Evidence that poor HAART adherence has a great impact on HIV/AIDS treatment failure more than severity of illness and opportunity of infection in Ethiopia: Systematic review and meta-analysis

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ABSTRACT

Background: The pooled burden of HIV treatment failure and its associated factors in Ethiopian context is required to provide evidence towards renewed ambitious future goal.

Methods: PubMed, Web of Science, Scopus, Google Scholar, and Ethiopian Universities' (University of Gondar and Addis Ababa University) online repository library were used to get the research articles. I-squared statistics was used to see heterogeneity. Publication bias was checked by Egger's regression test. A meta-analysis using the DerSimonian-Laird random-effects model was employed to estimate the overall prevalence of treatment failure. Subgroup analyses based on the geographical location of the study, age of study population, type of treatment failure, and study design were conducted to see variation in outcomes. The sensitivity analysis was also employed to see whether an outlier result found in the included studies.

Results: Overall HIV treatment failure found to be 15.9% (95% CI: 11.6%-20.1%). HIV treatment failure was 10.2% (6.9%-13.6%) using immunological definition, 5.6% (95% CI: 2.9%-8.3%) using virological definition, and 6.3% (4.6%-8.0%) using clinical definition. Poor HAART adherence (AOR= 8.5; 95% CI: 4.1-12.8), severity of illness (as measured by WHO clinical stage III/IV (AOR=1.9; 95% CI: 1.3-2.6), and presence of opportunistic infections (AOR=1.8; 95% CI: 1.2-2.4) were significantly associated with HIV treatment failure.

Conclusions: HIV treatment failure in Ethiopia found to be high and differed by adherence level, severity of illness, and presence of opportunistic infection. HIV

intervention programs, such as behavioral intervention is required to sustain HIV treatment adherence and improve treatment success as a result.

Protocol Registration: It has been registered in the PROSPERO database (CRD42018100254).

Keywords: HAART; HIV; Failure; Treatment; Ethiopia

BACKGROUND

The risk of death due to HIV has been decreased after the era of highly active antiretroviral therapy (HAART) (1). Evidence has shown that individuals on HAART with an undetectable viral load, absence of an advanced clinical finding, and high CD4 count are less likely to transmit HIV to others people (2, 3). However, the risk of HIV transmission is high due to treatment failure. Treatment failure can be a virological, immunological, or clinical failure. Virological failure is conceded when plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after three months with adherence support. Immunological failure is confirmed when CD4 count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm^3 for adults and adolescents or below 200 cells/mm^3 for children younger than five years. Clinical failure is defined as an occurrence or recurrence of advanced World Health Organization (WHO) clinical stage or conditions after at least 6 months of therapy (4).

Globally, United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 planned to have 90% of people on HAART are virally suppressed by 2030 and as a result, HIV treatment failure would be prevented (5). Despite this ambitious goal, as of a systematic analysis of national HIV treatment cascades of 69 countries by 2016, viral suppression was

between 7% in China and 68% in Switzerland (6). It can be prevented through the implementation of globally recommended strategies, such as increase HAART adherence, taking medication based on the appropriate prescription, prevent drug-drug interaction, increasing knowledge and attitudes of patients towards HAART, timely initiation of HAART, prevention and control of opportunistic infections, and implementation of effective food and nutrition policy (7-11).

HIV treatment failure is becoming a threat of different African countries: Burkina Faso (6.4%) (12), Ghana (15.7%) (13), and Tanzania (14.9%) (14). In Ethiopia, there is wide variation of reports and nationally representative pooled data on virological, immunological, and clinical failure is lacking. In order to provide evidence towards renewed ambitious future goal, it is now critical to reflect the pooled burden of HIV treatment failure in the Ethiopian context. The objective of this study was (1) to estimate the national burden of HIV treatment failure, (2) to perform meta-analysis on three key influencing factors (i.e. poor adherence, CD4 cell count, severity of illness (WHO clinical stage and presence of opportunities infections) of HIV treatment failure, and (3) review contextual factors of HIV treatment failure using globally accepted key performance indicators as a framework when sufficient number of studies are available for meta-analysis. Thus, this information will be helpful for healthcare professionals and further helps to enable the country to sustain treatment successes and achieve the goal of ending AIDS.

METHODS

Reporting

It is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (15) (Additional file-Research checklist). Its protocol is registered in the PROSPERO database with a registration number CRD42018100254.

Search strategy

PubMed, Web of Science, Scopus, and Google Scholar databases were used to get the research articles. The search strategy made in PubMed was: [("Human Immunodeficiency virus"[MeSH Terms] OR HIV OR AIDS OR "Acquired Immunodeficiency syndrome" AND ("antiretroviral therapy"[MeSH Terms] OR "highly antiretroviral therapy" OR HAART OR ART OR "ARV Therapy" OR "antiretroviral therapy") AND (outcome OR "treatment failure" OR failure OR "virological failure" OR "immunological failure" OR "Clinical failure") AND (Ethiopia)]. The PubMed search was done on 03/10/2018. In addition, Ethiopian Universities' (University of Gondar and Addis Ababa University) online repository library were searched. Endnote 7 reference manager software (Developer: Clarivate Analytics, website: endnote.com) was used to manage duplicated references and for citation in the text.

Inclusion and exclusion criteria

Those articles included in this meta-analysis were: (1) cohort, case-control, and cross-sectional studies, (2) studies that reported the prevalence and/or AOR (adjusted odds ratio) of associated factors of immunological, clinical, virological and overall HAART treatment failure, (3) studies conducted in Ethiopia, and (4) studies published in English.

Studies without full-text access, qualitative studies, and conference proceeding without full-text report were excluded.

Outcome measurement

According to WHO (4), HIV treatment failure could be a clinical, immunological, and virological failure.

The prevalence of treatment failure was ascertained by dividing the participants with the outcome of interests to the overall study participants and multiplied by 100.

Quality assessment

Two authors assessed the quality of the articles based on the Newcastle-Ottawa Scale (NOS) quality assessment tool for cross-sectional, case-control, and cohort studies (16). The criteria for cross-sectional studies have three sections, in which the first section mainly focused on selection and graded by four stars, the second section dedicated with the comparability of the study and graded by two stars, and the third section emphasized on the outcome and graded by three stars. The NOS quality criteria for case-control studies were: 1) selection evaluated by four stars, 2) comparability assessed by two stars, and 3) exposure graded by four stars. The NOS criteria for cohort studies were: 1) selection graded by six stars, 2) comparability graded by two stars, and 3) outcome graded by five stars. Whenever disagreement happened between the two quality assessors, the procedure would be repeated and further solved by an interference of the third reviewer. Cross-sectional, case-control, and cohort studies scored ≥ 6, ≥7, and ≥9 of the quality assessment criteria were included respectively.

Data extraction process

Two authors independently extracted the following data: first author and year of publication, sample size, an outcome of interest (treatment failure), study design, study population, geographical location of the study, source of funding, and response rate.

Data synthesis and statistical analysis

STATA 14 statistical software (Stata Corp, College Station, TX, USA) was used for meta-analysis. Publication bias assessed by funnel plot and more objectively by Egger's regression test. I-squared statistics was used to check the heterogeneity of the studies. Meta-analysis using the DerSimonian-Laird random-effects model was employed to estimate the overall prevalence of treatment failure. Whenever meta-analysis on associated factors was not possible due to lack of available studies, qualitative synthesis was done. Subgroup analysis based on the geographical location of the study, treatment failure type, age of study population, and study design was conducted to see variation in outcomes. The sensitivity analysis was also employed to see whether an outlier result found in the included studies.

RESULTS

Search results

A total of 873 articles were found from PubMed (n=187), Web of Science (n=21), Scopus (n=13), Google Scholar (n=134), and Ethiopian Universities' online repository library (University of Gondar and Addis Ababa University) (n=33). A total of 331 articles have remained after duplicate studies were removed. Then, 302 articles were removed based on the unmatched title and abstracts. Finally, 18 articles were retained for review and meta-analysis (Figure 1).

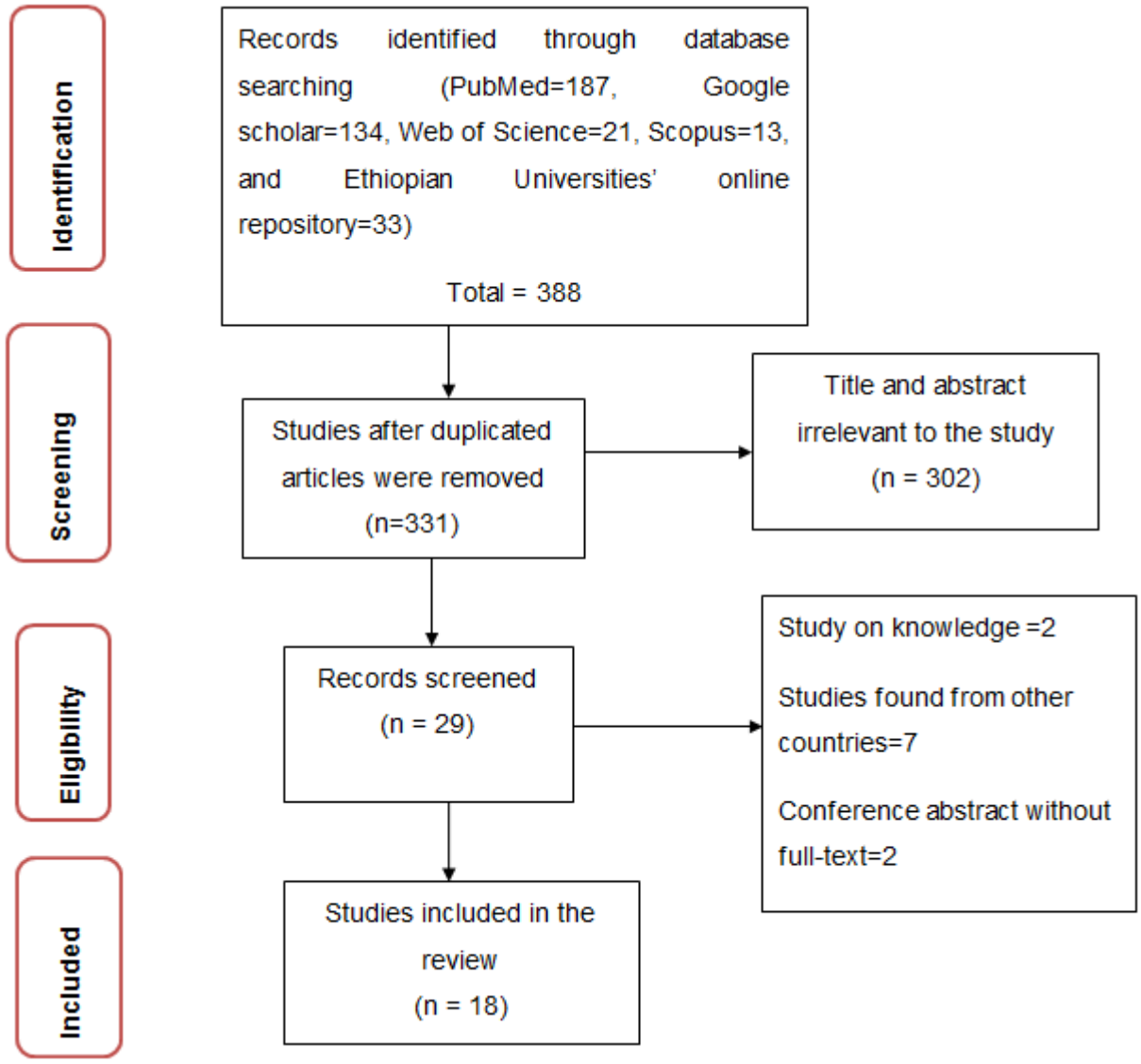

Figure 1: PRISMA flow-chart diagram describing the selection of studies

Characteristics of included studies

All studies were conducted between 2005 and 2016. Eight of the studies were conducted in Amhara region (17-24), whereas five in Addis Ababa (25-29), three in Oromia (30-32), one in Tigray (33), and one in Southern Nations, Nationalities, and Peoples' Region (SNNPR) (34). Three studies were done by case-control study design (23, 24, 29), four studies by cross-sectional (17-19, 33), and 11 by cohort study design

(20-22, 25-28, 30-32, 34). Ten studies were done on adult population (19, 21-26, 28, 29, 31), six on children (18, 20, 27, 30, 32, 34), and two on all age group (17, 33) (Table 1).

Table 1: Characteristic of included studies in systematic review and meta-analysis

First Author/Year	Study period	Region	Study design	Study population	Sample size	Response rate	Source of fund
Teshome W/2015 (28)	2007-2009	Addis Ababa	Retrospective cohort	Adult	293	100%	Not reported
Bokretsion BG et al/2017 (23)	2016	Amhara	Cross-sectional	All age group	421	100%	Bahirdar University and Ethiopian publi health institute
Yassin S/2017 (20)	2006-2015	Oromia	Retrospective cohort	children	269	86.8%	Not reported
Zeleke A/2016 (24)	2005-2013	Amhara	Retrospective cohort	children	225	100%	Not reported
Yimer YT/2015 (15)	2009-2013	Addis Ababa	Retrospective cohort	Adult	525	100%	Not reported
Bacha T et al/2012 (29)	2005-2011	Addis Ababa	Retrospective cohort	children	1,186	100%	Not reported
Ayalew MB et al/2016 (25)	2011-2015	Amhara	Retrospective study	Adult	340	100%	University of Gondar, Ethiopia
Sisay MM et al/2018 (17)	2010-2016	Amhara	Retrospective cohort	children	824	81.9%	University of Gondar, Ethiopia
Tsegaye AT et al/2016	2006-2014	Amhara	Retrospective cohort	Adult	356	100%	University of Gondar,Ethiopi

(19)							
Hailu GG et al/2017 (16)	2008-2016	Tigray	Cross-sectional	All age group	260	100%	Mekelle Univesity, Ethiopia
Yayehirad AM et al/2013 (18)	2007-2008	Amhara	Retrospective cohort	Adult	509	100%	University of Gondar,Ethiopi
Abdissa A et al/2014 (32)	2010-2012	Oromia	Prospective cohort	Adult	265	100%	Danish International Development Agency (DANIDA)
Tadesse BT et al /2017 (34)	2015 -2016	SNNPR	cohort	children	628	100%	Hawassa University, Ethiopia
Workneh N et al/2009 (33)	2005-2008	Oromia	Retrospective cohort	children	96	100%	Jimma University, Ethiopia
Sisay C et al/2017 (30)	2011-2016	Addis Ababa	Retrospective cohort	Adult	595	100%	Ethiopian publi health institute
Babo YD et al/2017 (26)	2014	Amhara	Case-control	Adult	304	100%	USAID
Bayu B et al/2017 (27)	2015	Amhara	Case-control	Adult	306	100%	Not reported
Getnet Y /2014 (31)	2005-2011	Addis Ababa	Case-control	Adult	309	100%	Jimma University, Ethiopia

Publication bias

Funnel plot for HIV treatment failure is shown below (Figure 2). Egger's regression test of the p-value for overall HIV treatment failure was 0.23. Both methods showed that there was no significant publication bias.

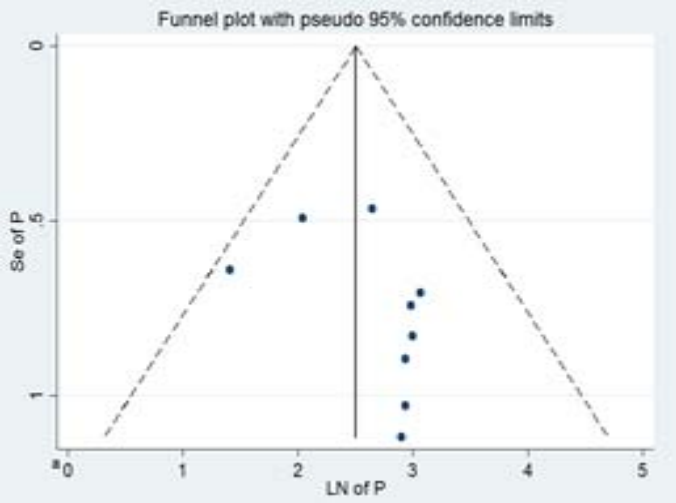

Figure 2: Funnel plot, in which the vertical line indicates the effect size whereas the diagonal line indicates the precision of individual studies with 95% confidence limit

Meta-analysis

HAART treatment failure

A total of 4,738 participants in nine studies were used to estimate the pooled prevalence of HIV treatment failure based on the definition of HAART failure. The pooled prevalence of HIV treatment failure was 15.9% (95% CI: 11.6%-20.1%) (Figure 3).

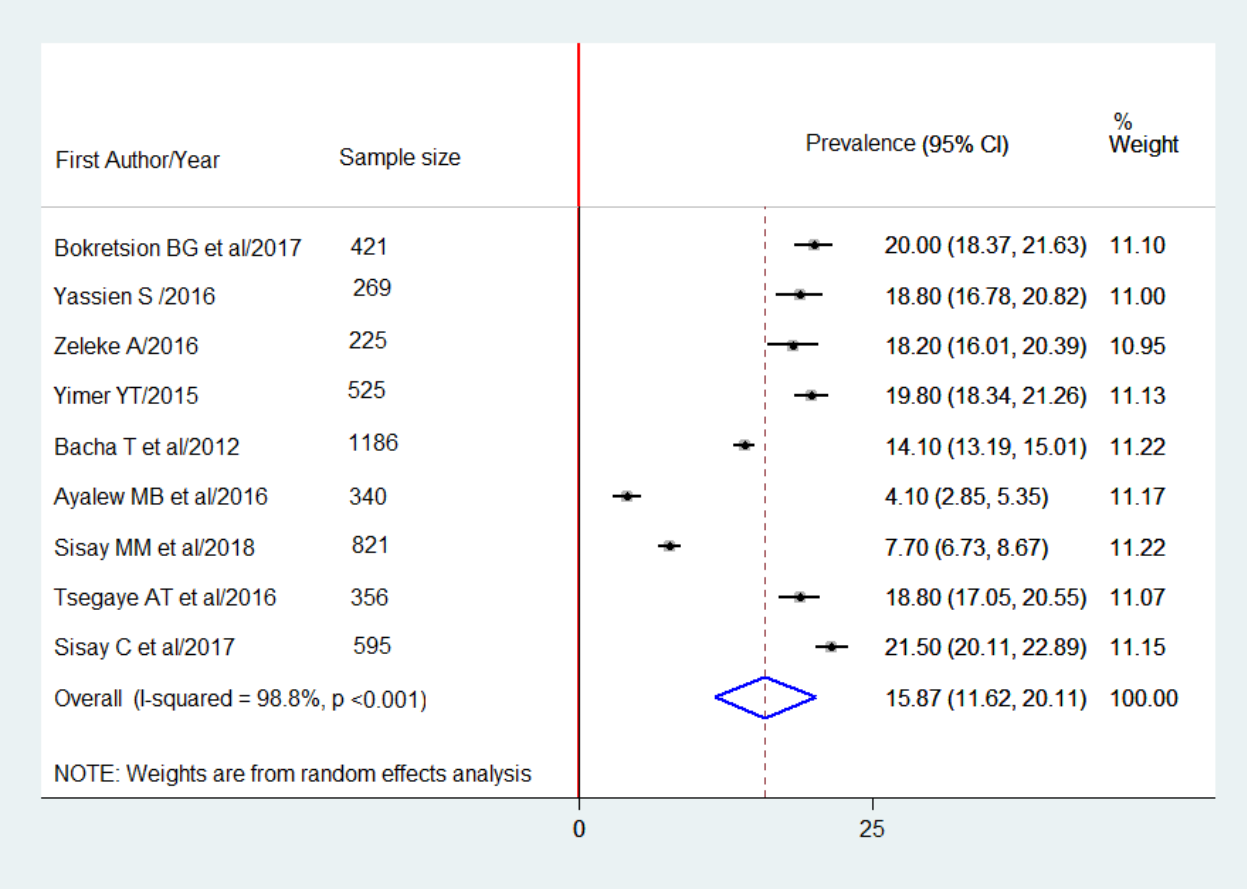

Figure 3: Forest plot of the prevalence of HAART failure in Ethiopia and its 95%CI, the midpoint of each line illustrates the prevalence rate estimated in each study. The diamond shows pooled prevalence.

Immunological and Virological failure

A total of 5,899 study participants in 13 studies were involved to determine HIV treatment failure based on the immunological definition. Of which, 10.2% (6.9%-13.6%) developed immunological failure. Regarding virological failure, the pooled prevalence from six studies with a total of 2,406 participants was 5.6% (95% CI: 2.9%-8.3%) (Figure 4).

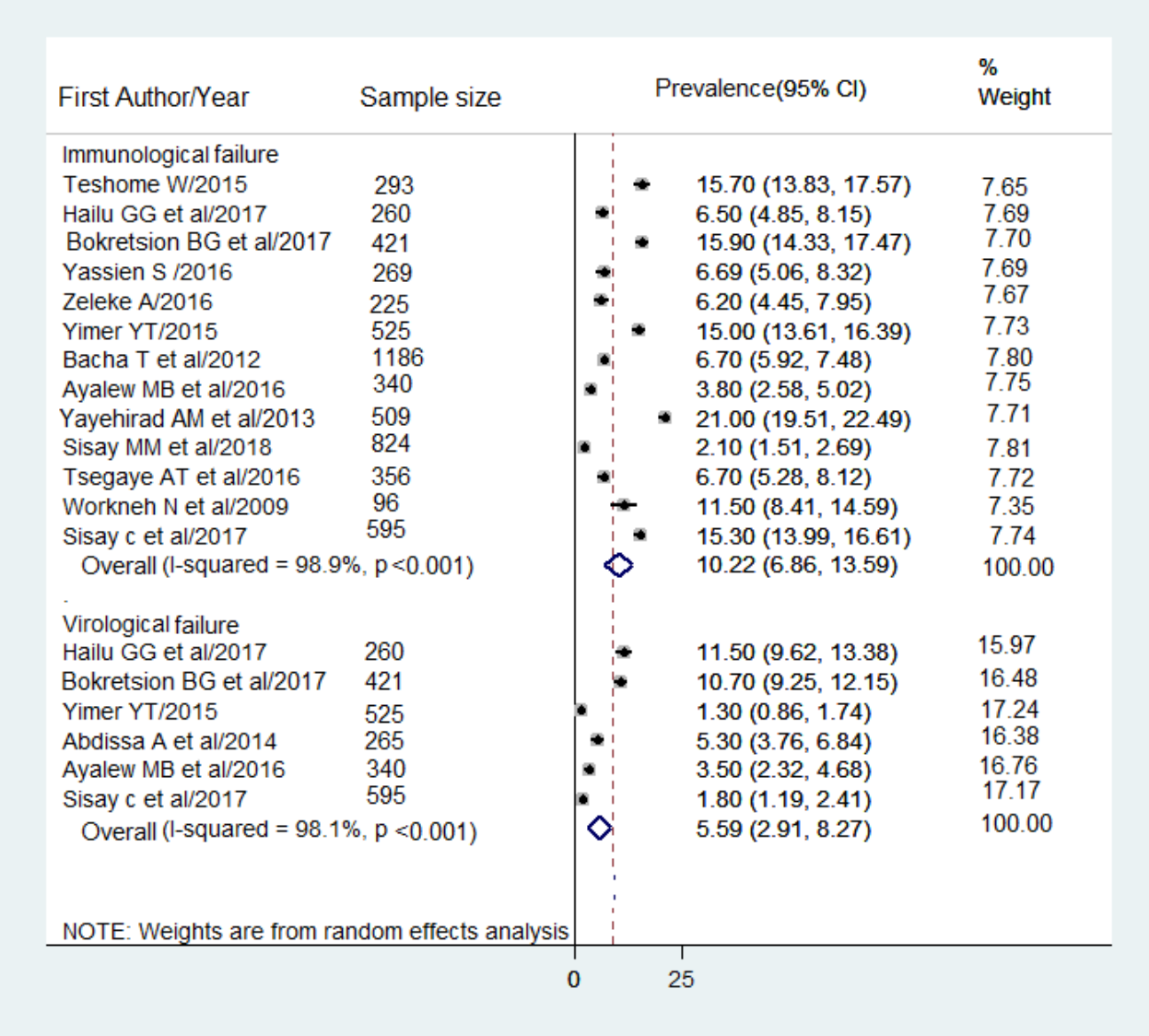

Figure 4: Forest plot of the prevalence of immunological and virological failure in Ethiopia and its 95%CI, the midpoint of each line illustrates the prevalence rate estimated in each study. The diamond shows pooled prevalence.

Clinical failure

A total of 4,497 study participants in nine studies found to estimate the clinical failure, in which the pooled prevalence was 6.3% (4.6%-8.0%) (Figure 5).

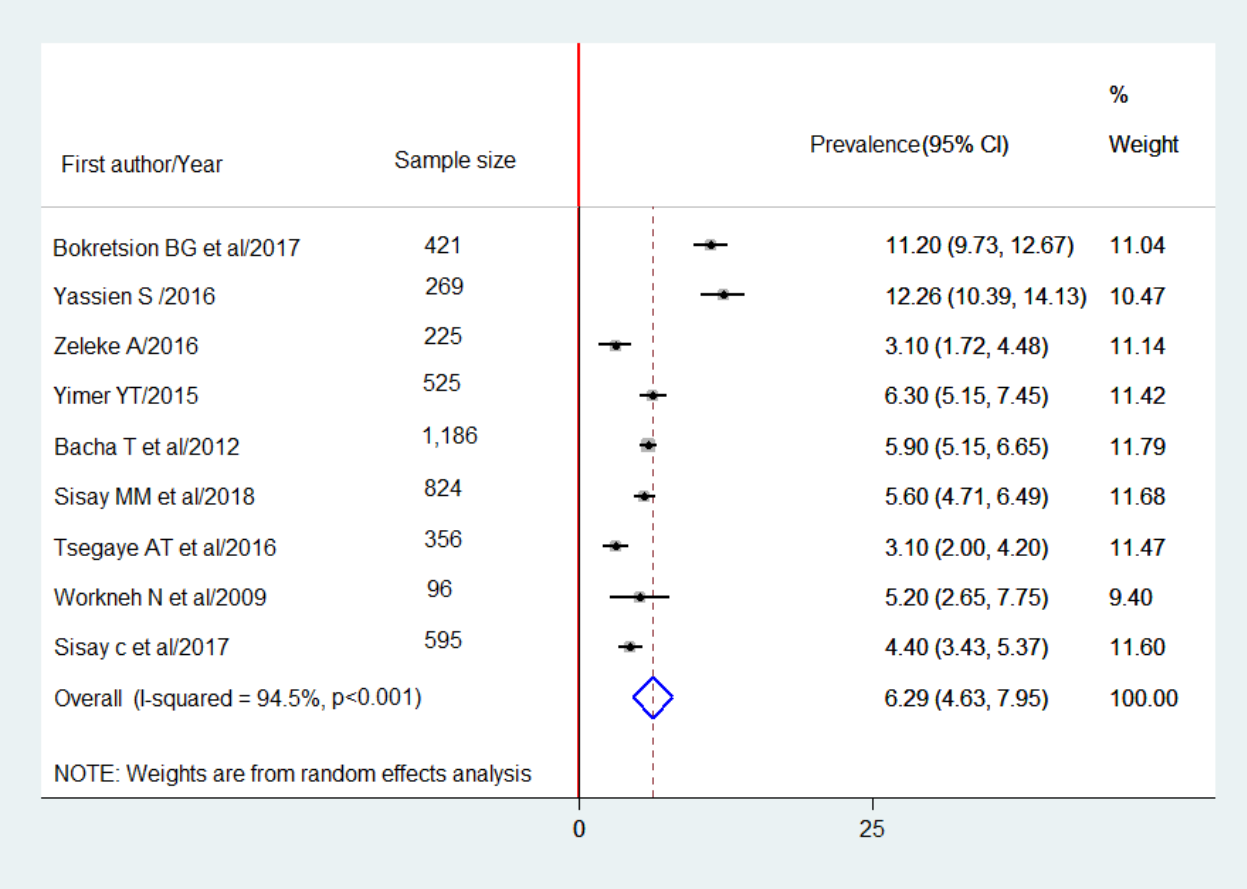

Figure 5: Forest plot of the prevalence of clinical failure in Ethiopia and its 95%CI, the midpoint of each line illustrates the prevalence rate estimated in each study. The diamond shows pooled prevalence.

Subgroup analysis

Subgroup analysis was employed based on region, age of the study participants, and study design. Prevalence of HIV treatment failure based on the definition of HAART, immunological, and virological failure is found in Amhara (13.7%), Tigray (6.5%), and Addis Ababa (1.5%) respectively. In adult population, prevalence of HIV treatment failure was is 16.0% based on the definition of HAART, 12.9% immunological, 2.8% virological, and 4.6% clinical failure. In children, prevalence of HIV treatment failure was

is 14.6% based on the definition of HAART, 6.4% immunological, and 6.4% clinical failure (Table 2).

Table 2: Subgroup analysis of the prevalence (p) of HIV treatment failure based on overall HAART, immunological, virological, and clinical definition by region, age, and study design in Ethiopia

Subgroup analysis	Overall HAART failure P (95%CI)	Immunological failure P (95%CI)	Virological failure P (95%CI	Clinical failure P (95% CI)
By Region				
Amhara	13.7 (7.3-20.2)	9.3 (3.3-15.2)	7.1 (0.03-14.1)	5.7 (2.6-8.9)
Oromia	18.8 (16.8-20.8)	8.9 (4.2-13.6)	5.3 (3.8-6.8)	8.8 (1.9-15.7)
Addis Ababa	18.4 (13.6-23.3)	13.2 (7.9-18.4)	1.5 (1.0-2.0)	5.5 (4.4-6.6)
Tigray	__	6.5 (4.9-8.2)	11.5 (9.6-13.4)	__
By age of participants				
All age group	20.0 (18.4-21.6)	11.2 (2.0-20.4)	11.0 (9.9-12.2)	11.2 (9.7-12.7)
Adult	16.0 (7.4-24.7)	12.9 (7.6-18.3)	2.8 (1.5-4.1)	4.6 (2.9-6.3)
Children	14.6 (9.7-19.6)	6.4 (3.6-9.3)	__	6.4 (4.2-8.5)
By Study design				
Cross-sectional	14.1 (3.0-25.2)	8.1 (2.7-13.5)	8.5 (3.2-13.9)	7.2 (0.8-15.8)
Cohort	16.8 (12.2-21.37)	11.2 (6.8-15.6)	2.6 (1.1-4.0)	6.0 (4.5-7.5)
Combined	15.8 (11.6-20.1)	10.2 (6.9-13.6)	5.6 (2.9-8.3)	6.3 (4.6-8.0)

__ *denotes no estimation due to lack of original studies*

Sensitivity Analysis

In the sensitivity analysis, the overall HIV treatment failure based on the definition of HAART failure was observed high (17.3%) and low (15.2%) when *Ayalew MB et al 2016* (19) and *Sisay C et al/2017(28)* was omitted respectively. The minimum (9.3%) and maximum (10.8%) pooled prevalence of HIV treatment failure based on immunological

definition were observed when *Yayehirad AM et al/2013* (22) and *Ayalew MB et al/2016* (19) was omitted respectively. The pooled prevalence of HIV treatment failure based on the virological definition was 4.4% when *Hailu GG et al /2015* (33) omitted and 6.5% when *Yimer YT/2015* (26) left from the analysis. Regarding the clinical definition of HIV treatment failure, the minimum (5.5%) pooled prevalence was observed when *Yassin S /2016* omitted (30).

Table 3: The prevalence (p) of HIV treatment failure based on HAART failure, immunological, virological, and clinical definition when the study omitted in Ethiopia

Study omitted	HAART failure P (95%CI)	Immunological failure P (95%CI)	Virological failure P (95%CI	Clinical failure P (95% CI)
Bokretsion BG et al/2017	15.3 (10.8-19.9)	9.7 (6.3-13.2)	4.5 (2.3-6.7)	5.6 (4.2-7.1)
Yassin S /2017	15.5 (10.9-20.1)	10.5 (6.9-14.1)	__	5.5 (4.1-7.1)
Zeleke A/2016	15.6 (11.0-20.2)	10.6 (7.0-14.1)	__	6.7 (4.9-8.4)
Yimer YT/2015	15.4 (10.8-19.9)	9.8 (6.4-13.3)	6.5 (2.7-10.3)	6.3 (4.4-8.2)
Bacha T et al/2012	16.1 (10.9-21.3)	10.5 (6.6-14.4)	__	6.4 (4.3-8.4)
Ayalew MB et al/2016	17.3 (13.5-21.2)	10.8 (7.1-14.4)	6.0 (2.9-9.2)	__
Sisay MM et al/2018	16.9 (12.6-21.2)	10.9 (7.7-14.1)	__	6.4 (4.4-8.4)
Tsegaye AT et al/2016	15.5 (10.9-20.1)	10.5 (6.9-14.1)	__	6.7 (5.0-8.4)
Teshome W/2015	__	9.8 (6.3-13.2)	__	__
Hailu GG et al/2015	__	10.5 (6.9-14.1)	4.4 (2.0-6.9)	__
Yayehirad AM et al/2013	__	9.3 (6.3-12.4)	__	__
Workneh N et al/2009	__	10.1 (6.6-13.6)	___	6.4 (4.6-8.2)
Sisay C et al/2017	15.2 (10.8-19.5)	9.8 (6.4-13.2)	6.4 (2.4-10.4)	6.5 (4.7-8.4)
Abdissa A et al/2014	__	__	5.6 (2.7-8.6)	__

Combined	15.8 (11.6-20.1)	10.2 (6.8-13.6)	5.6 (2.9-8.3)	6.3 (4.6-7.9)

__ *denotes no estimation due to lack of original studies*

Associated factors of HIV treatment failure

HIV treatment failure is attributed to various behavioral, drug, and clinical-related associated factors.

Behavioral and drug-related factors

The pooled effect of poor HAART adherence on HIV treatment failure was found to be 8.5 (95% CI: 4.1-12.8) (Figure 6).

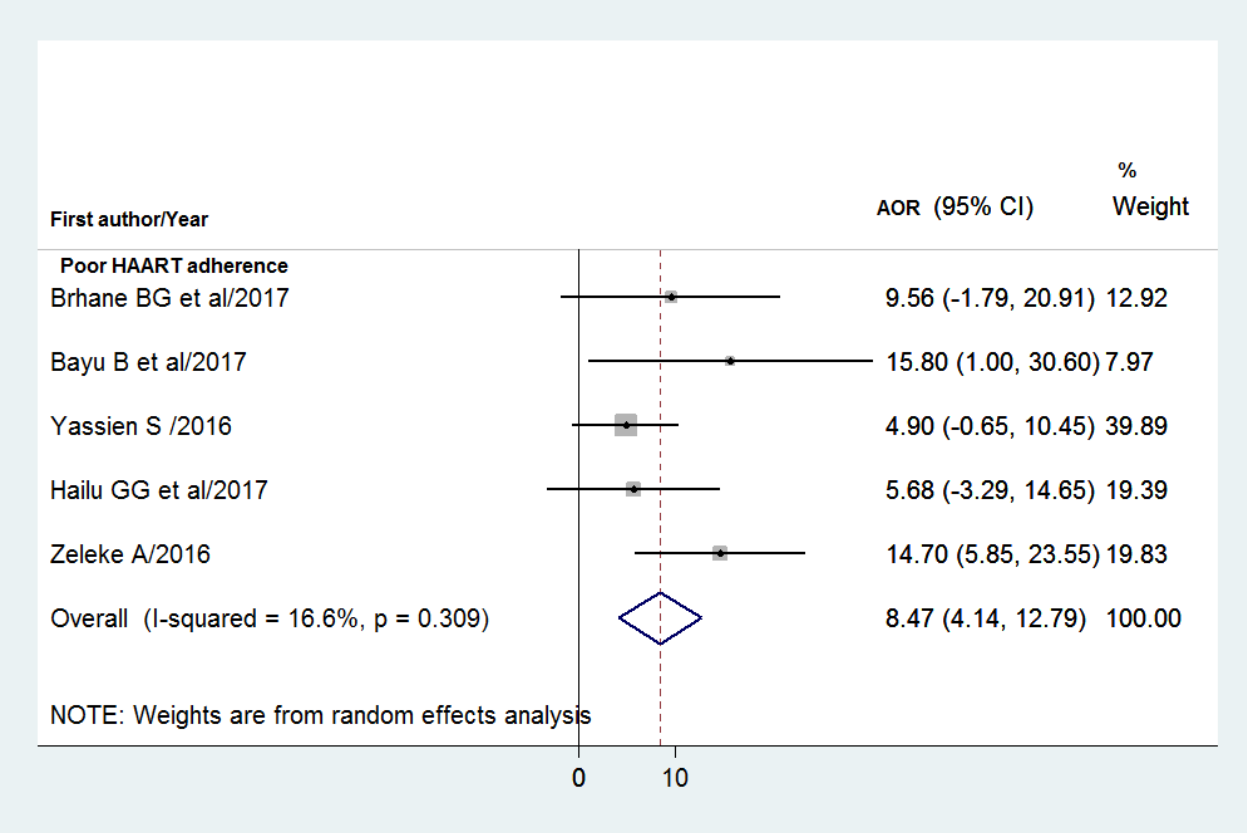

Figure 6: Forest plot of the adjusted odds ratios with corresponding 95% CIs of studies on the association of poor HAART adherence and HIV treatment failure

Another study (17) showed that lack of consultation significantly associated with HIV treatment failure (AOR=4.9,95% CI:1.5-15.8). Regarding drug-related factors, stavudine based regimen (AOR = 3.5; 95% CI: 1.3-10.6) (23), ART drug substitution (AHR=1.7; 95% CI:1.1-2.7) (27), substitution of original regimen (AOR=3.3; 95% CI=1.6-6.7) (18), absence of PMTCT prophylaxis (AOR=1.4; 95% CI: 1.2-2.5) (18), and using faith healing medicine (AOR=8.1, 95% CI: 3.1-21.5) (17) were reported significant predictors of HIV treatment failure.

Clinical-related factors

The pooled effects of low CD4 cell count was 7.2 (95% CI: 2.5-12.0) when <200 cells/mm^3, 2.1 (95% CI: 1.4-2.8) when ≤ 100 cells/ mm^3, and 3.3 (95% CI: 1.4-5.3) when <50 cells/mm^3 (Figure 7).

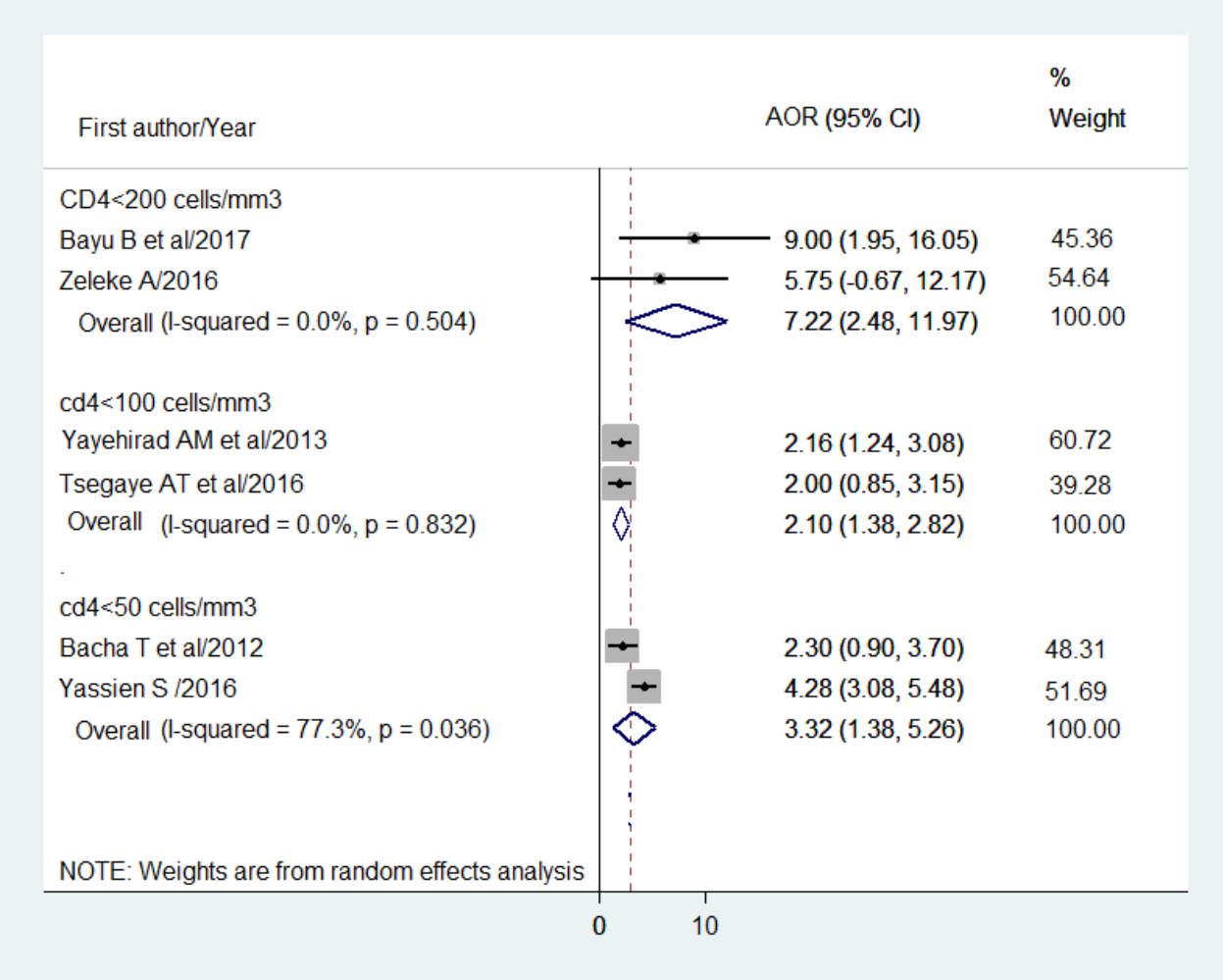

Figure 7: Forest plot of the adjusted odds ratios (AOR) with corresponding 95% CI of studies on the association of CD4 cells and HIV treatment failure

The pooled effect of severity of illness (i.e. being on WHO clinical stage III/IV) on HIV treatment failure was 1.9 (95% CI: 1.3-2.6) compared with stage II/I. The pooled effect of presence of opportunistic infections was 1.8 (95% CI: 1.2-2.4) (Figure 8).

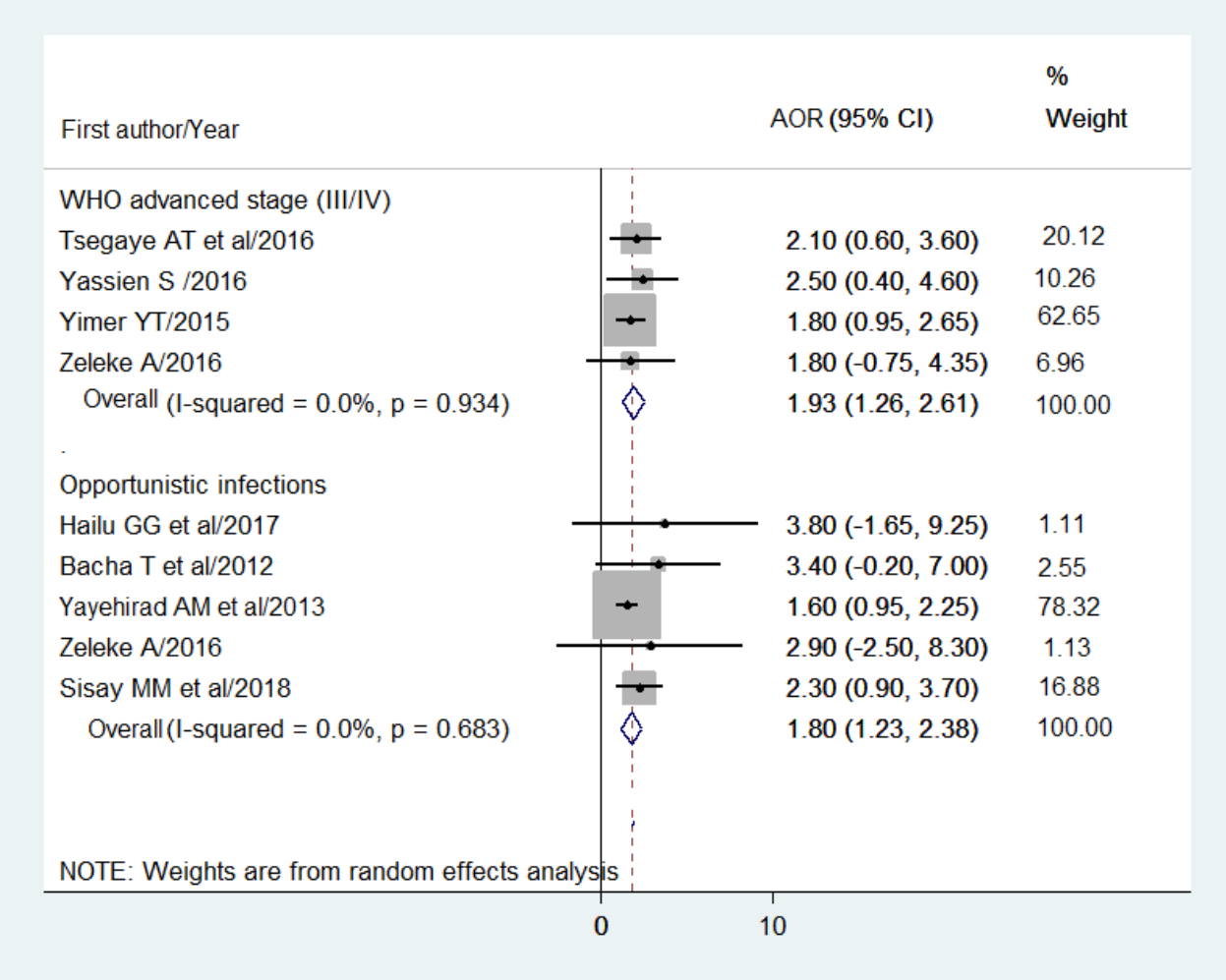

Figure 8: Forest plot of the adjusted odds ratios (AOR) with corresponding 95% CIs of studies on the association of WHO clinical stage, opportunistic infections, and HIV treatment failure

Previous studies also showed that lower baseline body mass index (BMI) (AOR = 2.8; 95% CI: 1.01-7.5) (23), low height for age (AHR= 3.3; 95% CI: 1.0-10.6) (27), increased weight (AHR=0.9, 95% CI: 0.9-0.9) (21), and low weight at baseline (AHR=0.58, 95% CI:0.38-0.89) (26) were significantly associated with HIV treatment failure. Further, studies showed that ambulatory patients (AOR=2.9, 95%CI: 1.2-7.5) (22) and children

who did not know their HIV status (AHR=4.4, 95% CI: 1.8-11.3) (20) had high risk for HIV treatment failure compared with their counterparts.

DISCUSSION

To our knowledge this first meta-analysis study to report the national prevalence of HIV treatment failure and its important risk factors. The prevalence of HAART failure was 15.9% whereby immunological failure was 10.2%, clinical failure was 6.3%, and virological failure was 5.6%. We found that poor HAART adherence, low CD4 cell count, severity of illness (WHO clinical stage III/IV) and presence of opportunistic infections were key significantly associated factors of treatment failure.

In this study, we uncovered that HIV treatment failure was 15.9% (95% CI: 11.6%-20.1%) using the definition of HAART failure. In Ethiopia, HIV treatment failure is becoming increased and appointed discussion. This might be due to implementation of poor HIV care, delaying on recognition of symptom of treatment failure, (35), late initiation of HAART (36), high burden of opportunistic infections (37), lack of well nutritional support (38), ART-associated adverse reaction (39), and frequent psychological problem (40, 41). Besides, the absence of frequent therapeutic drug monitors and/ or resistance testing while the patient is still on the suspect or failing regimen. All four markers of lower socioeconomic status (financial hardship, non-employment, rented or unstable housing status, and non-university education) can be considered for a higher burden of HIV treatment failure in Ethiopia. These evidence implicates ART should be switched only after considering supplementary treatment failure prevention activities. In resource-limited setting, it is recommended to keep

patients longer on first-line ART regimen which preserves the more toxic and expensive second-line ART regimen.

This meta-analysis finding showed that HIV treatment failure using the immunological definition (10.2%) was higher than clinical (6.3%) and virological (5.6%) failure. The variations might be due to the difference in number of studies included to the pooled analysis. Given that the WHO immunological criteria have a very low sensitivity and high specificity (42), false positive finding may be evident in primary studies. The lower prevalence of HIV treatment failure using clinical definition might be due to limited diagnostic capabilities. It might be difficult to identify treatment failure in patients under clinical monitoring since not all HIV care clinic sites had a systematic approach and well-trained health professionals to collect data on opportunistic infections. Using viral load based HIV treatment failure could provide better prognostic information about the risk of developing active AIDS stage which will promote more effective second-line ART. However, in most Ethiopian health institutions, virological ART failure is likely to be under-diagnosed in the routine health system and might be under reported compared with clinical and/or immunological failure as a result. Additionally, only five studies were used to estimate virological failure that might result in under-estimation.

Based on the subgroup analysis, HIV treatment failure is lower in children. This may be due to the fact that ART monitoring using clinical and immunological criteria is problematic in children, and misclassification rates using the WHO pediatric guidelines remain high (42).

In agreement with previous studies (43, 44), we found low CD4 cell count, advanced WHO clinical stage, and presence of opportunistic infections leads to HIV treatment

failure. Despite this fact, these risk factors are highly interconnected. CD4 cell count is the backbone of immunity construction that helps the human body to protect from the disease and can prevent HIV replication (45). As patients' immune status becomes compromised, the rate of viral replication increase and the chance of acquiring opportunistic infections is high which leads to advanced stage of the disease. Consequently, the patient gives more emphasis to the current problem than the chronic HIV, stop taking drugs and interrupt follow-up which cause HIV treatment failure.

Poor HAART adherence found to have a great impact on the occurrence of HIV treatment failure. It is widely agreed that once treatment is initiated, it should not be interrupted. In Ethiopia, within 7 days, nearly 11.3% of children have poorly adhered to ART (46). It is expected that as duration increased, the probability of ART interruptions would be more likely. Similarly, in adult HIV patients', treatment interruption is fall in the range between 11.8-25.8% (47, 48). Acquired HIV drug resistance develops when HIV mutations emerge due to viral replication in individuals on an imperfect ART adherence. Poor ART adherence could lead to incomplete viral suppression and causes HIV treatment failure. Global recommendation like on-time pill pick-up, electronic or paper-based appointment scheduling, SMS or telephone call reminders, peer counseling, cognitive behavioral therapy, and reduction of the HIV-associated stigma that prevent missing of ART drugs are not well implementing in Ethiopia.

The current finding will have healthcare policy and clinical implication for therapeutic management decisions. Early identification of ART treatment failure allows patients a higher chance of treatment success when switching to a second line ART. The current

evidence will also be used to monitor the progress of the national action plan of 90-90-90 strategies.

LIMITATION OF THE STUDY

Lack of studies in some geographical areas of Ethiopia makes the finding to be interpreted with caution. Besides, since the study design of included studies are observational (cross-sectional and cohort), establishing causal relationship between studied variables required caution.

CONCLUSION AND FUTURE DIRECTIONS

To conclude, HIV treatment failure in Ethiopia found to be high. This review revealed HIV treatment failure is attributed to behavioral, clinical, and drug-related factors. HIV intervention programs need to be addressed the specified contributing factors of HIV treatment failure. Behavioral intervention to prevent treatment interruption is required to sustain HIV treatment adherence.

Disclaimer: This study is based on data from primary studies. The analysis, discussions, conclusions, opinions and statements expressed in this text are those of the authors.

Funding: There was no fund to conduct this systematic review and meta-analysis

Compliance with Ethical Standards

Conflict of interest: Author AE declares that he has no conflict of interest. Author MM declares that he has no conflict of interest. Author DD declares that he has no conflict of interest. Author FA declares that he has no conflict of interest. Author HT declares

that he has no conflict of interest. Author TDH declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors because it relies on primary studies.

Informed consent: Not applicable

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