in this region has rapidly increased over the past decade [2]. The greatest gains in access to ART occurred in SSA [3]. In 2019, only 15 million (73%) PLWH in the region were accessing ART, while 3.5 million (60%) in Asia and the Pacific region [1]. Increasing the use of ART has contributed to a prominent decline in HIV-associated morbidity and death/mortality in SSA [2]. United Nations program on HIV/AIDS (UNAIDS) has suggested universal targets for the year 2020 (90-90-90), which means diagnosing 90% of all PLWH who should know their status (PLHIV), initiating antiretroviral treatment (ART) for 90% of those diagnosed with HIV infection, and attaining an undetectable viral load in 90% of those on ART [4]. Significant progress has been made in achieving that goal. Globally, PLWH accessing ART has increased from 21.7 million in 2015 to 25.4 million in 2019, an increase from 45 to 67% of all PLWH [3, 5].

Antiretroviral treatment failure

Patients with ART failure are increasingly encountered in resource-limited settings, while recent estimates suggest only 2% of those currently on ART are on second-line [6], a far greater number is likely to be failing virologically but have not switched to an alternative regimen. Furthermore, an increase in the coverage of ART use among PLHIV, which has resulted in an increase in the number of individuals failing first-line ART, and therefore, the magnitude increases with prolonged use of ART. The WHO predicted earlier on that 500,000 and 800,000 PLWH on the first-line combination of ART will require a switch to the second-line therapy by 2010 [2]. However, the burden of treatment failure is not well-documented, while there is a large scale of ARV in resource-limited countries. Meta-analysis data showed that the rate of the treatment failure for the first-line was 6.08% globally; however, the study noted a substantial heterogeneity across regions with 7.10% in Africa and 2.55% in Asia [3].

A retrospective cohort study done in South Africa found that among patients on non-nucleotide reverse transcriptase inhibitor (NNRTI)-based ART, after a median of 15 months on ART treatment, 19% had failed virologically and immunologically [6]. Studies in East Africa have shown a high prevalence of immunologic failure ranging from 8 to 57% among clients on the first-line ART [7–9].

Treatment failure is typically measured in three ways in poor-resource settings: (i) clinically, as evidenced by disease progression; (ii) immunologically, as evidenced by trends in CD4 counts over time; and (iii) virologically, as evidenced by measurement of HIV RNA levels. In 2013, WHO recommended viral load testing as the preferred monitoring approach to diagnose and to confirm ARV treatment failure [10].

Factors associated with treatment failure

Earlier studies have emphasized a number of factors that may be associated with virological suppression in ART; these are reasons for testing: routine testing, suspected treatment failure, and repeat testers after suspected failure [9–11]. While a significant number of studies have found that treatment failure is significantly associated with young
age, unsatisfactory adherence, low hemoglobin, history of lost to follow-up, being male and educational status, and treatment regimen [12–14], some studies have recognized low baseline CD4 cell count, rate of CD4 decline, prior exposure to ART and treatment interruptions, and non-adherence as determinants of treatment failure [15, 16]. In 2016, WHO most recent guideline defined a clinical failure as a new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment. Immunological failure is defined as CD4 count at or below 250 cells/mm$^3$ following a clinical failure or persistent CD4 levels below 100 cells/mm$^3$, and virological failure is defined as viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test [17]. The results from a previous study have confirmed that low baseline CD4 cell count, particularly < 100 cells/mm$^3$, and history of loss to follow-up are risk factors for immunological discordance [18]. Independent risk factors associated with virological failure were being followed-up at the semirural center, having experienced unstructured treatment interruptions, and having low CD4 counts at enrolment [19].

Gender, time on ART, baseline CD4 T cell count, WHO stage, ART regimen, adherence, and TB co-infection were associated with viral suppression [20]. The history of the antiretroviral use before starting ART, change of antiretroviral therapy due to toxicity, opportunistic infections while on ART treatment, level of CD4 + lymphocytes below 100 cells/ml at start of ART, adherence, and clinical stage were independently associated with virological failure [21]. Age younger than 40 years was also associated with virologic failure [22]. The relative contribution of the main predictors to virological failure may differ across settings and population groups and context. Thus, specific data are critical to the carrying out of corrective measures.

**Importance of the review**

Viral load testing provides early and accurate indications of the treatment failure and the need to switch from the first-line to second-line drugs, thereby reducing the accumulation of the drug-resistant mutations and improving clinical outcomes [23].

However, regular access to routine viral load testing remains a challenge due to the high cost. In such a situation, clinical and immunological monitoring is used for detecting treatment failure [24–27]. The number of people accessing ART has significantly increased in many poor resource settings [28]. Hence, it is significant to sustain treatment success and limit the development of treatment failure. For the timely detection of treatment failure, WHO reconfirmed the use of viral load testing as the gold standard test to monitor patients’ response to ART [29]. Where the viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure. In spite of a large number of patients receiving ARTs in low- and middle-income countries (LMICs) and poor settings, there are few reports on ART outcomes in these settings. Identifying baseline predictors of the first-line ART outcome among PLWH on ART in LMICs where access to viral load testing is limited is of paramount importance.

The technique and accuracy of identifying treatment failure in poor settings are important but challenging. Delayed detection of ART failure may increase drug toxicity and may result in increased morbidity and mortality. Early detection of treatment failure is crucial to ensure the effectiveness of the first-line therapy [6].

The main objective of this review was to identify factors associated with antiretroviral treatment failure among PLWH on ART in resource-poor settings.

**Objective**

**Primary objective**

The primary objective of the study was to determine the clinical, immunological, and virological factors associated with antiretroviral treatment failure among PLWH in resource-poor settings.

**Secondary objective**

The secondary objective of the study is to identify the socio-demographic and economic factors associated with antiretroviral treatment failure among PLWH in resource-poor settings.

**Methods**

The methods of this systematic review and meta-analysis were reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist [30]. We registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number: CRD42019136538.

**Criteria for considering studies for review**

**Types of studies**

We included all types of observational studies including prospective/retrospective or ambi-directional cohort studies, case-control studies, population-based/nested or hospital-based case-control studies, and cross-sectional studies. Interventional studies were excluded from this review.

**Types of participants**

Adolescents and adults living with HIV who were on ART for $\geq$ 6 months, regardless of the regimen. Only participants with documented baseline CD4 and VL were considered for this systematic review.
Type of outcome
Primary outcome
Treatment failure was defined as follows:

Virological failure
Virological failure is defined as a plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support. A viral load test is a measurement of the amount of HIV in a sample of the blood. This is usually reported as the number of copies per milliliter (copies/mm³) [17].

Immunological failure
Immunological failure is defined as a fall in CD4 count to the baseline (or below) or persistent CD4 levels below 100 cells/mm³. The CD4 lymphocyte count is an excellent indicator of how healthy the immune system is. These are a type of white blood cells, called T cells, which move throughout the human body to find and destroy bacteria, viruses, and other invading germs. The CD4 cell count is indicated in cells per mm³, and it is measured by taking a blood sample [17].

Clinical failure
Clinical failure is defined as the occurrence of new opportunistic infections (excluding immune reconstitution inflammatory syndrome [IRIS]) and/or other clinical evidence of HIV disease progression during therapy. AIDS-defining illnesses (opportunistic infections) are those which the Centers for Disease Control and Prevention (CDC) have classified as being directly associated with advanced HIV infection. We considered the common diseases, which are pneumonia, TB, lymphoma, and cryptococcosis [17].

Secondary outcome
Secondary outcomes for this study are all the predictors’ variables that contribute to treatment failure. The following information was collected if measured at baseline: CD4 cells (cells/mm³), viral load (copies/ml), WHO clinical, tuberculosis, opportunistic infection, treatment regimen (NRTI or NNRTI), BMI, weight, study site (rural versus urban), gender, age, educational status, employment status, marital status, and spouse HIV sero-status.

Inclusion and exclusion criteria
Included studies
Participants in the study were (1) those who had been on ART for ≥ 6 months and (2) those who had documented CD4 cell count and viral load measurement at baseline and 6 months.

Excluded studies
All studies with participants who had pregnancy history the past 6 months while on treatment and at 6 months’ visit or had missing values of CD4 cell count and viral load at baseline and 6 months’ visit were excluded.

Search methods for identification of the studies
We conducted a comprehensive search on 5 databases from December 1, 2000, to November 2019. With assistance from an information specialist, we searched in the following databases: MEDLINE (Pubmed), EMBASE (OVID), LILACS (BIREME), Science Citation Index Expanded (SCI-EXPANDED, Web of Science), Social Sciences citation index (SSCI, Web of Science), Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH, Web of Science), and Cinahl (EBSCOHost). A detailed search strategy is provided in Appendix 1. A hand search of citations from selected studies was conducted to identify additional studies missing from the original electronic searches.

Screening and assessments of study eligibility
All potential studies were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), and two review authors (YL and SJ) independently screened the titles and abstracts. Both authors also assessed full-text eligibility. All published full-text articles, abstracts, and brief reports were included, and provided/available complete data were elicited from them. The disagreements between the two authors who assessed study eligibility were resolved by discussion and consensus.

Data extraction, management, and analysis
Data from the full-text articles were extracted by two independent review authors (YL, SJ) using a standardized pre-piloted data extraction form. A third reviewer (MK, PN) checked whether the extracted data were correct. Extracted data were categorized into four main headings: general information, socio-demographic and economic characteristics of participants, and clinical and immunological information of the participant. In case of missing information, we clarified the conducted study or the studies that had relevant data, which were not reported in the published manuscript, and we contacted the authors for additional information.

Risk of bias and quality of evidence
Two authors independently assessed the risk of bias in each study by examining the study population, study attrition, prognostic factor measurement, outcomes measurement, study confounding, and statistical reporting (YL and OA). They coded studies as at high, medium, low, or unclear risk of bias for each of these features.
using the Quality in Prognosis Studies tool (QUIPS tool) [31]. Finally, we assessed the quality of the evidence using the Grading of Recommendations Assessment Development and Evaluations (GRADE) approach using the five criteria of the GRADE system.

**Statistical analysis**
For the studies that were relatively homogeneous in terms of methodology and outcomes, a meta-analysis of the data was performed. Sufficiently, similar data was pooled using the inverse variance approach to accommodate crude and adjusted odds ratios, where possible. Additionally, the meta-analysis was summarized using pooled estimates, the 95% confidence interval, and the between-study variance was estimated using Tau². We extracted all unadjusted and adjusted measures of the association from all included studies and converted effect sizes as necessary to possible selection bias, thus allowing us to use the data from as many studies as possible. We anticipated that results from multivariate analyses would have been reported as odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), if so, we would use ORs as the common measure of the association, using RRs and HRs to estimates ORs at a particular time point [32]. Furthermore, measures of effect were analyzed using RevMan statistical software for systematic reviews. Statistical heterogeneity was quantified using the I² statistic [33]. If the I² statistic is high (75 to 100%—as suggested by Higgins et al.) indicating high heterogeneity [33], a random effect model was used.

**Results**
**PRISMA flow chart**
We retrieved 2418 articles regarding treatment failure among ART users in poor resource setting as identified in MEDLINE (PubMed); EMBASE (OVID); LILACS (BIREME); Science Citation Index Expanded (SCI-EXPANDED, Web of Science), Social Sciences citation index (SSCI, Web of Science), and Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH, Web of Science), and CINAHL (EBSCOHost). These are shown in Fig. 1.

Of these initial articles, 3 articles were duplicates; 2158 articles were excluded after reviewing their titles and abstracts and confirmed irrelevant to this review. Thus, 237 potential full-text articles were assessed for eligibility, which resulted in further exclusion of 100 articles.
57 had wrong outcomes, 19 assessed HIV drug-resistant mutations, 12 had the wrong study design, 7 had a wrong patient population, 2 were not in English 1 and was a duplicate, 1 had a wrong setting, and 1 was pediatric population. Finally, 137 studies met the eligibility criteria. These are shown in Table 1.

**Meta-analysis**
The association between adherence and treatment failure was based on six cross-sectional studies [14, 35, 37, 40, 42, 47]. The results as presented in Fig. 2 showed a strong relationship between treatment failure and poor treatment adherence. The odds of treatment failure were nearly 6 times higher among patients who had poor adherence (OR = 5.90, 95% CI 3.50, 9.94, moderate strength of evidence). The test statistics, however, showed a substantial heterogeneity ($I^2 = 65\%$ and $p = 0.02$).

Similarly, the association between poor adherence and treatment failure was examined using four cohort studies [36, 39, 41, 46]. The results as presented in Fig. 3 showed that the hazard ratio of treatment failure was nearly 2.5 higher among patients who had poor adherence (HR =

| References  | Year of publication | Study design | Country | Patients groups | ART used | Sample size | Number of Treatment failure |
|-------------|----------------------|--------------|---------|----------------|----------|-------------|-----------------------------|
| Babo et al. [34] | 2017 | Case-control study | Ethiopia | Adult | Stavudine vs. Zidovudine Nevirapine vs. Efavirenz | 307 | 230 |
| Bayu et al. [35] | 2017 | Case-control study | Ethiopia | Adults aged ≥ 15 years | D4T-based AZT-based TDF-based | 306 | 160 |
| Bilcha et al. [36] | 2019 | Retrospective cohort study | Ethiopia | Adult | Nevirapine-based Efavirenz-based | 396 | 47 |
| Bisson et al. [37] | 2008 | Case-control study | Botswana | Adults older than 18 years | NR | 302 | 247 |
| Fatti et al. [38] | 2019 | Prospective cohort study | South Africa | Adults aged ≥ 18 years | NRTI and NNRTI | 1901 | 60 |
| Ford et al. [39] | 2010 | Observational cohort | South Africa | Adult | EFV, NVP, and other | 207 | 32 |
| Gunda et al. [40] | 2019 | Case-control study | Tanzania | Adult | AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/NVP, TDF/3TC/EFV | 197 | 24 |
| Haile et al. [41] | 2016 | Retrospective cohort study | Ethiopia | Adult (≥ 15 years old) | 1a(d4T + 3TC + NVP), 1b(d4T + 3TC + EFV), 1c(AZT + 3TC + NVP), 1d(AZT + 3TC + EFV), 1e(TDF + 3TC + EFV), 1f(TDF + 3TC + NVP) | 4809 | 113 |
| Hailu et al. [42] | 2018 | Retrospective follow-up study | Ethiopia | Adults (≥ 20 years) | TDF 3TC/EFV/NVP, AZT 3TC NVP/EFV, D4T 3TC NVP/EFV, ABC 3TC EFV | 260 | 30 |
| Hassan et al. [14] | 2014 | Cross-sectional study | Kenya | Adult | Zidovudine-based and Stavudine-based | 232 | 57 |
| Izudi et al. [43] | 2016 | Retrospective cohort | Uganda | Adult | | 383 | 28 |
| Karade et al. [44] | 2016 | Cross-sectional studies | India | Adult | AZT + 3TC + NVP, AZT + 3TC + EFV, TDF + 3TC + NVP, TDF + 3TC + EFV, d4T + 3TC + NVP/EFV | 844 | 104 |
| Lay et al. [45] | 2017 | Retrospective cohort study | Cambodia | Adult (≥ 18 years old) | d4T/3TC/EFV, d4T/3TC/NVP, AZT/3TC/EFV, AZT/3TC/NVP Other | 3581 | 137 |
| Ndahimana et al. [46] | 2016 | Retrospective cohort | Rwanda | 15 years and older | NRTIs, NNRTIs, and PIs | 828 | 70 |
| Ahmed et al. [47] | 2019 | Case-control study | Ethiopia | Adult | d4T + 3TC + NVP, AZT + 3TC + NVP, AZT + 3TC + EFV, TDF + 3TC + EFV | 308 | 199 |
2.46, 95% CI 1.72, 3.51, high strength of evidence). The result of test statistics showed no heterogeneity ($I^2 = 0\%$ and $p = 0.90$). Here too, a random effect meta-analysis model was used to determine the association with the outcome.

Furthermore, the association between CD4 and treatment failure was examined by using three cross-sectional studies [35, 40, 47]. The results as presented in Fig. 4 showed that treatment failure was strongly associated with CD4 count. The odds of treatment failure were nearly 5 times higher among patients who had a CD4 cell count of 200 cells/mm$^3$ (OR = 4.82, 95% CI 2.44, 9.52, low strength of evidence). However, the test statistics showed substantial heterogeneity ($I^2 = 71\%$ and $p = 0.03$). Hence, a random effect meta-analysis model was used to determine the association with the outcome.

Likewise, the association between low CD4 count and treatment failure was also observed using four cohort studies [36, 38, 45, 46]. Results presented in Fig. 5 showed that the hazard ratio of treatment failure was nearly 3 times higher among patients who had CD4 lower than 200 cells/mm$^3$ (HR = 2.98, 95% CI 2.23, 4.00, moderate strength of evidence). The result of the test statistics showed no evidence of heterogeneity ($I^2 = 0\%$ and $p = 0.55$). A random effect meta-analysis model was used to determine the association with the outcome.

Our study also demonstrated similar findings to the above through data abstracted from two cross-sectional studies [34, 44]. We also found that treatment failure was significantly associated with low CD4 count, where the odds of treatment failure were 1.14 times higher among patients with CD4 lower than 100 cells/mm$^3$ (OR = 1.14, 95% CI 0.52, 2.47, low strength of evidence). The test statistics showed moderate heterogeneity ($I^2 = 49\%$ and $p = 0.75$), see Fig. 6. Consequently, a random effect meta-analysis model was computed to determine the association.

**Risk of bias assessment**

Most of the studies had a low risk of bias on prognostic factors that accounted for 125/137, followed by study participants (123/135), statistical analysis and reporting (116/137), and outcome measurement (115/137). Moreover, 109/137 studies had a low risk of bias on study confounding and 103/137 studies had a low risk of bias on study participant attrition. The full table of results is shown in Appendix 3: risk of bias assessment.

**Discussion**

This review was aimed at identifying factors associated with antiretroviral treatment failure among individuals living with HIV and showed that low CD4 T cell count ($\leq 200$ cells/mm$^3$) and poor adherence to ART were significantly associated with virological failure.

In this review, the odds of virological failure were higher among those who had a CD4 cell count of $\leq$
200 cells/mm$^3$ in both case-control and cohort studies. The finding is supported by the studies conducted in SSA [35, 43], while a retrospective analysis of a large ART program in Cambodia showed that previous ART experience, nevirapine-based regimen, and CD4 count $\leq$ 200 cells/mm$^3$ were independently associated with an increased risk of treatment [48]. Similar findings were reported in a meta-analysis data from India, where CD4 count $\leq$ 200 had a significantly greater risk of treatment failure [49]. As CD4 cell count increases, viral replication decreases, which means it has an inverse relationship with viral load. As patients’ immune status drops, and the rate of viral load increases compared to the immuno-competent individuals with HIV infection. In addition, users with compromised immunity are more susceptible to different opportunistic infections that endure the cruel cycle of immunity depletion and viral replication [50].

Moreover, the results found from case-control studies shown that the odds of virological failure were 6 times more among those who had poor adherence compared with those who had good adherence to antiretroviral treatment. Likewise, the finding from cohort studies showed that the odds of virological failure were higher among those who had poor adherence compared with those who had good adherence to antiretroviral treatment. This finding is supported by findings from primary studies conducted in African countries [11, 51, 52], but also consistent with the finding from a study conducted in Vietnam and other developed countries [53–55]. It is obvious that poor adherence to medication compromises treatment response due to suboptimal drug concentration hence creates a conducive environment for viral replication leading to virological failure [56, 57]. This reaffirms the need for reinforcement of drug adherence counseling for HIV patients before and during their life course of taking ART.

Poor adherence may lead to a number of adverse consequences on both individual and public HIV healthcare levels. Therefore, the measured efforts are immediately needed in HIV care by responsive bodies like ART case managers, adherence counselors in the hospitals on patients with low current CD4 count through improving poor adherence to ART treatment by strengthening enhanced adherence counseling. Each low-income country national HIV program should give attention to improving HIV services to strengthen adherence among patients on ART in order to reduce the proportion of patients who are failing the treatment.

Our systematic review has some strengths. We planned the review a priori with clearly defined selection criteria. We conducted a comprehensive and exhaustive search, using many additional sources to identify relevant studies, including reference searches of other HIV/AIDS conferences (IAS and CROI) for the past 20 years.

Our systematic review has some strengths. We planned the review a priori with clearly defined selection criteria. We conducted a comprehensive and exhaustive search, using many additional sources to identify relevant studies, including reference searches of other HIV/AIDS conferences (IAS and CROI) for the past 20 years.

This review had several limitations mainly related to the quality of the evidence available. To our knowledge, we suspect publication or reporting biases, or both, suggesting that our results may be overestimated. Positive study bias is likely to be problematic in this review. Our
literature search for relevant and potential studies included focused searches, i.e., including search terms related to the “less CD4 count,” “viral load” in our electronic search. Studies that report a relationship between the prognostic factors and common outcomes are therefore more likely to have been identified in these searches due to reporting of positive results in the study abstract.

In addition, we also observed that some studies reported positive unadjusted association of factors with outcomes of interest, but did not report the association adjusted for other important covariates. This may contribute to a likely overestimation of the adjusted results. Therefore, future research is required to investigate the impact and potential strategies to alleviate reporting and publication bias, as well as initiatives to require registration of protocols and publication of prognostic studies.

Furthermore, our review was the pooling of the adjusted results despite studies did not include identical sets of covariates. Studies included in this review were homogenous; therefore, pooling of the adjusted results was feasible. However, comparison and interpretation may be challenging in this case. Our review only focused on studies conducted in poor resource settings limiting its generalizability to high-income settings.

**Strength of evidence**

The strength of evidence contributing to several outcomes in this review was graded as low, moderate, or high. We used the GRADE approach to assess the strength of evidence as shown in the summary of the finding table, Appendix 4. The certainty of evidence was downgraded in most instances due to a high risk of bias as well as inconsistency.

**Conclusion**

ART failure among individuals living with HIV is a public health concern; the timing and accuracy of identifying treatment failure in resource-limited settings are fundamental but challenging. The findings of this review highlighted that low CD4 counts and poor adherence to ART were associated to ART treatment failure. There is an urgent need that health professionals and HIV programs should focus on novel approaches for patients who have these characteristics in order to prevent ART failure. Further review is required to be done in multiple ART centers and a broader community as well as the different factors associated with treatment failure to decide whether there are discrepancies in virological and immunological responses to antiretroviral therapy at different stages of HIV infection.

**Appendix 1**

**Search strategy—database**

#1 Search ((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immunodeficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immune deficiency syndromes OR acquired immune deficiency syndrome OR HIV/AIDS))

#2 Search (((HIV infections [MeSH] OR HIV [MeSH])

#3 Search (#1 OR #2)

#4 Search ((Antiretroviral* OR ((anti) AND (retro-viral*)) OR ARV* OR ART OR “antiretroviral therapy” OR HAART OR ((highly) AND (active) AND (anti-retroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR ((anti) AND (acquired immun*) AND (deficienc*)))))

#5 Search ((antiretroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh])))

#6 Search (#4 OR #5)

#7 search #3 AND #6

#8 Search (virological failure OR Immunological failure OR less CD4 count OR viral load)

#9 Search (low-income setting OR disadvantaged communities OR resource limited setting OR Sub-Saharan Africa)

#10 Search (#7 AND #8 AND #9)
### Appendix 3

#### Risk of bias assessment

**Table 2** Risk of bias assessment

| #  | Study ID | Study participant | Attrition | Prognostic Factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|----|----------|-------------------|-----------|-------------------------------|---------------------|------------------|----------------------------------|
| 1  | Abah 2018| Low               | High      | Low                           | Low                 | Low              | Low                              |
| 2  | Ahmed 2019| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 3  | Ahn 2019 | Low               | High      | Low                           | Low                 | Low              | Low                              |
| 4  | Ahoua 2009| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 5  | Assefa 2014| Low              | High      | Low                           | Low                 | Low              | Low                              |
| 6  | Ayalew 2016| Low              | Low       | Low                           | Low                 | Low              | Low                              |
| 7  | Ayele 2018| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 8  | Babo 2017| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 9  | Bayou 2015| Low               | High      | Low                           | Low                 | Low              | Low                              |
| 10 | Bayu 2017 | Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 11 | Billoux 2015| Low              | Low       | High                          | High                | Low              | Low                              |
| 12 | Biscione 2014| Low             | Low       | High                          | High                | Low              | Low                              |
| 13 | Bisson 2008| Low               | Low       | High                          | Low                 | Low              | Low                              |
| 14 | Boender 2016a| Low             | Low       | Low                           | Low                 | Low              | Low                              |
| 15 | Boender 2016b| Low             | Low       | Low                           | Low                 | Low              | Low                              |
| 16 | Boettiger 2016c| Low           | Low       | Low                           | Low                 | Low              | Low                              |
| 17 | Boettiger 2015| Low             | Low       | Low                           | Low                 | Low              | Low                              |
| 18 | Boettiger 2016d| Low            | Low       | Low                           | Low                 | Low              | Low                              |
| 19 | Boettiger 2014| Low             | Low       | Low                           | Low                 | Low              | Low                              |
| 20 | Boulle 2015| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 21 | Braun 2017| Low               | Low       | Low                           | Low                 | Low              | High                             |
| 22 | Brooks 2016| Low               | Low       | Low                           | Low                 | Low              | High                             |
| 23 | Bulage 2017| Low               | High      | Low                           | Low                 | Low              | Low                              |
| 24 | Byabene 2017| Low              | Low       | Low                           | Low                 | Low              | Low                              |
| 25 | Cao 2018  | Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 26 | Carriquiry 201| Low             | Low       | Low                           | Low                 | Low              | Low                              |
| 27 | Caseiro 2018| Low              | Low       | Low                           | Low                 | High             | Low                              |
| 28 | Castelnuovo 2016| Low          | Low       | Low                           | Low                 | Low              | Low                              |
| 29 | Cesar 2015| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 30 | Cesar 2014| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 31 | Chaiwarith 2011| Low            | Low       | Low                           | Low                 | Low              | Low                              |
| 32 | Chaiwarith 2007| Low            | Low       | High                          | Low                 | Unclear          | Low                              |
| 33 | Chakravarty 2015| Low           | Low       | Low                           | Low                 | Unclear          | Low                              |
| 34 | Charles 2013| Low               | Unclear   | Low                           | Low                 | Unclear          | Low                              |
| 35 | Chawana 2014| Low               | Low       | Low                           | Low                 | Unclear          | Low                              |
| 36 | Chen 2014 | Low               | High      | Low                           | Low                 | High             | Low                              |
| 37 | Chhim 2018 | Low               | High      | Low                           | Low                 | Low              | Low                              |
| 38 | Chkhartishvili 2014| Low       | Low       | Low                           | Low                 | Unclear          | Low                              |
| 39 | Collier 2017| Low               | Low       | Low                           | Low                 | Low              | Low                              |
| 40 | Costiniuk 2014| High            | Unclear   | Low                           | Low                 | High             | Low                              |
| #  | Study ID         | Study participant | Attrition | Prognostic factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|----|------------------|-------------------|-----------|-------------------------------|---------------------|-------------------|----------------------------------|
| 41 | Court 2014       | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 42 | Datay 2010       | Low               | Low       | Low                           | Low                 | Unclear           | Low                              |
| 43 | DeBoni 2018      | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 44 | deLaHoz 2014     | Low               | Low       | Unclear                       | Unclear            | Unclear           | Low                              |
| 45 | Dolling 2017     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 46 | Dray-Spira 2007  | Low               | Low       | Low                           | Low                 | Unclear           | Low                              |
| 47 | Ekstrand 2011    | Low               | Low       | High                          | Unclear            | Unclear           | High                             |
| 48 | Rusine 2013      | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 49 | Sadashiv 2017    | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 50 | Safren 2014      | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 51 | Saracino 2014    | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 52 | Singini 2016     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 53 | Sithole 2018     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 54 | Sovershaeva 2019| Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 55 | Syed 2016        | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 56 | Telele 2018      | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 57 | Teshome 2014     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 58 | Thiha 2016       | High              | Low       | Low                           | Low                 | Low               | Low                              |
| 59 | Tran 2014        | Low               | High      | Low                           | Low                 | Low               | Low                              |
| 60 | Tsegaye 2016     | Low               | High      | Low                           | Low                 | Low               | Low                              |
| 61 | vandenBerg 2005  | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 62 | Vanobberghen 2015| Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 63 | Wang 2011        | High              | High      | Low                           | Low                 | Low               | Low                              |
| 64 | Yimer 2015       | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 65 | Yirdaw 2015      | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 66 | Zhao 2017        | Low               | High      | Low                           | Low                 | Low               | Low                              |
| 67 | Zoufaly 2015     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 68 | Elema 2009       | Low               | Low       | Unclear                       | Low                 | Unclear           | Low                              |
| 69 | Enderis 2009     | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 70 | Eshleman 2017    | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 71 | Evans 2018       | Low               | High      | Low                           | Low                 | Low               | Low                              |
| 72 | Evans 2013       | Low               | High      | Low                           | Low                 | Low               | Low                              |
| 73 | Fatti 2019       | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 74 | Fatti 2014       | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 75 | Ferradini 2007   | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 76 | Ferreyra 2012    | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 77 | Fibriani 2013    | Low               | Low       | Low                           | Unclear            | Unclear           | Low                              |
| 78 | Flynn 2017       | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 79 | Fogel 2017       | unclear           | Unclear   | Low                           | Low                 | Unclear           | Low                              |
| 80 | Ford 2010        | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 81 | Fox 2012         | Low               | Low       | Low                           | Low                 | Low               | Low                              |
| 82 | Fox 2010         | Low               | Low       | Low                           | Low                 | Low               | Low                              |
Table 2 Risk of bias assessment (Continued)

| #  | Study ID     | Study participant Attrition | Prognostic Factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|----|--------------|----------------------------|-------------------------------|---------------------|-------------------|-----------------------------------|
| 83 | Goldman 2008 | Low                        | Low                           | Low                 | Unclear           | Low                               |
| 84 | Gross 2017   | Low                        | Low                           | Low                 | Low               | Low                               |
| 85 | Gunda 2019   | Low                        | Low                           | Low                 | Low               | Low                               |
| 86 | Haggblom 2016 | Low                      | Low                           | Low                 | Low               | Low                               |
| 87 | Haile 2016   | Low High                   | Low                           | Low                 | High              | Low                               |
| 88 | Hailu 2018   | Low                        | Low                           | Low                 | Low               | Low                               |
| 89 | Hamers 2012  | Low                        | Low                           | Low                 | Low               | Low                               |
| 90 | Hare 2014    | Low                        | Low                           | Low                 | Low               | Low                               |
| 91 | Hassan 2014  | Low                        | Low                           | Low                 | Low               | Low                               |
| 92 | Hawkins 2015 | Low High                   | Low                           | Low                 | Low               | Low                               |
| 93 | Hawkins 2016 | Low Low                    | Low                           | Low                 | Low               | Low                               |
| 94 | Hermans 2018 | Low High                   | Unclear                       | Low                 | Unclear           | Low                               |
| 95 | Huang 2015   | Low High                   | Low                           | Low                 | Low               | Low                               |
| 96 | Hunt 2017    | Low Low                    | Low                           | Low                 | High              | Unclear                           |
| 97 | Huong 2011   | Low                        | Low                           | Low                 | Unclear           | Low                               |
| 98 | Inzaule 2018 | Low                        | Unclear                       | Low                 | Low               | Low                               |
| 99 | Izudi 2016   | Low Low                    | Unclear                       | Low                 | Low               | Low                               |
| 100| Jiamsakul 2016 | Low                  | High                          | Low                 | Low               | Low                               |
| 101| John 2016    | Low                        | Low                           | Low                 | Low               | Low                               |
| 102| Joram 2017   | Low High                   | Low                           | Low                 | Low               | Low                               |
| 103| Joseph Davey 2018 | Low          | Low                           | Low                 | Low               | Low                               |
| 104| Kamya 2007   | Low                        | Unclear                       | Low                 | Low               | Low                               |
| 105| Kan 2017     | Low Low                    | Low                           | High                | Low               | Low                               |
| 106| Karade 2016  | Low Low                    | Low                           | Low                 | High              | Low                               |
| 107| Kazooba 2018 | Low High                   | Low                           | Low                 | Low               | Low                               |
| 108| Khienprasit 2011 | Low      | Low                           | High                | Low               | High                              |
| 109| Kyaw 2017    | Low High                   | Low                           | High                | Low               | Low                               |
| 110| Lay 2017     | Low                        | Low                           | Low                 | High              | Low                               |
| 111| Leng 2014    | Low Low                    | High                          | High                | Low               | Low                               |
| 112| Lenjisa 2015 | Low                        | High                          | Low                 | Low               | High                              |
| 113| Levison 2011 | Low Low                    | Low                           | Low                 | High              | High                              |
| 114| Liegeois 2013 | Low         | Low                           | High                | Low               | High                              |
| 115| Maskini 2019 | High Low                   | Low                           | Low                 | High              | Low                               |
| 116| Meloni 2016  | Low                        | Low                           | High                | Low               | Low                               |
| 117| Mpawa 2017   | High High                  | Low                           | High                | Low               | High                              |
| 118| Mujugira 2016 | Low         | Low                           | Low                 | Low               | Low                               |
| 119| Mungwira 2018 | Low         | Low                           | High                | Low               | Low                               |
| 120| Musa 2015    | Low                        | Low                           | Low                 | Low               | Low                               |
| 121| Nachega 2008 | High Low                   | Low                           | Low                 | High              | Low                               |
| 122| Ndahimana 2016 | High      | Low                           | Low                 | Low               | High                              |
| 123| Negi 2018    | Low High                   | Low                           | Low                 | Low               | High                              |
| 124| Nsanzimana 2019 | High  | Low                           | Low                 | Low               | Low                               |
Appendix 2
Risk of bias criteria and justifications

| Assessment for risk of bias | Rating of risk of bias |
|-----------------------------|------------------------|
| First author Reviewer-------| High, moderate, low    |
| Biases                      |                        |
| Issues to consider for judging overall rating of “risk of bias” |                        |
| Study methods and comments  |                        |
| Assess the risk of each potential bias |                        |
| These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. |                        |
| 1) Study participation |                        |
| The study sample adequately represents the population of interest |                        |
| Risk of bias criteria and justifications (Continued) |                        |
| e. Adequate description of the period and place of recruitment |                        |
| f. Adequate description of inclusion and exclusion criteria |                        |
| 2) Study attrition | The study data available (i.e., participants not lost to follow-up) adequately represent the study sample |                        |
| a. Adequate response rate for study participants (> 80%) |                        |
| b. Description of attempts to collect information on participants who dropped out |                        |
| c. Reasons for loss to follow-up are provided |                        |
| d. Adequate description of participants lost to follow-up |                        |
| e. There are no important differences between participants who completed the study and who did not |                        |
| 3) Prognostic factor measurement | The PF is measured in a similar way for all participants |                        |
| a. A clear definition or description of the PF is provided |                        |
| b. Method of PF measurement is adequately valid and reliable (i.e., direct |                        |

| Study ID | Study participant | Attrition | Prognostic Factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|----------|-------------------|-----------|-------------------------------|---------------------|------------------|-------------------------------|
| 125      | Low               | High      | Low                           | Low                 | Low              | High                          |
| 126      | High              | High      | Low                           | Low                 | Low              | High                          |
| 127      | Low               | High      | Low                           | Low                 | Low              | Low                           |
| 128      | High              | Low       | Low                           | Low                 | Low              | Low                           |
| 129      | Low               | Low       | Low                           | High                | Low              | High                          |
| 130      | High              | Low       | Low                           | High                | Low              | High                          |
| 131      | Low               | Low       | Low                           | Low                 | Low              | Low                           |
| 132      | Low               | Low       | Low                           | High                | Low              | Low                           |
| 133      | High              | Low       | Low                           | Low                 | Low              | High                          |
| 134      | Low               | High      | Low                           | Low                 | Low              | Low                           |
| 135      | Low               | High      | Low                           | Low                 | Low              | Low                           |
| 136      | High              | Low       | Low                           | Low                 | Low              | Low                           |
| 137      | High              | Low       | Low                           | Low                 | Low              | Low                           |
Risk of bias criteria and justifications (Continued)

ascertainment; secure record, hospital record)
c. Continuous variables are reported or appropriate cut-points are used
d. The method and setting of measurement of PF is the same for all study participants
e. Adequate proportion of the study sample has complete data for the PF (> 80%)
f. Appropriate methods of imputation are used for missing PF data

4) Outcome measurement

The outcome of interest is measured in a similar way for all participants

a. A clear definition of the outcome of interest is provided (including the time of death)
b. Method of outcome measurement used is adequately valid and reliable (i.e. independent blind assessment, hospital record or record linkage)
c. The method and setting of outcome measurement is the same for all study participants

5) Study confounding

Important potential confounder is appropriately accounted for

a. Most important confounders are measured
b. Clear definitions of the important confounders measured are provided
c. Measurement of all important confounders is adequately valid and reliable
d. The method and setting of confounding measurement are the same for all study participants
e. Appropriate methods are used if imputation is used for missing confounder data
f. Important potential confounders are accounted for in the study design (by limiting the study to specific population groups, or by matching)
g. Important potential confounders are accounted for in the analysis (by

6) Statistical analysis and presentation

The statistical analysis is appropriate, and all primary outcomes are reported

a. Sufficient presentation of data to assess the adequacy of the analytic strategy
b. Strategy for model building is appropriate and is based on a conceptual framework or model
c. The selected statistical model is adequate for the design of the study
d. There is no selective reporting of results (based on the study protocol, if available, on the "Methods" section)

Summary

High bias: The measurement of the PF may be different for different levels of the outcome of interest

Low bias: The measurement of the PF is unlikely to be different for different levels of the outcome of interest

Moderate bias: The measurement of the PF is likely to be different for different levels of the outcome of interest

Lailulo et al. Systematic Reviews (2020) 9:292
### Appendix 4

**Strength of evidence**

**Table 3** Summary of findings of included studies using the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation)

| Factors assessed | Number of studies (SD) | Main findings | Strength of evidence (high, moderate, low, very low) |
|------------------|------------------------|---------------|--------------------------------------------------|
| Adherence (poor versus good) | 6 (cross-sectional) | Odds ratio: 5.90 (95%CI, 3.50–9.94) | Moderate |
| Adherence (poor versus good) | 4 (cohort studies) | Hazard ratio: 2.46 (95% CI, 1.72–3.51) | High |
| CD4 cell count (< 200 versus ≥ 200 cells/mm³) | 3 (cross-sectional) | Odd ratio: 4.82 (95% CI, 2.44–9.52) | Lowb |
| CD4 cell count (< 200 versus ≥ 200 cells/mm³) | 4 (cohort studies) | Hazard ratio: 2.98 (95% CI, 2.23–4.0) | Moderatec |
| CD4 cell count (< 100 versus ≥ 100 cells/mm³) | 2 (cross-sectional) | Odds ratio: 1.14 (95% CI, 0.52–2.47) | Lowd |

**SD study design**

*aDowngraded once to indirectness, the final sample of some of the included studies only represents the population of interest

*bImprecision and inconsistency were major concerns, imprecision due to a limited number of studies and wide confidence intervals, and there was a substantial heterogeneity statistical heterogeneity (heterogeneity: Tau² = 0.25; chi² = 6.25, df = 2 (P = 0.03), I² = 71%) and marked clinical heterogeneity

*cDowngraded once due to a risk of bias, bias to statistical analysis and reporting, and potential confounding factors

*dImprecision due to a limited number of participants and studies included. Inconsistency as there was a moderate statistical heterogeneity (heterogeneity: Tau² = 0.18; chi² = 1.95, df = 1 (P = 0.16); I² = 49%)

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

### Abbreviations

AIDS: Acquired immune deficiency syndrome; ART: Antiretroviral therapy; BMI: Body mass index; CDC: Centers for Disease Control and Prevention; CENTRAL: Cochrane Central Register of Controlled Trials; EMBASE: Excerpta Medica Database; HRs: Hazard ratios; HIV: Human immunodeficiency virus; IRIS: Immune reconstitution inflammatory syndrome; LMICs: Low- and middle-income countries; MEDLINE: Medical Literature Analysis and Retrieval System Online; NNRTI: Non-nucleotide reverse transcriptase inhibitors; NRTI: Nucleotide reverse transcriptase inhibitors; OR: Odds ratio; PLHIV: People living with human immunodeficiency virus; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PROSPERO: Prospective Register of Systematic Reviews; PubMed: Public/Publisher MEDLINE; RRs: Risk ratios; SSA: Sub-Saharan Africa; TB: Tuberculosis; UNAIDS: United Nations Programme on HIV; WHO: World Health Organization

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### Authors’ contributions

YL, MK, and PN contributed to the conceptualization of the project. YL, MK, SJ, OA, and PN designed the search strategy, study selection process, and drafting of the manuscript. YL, MK, SJ, OA, and PN contributed to critically reviewing the manuscript. PN is the guarantor. The authors gave the final approval of the manuscript for publication.

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### Ethics approval and consent to participate

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### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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