

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of anemia and its associated factors among HIV-infected adults at the time of ART initiation at Debre-Markos comprehensive specialized hospital, Northwest Ethiopia: a retrospective cross-sectional study
AUTHORS	Aemro, Agazhe; Workneh, Belayneh; Mekonen, Enyew; Wassie, Mulugeta; Chekol, Basazine

VERSION 1 – REVIEW

REVIEWER	Sah, Shiv Purbanchal University, Pharmacy
REVIEW RETURNED	22-Nov-2021

GENERAL COMMENTS	<p>General Comments</p> <p>This institution-based retrospective cross-sectional study conducted in Northwest Ethiopia will add value to the existing literature. In this study the authors have found a high prevalence of anemia in HIV-infected persons, with increased risk of anemia in the male population, lower body mass index, baseline CD4 count ≤ 200 cells/mm³, and ambulatory/bed-ridden functional status. There are, however, some major issues regarding study population pre-selection which need to be analyzed and discussed in detail. Moreover, there are some language issues that need to be polished entire the text.</p> <p>My Specific comments are below</p> <p>Abstract</p> <ol style="list-style-type: none">1. In the abstract, consider presenting confidence interval along with prevalence.2. The conclusion must be drawn in light of the data presented, and future direction should be highlighted accordingly.3. Keywords: please consider adding- Prevalence, associated factors <p>Strength and limitation</p> <ol style="list-style-type: none">4. This study has been accomplished with many limitations than presented in the manuscript, and need to be discussed in detail, with a major focus on inclusion criteria, study nature, missing data, etc... <p>Introduction</p> <ol style="list-style-type: none">5. Please provide a logical background that addresses the problem of your study. I would consider removing the first paragraph in the introduction section.6. Please add more recent literature on the risk factor for developing anemia in HIV-infected patients. <p>Methods</p> <p>Page27-30: The study was conducted by reviewing patients' charts from January 1, 2014, to December 3.</p> <ol style="list-style-type: none">7. The above statement seems to be exaggerated. Please consider
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	<p>removing this.</p> <p>Page 39-45: Study population: randomly selected HIV-positive adults age 15 years old and above who were newly enrolled in ART Clinic at Debre-Markos Referral Hospital from January 1, 2014, to December 31, 2018, Northwest Ethiopia.</p> <p>8. In the above statement, the authors have described the newly enrolled patients in the ART clinics. How did you identify these new enrolled patients, as the data was collected retrospectively?</p> <p>9. How did you handle missing data?</p> <p>10. How did you address the potential confounders that may contribute to developing anemia? Of total 1264 patients, 1117 patients were eligible for the study. Could you elaborate on the eligibility criteria in detail, with more focus on exclusion criteria?</p> <p>11. consider providing confidence interval for anemia prevalence</p> <p>12. categorical analysis indicating P-value is essential to present the data.</p> <p>Results: Table 1: 13. Percentage of male and female anemic patients should reflect the total gender. E.g., 86 (52.76%) and female 77(47.23%)</p> <p>14. Consider presenting P value, whether the difference of being anemic among the groups are significant or not.</p> <p>15. I would consider presenting frequency and percentage while describing the table in the text. e.g., Of all study participants included in the analysis, around 29.06% had started ART six months....</p> <p>16. The figure should self-explanatory. Consider including confidence interval in figure 1</p> <p>Discussion In this study, the male sex was found to be an independent predictor of anemia at the time of ART initiation. The odd of being anemic at the time of ART initiation among males is 2.45 times that of females (95% CI: 1.51 - 3.98). This is in line with studies conducted in Zewditu memorial hospital and Arba minchi town, Ethiopia [19, 21]. More alcohol consumption among males than females might contribute to this difference between males and females..</p> <p>17. Referring to the above statement, the authors have argued that the increased risk of developing anemia in the male population could be due to more alcohol consumption. However, the authors have failed to show the data on alcohol consumption in the male population.</p> <p>18. Be specific on your finding rather than elaborating on literature. Page 25-34: This may be explained by patients with no formal education are less aware of better nutrition and better health care. When HIV infection is observed among those with no formal education, the risk of poor nutrition and occurrence of anemia will be double burdened. Additionally, non-educated patients are not fully aware of anemia symptoms so that they will come to the hospital quite late with high anemic grades.</p> <p>19. In the above statement, could you provide evidence that support the correlation between the knowledge level and occurrence of anemia</p>
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	<p>Page 3-17: the authors have stated that lower BMI could contribute to developing anemia due to deficiency of iron, folate, and VitB12.</p> <p>20. in the above explanation, did you assess the rate of megaloblastic anemia in this particular population?</p> <p>Page 26-34: Being in ambulatory or bedridden functional status could be an indicator of HIV infection advancement and the occurrence of other opportunistic infections. Patients in ambulatory or bedridden functional status may also be at risk for loss of appetite which may expose them to malnutrition and result in anemia.</p> <p>21. Please provide evidence to support your explanation.</p> <p>22. I think the study has several limitations, taking into account sources of potential biases, which need to be discussed in detail</p> <p>Conclusion:</p> <p>22. Please discuss the implication of this finding in this particular setting</p> <p>23. Please provide the future direction for this finding.</p>
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REVIEWER	Bishaw, keralem Debre Markos University, Midwifrey
REVIEW RETURNED	02-Dec-2021

GENERAL COMMENTS	<p>Consider using reporting format like the STROBE checklist.</p> <p>Date: November 2, 2021</p> <p>Manuscript ID: BMJ open-2021-057235</p> <p>Title: PREVALENCE OF ANEMIA AND ITS ASSOCIATED FACTORS AT THE TIME OF ART INITIATION AMONG HIV-INFECTED ADULTS AT DEBRE-MARKOS REFERRAL HOSPITAL, NORTHWEST ETHIOPIA: A RETROSPECTIVE CROSS-SECTIONAL STUDY</p> <p>First, I would like to thank you for inviting me to review this paper. This manuscript focuses on important public health problems in developing countries including Ethiopia. International volunteers and organizations may refer to this literature when designing aid programs.</p> <p>Comments</p> <p>Title:</p> <p>Comment 1. Why do you focus to determine the magnitude of anemia at the time of starting ART? Is there any unique significance determining it without considering ART starting time or determining among HIV-positive patients? Reason out</p> <p>Comment 2. The name has been changed to DEBRE-MARKOS REFERRAL HOSPITAL to Debre-Markos comprehensive specialized hospital, correct it throughout the document.</p>
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	<p>Abstract</p> <p>Comment 3. Spelling and capitalization error</p> <p>Comment 4. Line 22 “ART” makes its long-form.</p> <p>Comment 5. page 3 line “had no formal education”, if I were you, I prefer to use not attending formal education over it. Consider it throughout the document.</p> <p>Discussion: The discussion section can be concise more rather than repeat the result.</p> <p>Comment 5. The discussion part especially the prevalence should be paraphrased and put the possible justification why the difference happened when it compare to studies conducted in Ethiopia. You didn’t reason out why the difference occurred. And also omit unnecessary extra words, Hawassa University Referral Hospital makes it simply South Ethiopia, similarly for others if possible.</p> <p>Comment 6: Similarly, the current study showed that the odds of being anemic among patients with no formal education was 2.38 times that of college and above educational status (AOR = 2.38; 95% CI: 1.12 - 5.05). Information like this (AOR = 2.38; 95% CI: 1.12 - 5.05) you wrote again in the discussion part, no need of repeating in the discussion once wrote the result part. So, do it for all variables.</p> <p>Comment 6. This information should be cited. “When HIV infection is observed among those with no formal education, the risk of poor nutrition and occurrence of anemia will be double burdened”. cite. Line 28, 29.</p> <p>Conclusion: would please revise your recommendation based on your finding especially on the modifiable factors also....</p> <p>General comment</p> <p>This literature may offer insights on HIV-infected adults in the study setting. But the following should be addressed before publication.</p> <ol style="list-style-type: none"> 1. The manuscript is had full of grammatical, spelling, and punctuation errors. It should be edited. 2. The discussion part should be paraphrased and possible questions along with citations should be considered. 3. Authors should read carefully the author’s submission guideline and strictly follow it for all
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	sections of the manuscript.
	Decision: major revision

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:

General Comments:

This institution-based retrospective cross-sectional study conducted in Northwest Ethiopia will add value to the existing literature. In this study the authors have found a high prevalence of anemia in HIV-infected persons, with increased risk of anemia in the male population, lower body mass index, baseline CD4 count ≤ 200 cells/mm³, and ambulatory/bed-ridden functional status. There are, however, some major issues regarding study population pre-selection which need to be analyzed and discussed in detail. Moreover, there are some language issues that need to be polished entire the text.

Author response:

- Thank you for your valuable comments.
- Every issue regarding the study is addressed bellow in detail.
- The authors revised the manuscript and corrected language issues.

Abstract:

1. In the abstract, consider presenting confidence interval along with prevalence.

Author response:

Based on the comment, confidence interval along with the prevalence is added to the revised document.

2. The conclusion must be drawn in light of the data presented, and future direction should be highlighted accordingly.

Author response:

Based on the comment, the authors tried to conclude based on the findings, and future directions are highlighted.

3. Keywords: please consider adding- Prevalence, associated factors

Author response:

These words are added to the revised manuscript.

Strength and limitation

4. This study has been accomplished with many limitations than presented in the manuscript, and need to be discussed in detail, with a major focus on inclusion criteria, study nature, missing data, etc...

Author response:

- In the revised manuscript, the authors described the limitations of the study in detail. We also incorporated a paragraph regarding the limitation at the end of the discussion section.

Introduction:

5. Please provide a logical background that addresses the problem of your study. I would consider removing the first paragraph in the introduction section.

Author response:

- Thank you.
- The authors revised and corrected it based on the comment.

6. Please add more recent literature on the risk factor for developing anemia in HIV-infected patients.

Author response:

- Based on the comment, the authors revised this section.

Methods:

Page27-30: The study was conducted by reviewing patients' charts from January 1, 2014, to December 3.

7. The above statement seems to be exaggerated. Please consider removing this.

Author response:

Thank you, the authors removed this statement in the revised manuscript.

Page 39-45: Study population: randomly selected HIV-positive adults age 15 years old and above who were newly enrolled in ART Clinic at Debre-Markos Referral Hospital from January 1, 2014, to December 31, 2018, Northwest Ethiopia.

8. In the above statement, the authors have described the newly enrolled patients in the ART clinics. How did you identify these new enrolled patients, as the data was collected retrospectively?

Author response:

- The authors used the term 'newly enrolled' which is to mean 'HIV-infected adults who started ART since January 1, 2014', and to exclude those who started ART before this specified time and continued on ART after this time.
- Since the patient's data was recorded on the computer, and with the help of the data clerk, patient's chart numbers who started ART since January 1, 2014 were identified by using the computer.

9. How did you handle missing data?

Author response:

- Actually, the authors did not encounter too much missing data because the healthcare providers tried to record all the necessary baseline patient information.
- Very few data points were missed, and they were handled by using the most recent follow-up information (after 2 weeks or 1 month from the first ART start date).

10. How did you address the potential confounders that may contribute to developing anemia?

Author response:

In order to reduce the potential confounding effect of variable/s:

- First, the authors leave out or exclude a variable that can result in anemia. In this study, the authors excluded patients' charts labeled as 'pregnant' from the record because pregnancy can cause anemia by itself.
- Second, confounders were managed at the recruitment of participants using randomization. Patient chart numbers were selected randomly by generating a random number on the computer in which all participants had an equal chance of being selected.
- Third, confounders were controlled at the analysis level by multivariate analysis.

Of total 1264 patients, 1117 patients were eligible for the study. Could you elaborate on the eligibility criteria in detail, with more focus on exclusion criteria?

Author response:

- Adults aged 15 years and above who were enrolled in the ART Clinic between January 1, 2014, and December 31, 2018 were eligible for the study.
- But, HIV-infected adults who transferred in from other health institutions (started ART between January 1, 2014, and December 31, 2018 in other health institutions but transferred to Debre Markos hospital for any reason) were excluded because these patients' charts may lack baseline information.
- Additionally, being pregnant at baseline was excluded from the study, to reduce the potential confounding of pregnancy.

11. Consider providing confidence interval for anemia prevalence

Author response:

- Based on the comment, the authors considered CI in the revised manuscript.

12. Categorical analysis indicating P-value is essential to present the data.

Author response:

- Yes, the authors considered it in the revised manuscript.

Results:

Table 1:

13. Percentage of male and female anemic patients should reflect the total gender.

E.g., 86 (52.76%) and female 77(47.23%)

Author response:

- Thank you for the comments.
- But, only a percentage of male and female anemic patients couldn't reflect the total gender. Rather, the sum of anemic and not-anemic males and females represents the total gender.
- Additionally, the authors calculated the percentage of anemia and not anemia among males and females (across the raw).

14. Consider presenting P value, whether the difference of being anemic among the groups are significant or not.

Author response:

- Thank you, the authors added a p-value in the revised manuscript.

15. I would consider presenting frequency and percentage while describing the table in the text. e.g., Of all study participants included in the analysis, around ? (29.06%) had started ART six months....

Author response:

- Thank you, the authors considered it based on the comment in the revised manuscript.

16. The figure should self-explanatory. Consider including confidence interval in figure 1

Author response:

- Based on the comment, the authors considered including confidence interval in fig 1.

Discussion:

In this study, the male sex was found to be an independent predictor of anemia at the time of ART initiation. The odd of being anemic at the time of ART initiation among males is 2.45 times that of females (95% CI: 1.51 - 3.98). This is in line with studies conducted in Zewditu memorial hospital and Arba minchi town, Ethiopia [19, 21]. More alcohol consumption among males than females might contribute to this difference between males and females.

17. Referring to the above statement, the authors have argued that the increased risk of developing anemia in the male population could be due to more alcohol consumption. However, the authors have failed to show the data on alcohol consumption in the male population.

Author response:

- Actually, there is no information stated in the manuscript regarding alcohol consumption.
- But, the authors' justification was based on the usual habit practiced by which males consume more alcohol than females, especially in Ethiopia.

18. Be specific on your finding rather than elaborating on literature.

Author response:

- Thank you, the authors accepted the comment.

Page 25-34: This may be explained by patients with no formal education being less aware of better nutrition and better health care. When HIV infection is observed among those with no formal education, the risk of poor nutrition and the occurrence of anemia will be double burdened.

Additionally, non-educated patients are not fully aware of anemia symptoms so that they will come to the hospital quite late with high anemic grades.

19. In the above statement, could you provide evidence that support the correlation between the knowledge level and occurrence of anemia

Author response:

- Thank you for the comment.
- In the revised manuscript, the authors cited this description.

Page 3-17: the authors have stated that lower BMI could contribute to developing anemia due to deficiency of iron, folate, and VitB12.

20. In the above explanation, did you assess the rate of megaloblastic anemia in this particular population?

Author response:

- No, the authors did not assess the specific type of anemia, rather they assessed the whole type of anemia.

- HIV can cause anemia through different mechanisms, of which decreased BMI as a result of reduced dietary consumption secondary to the infection may lead to micronutrient deficiency and lastly, anemia.

Page 26-34: Being in ambulatory or bedridden functional status could be an indicator of HIV infection advancement and the occurrence of other opportunistic infections. Patients in ambulatory or bedridden functional status may also be at risk for loss of appetite which may expose them to malnutrition and result in anemia.

21. Please provide evidence to support your explanation.

Author response:

- Thank you, the authors cited this explanation in the revised manuscript.

22. I think the study has several limitations, taking into account sources of potential biases, which need to be discussed in detail.

Author response:

- Based on the comments, the authors incorporated a paragraph regarding the limitations of the study at the end of the discussion.

Conclusion:

23. Please discuss the implication of this finding in this particular setting

Author response:

- Based on the comments, the authors added the implications of the study for Debre Markos hospital in the revised manuscript.

24. Please provide the future direction for this finding.

Author response:

- Yes, the authors considered it in the revised manuscript.

REVIEWER 2:

Title:

Comment 1. Why do you focus to determine the magnitude of anemia at the time of starting ART? Is there any unique significance determining it without considering ART starting time or determining among HIV-positive patients? Reason out

Author response:

Because assessing anemia at the start of ART is important for:

- Having baseline information to compare it with anemia status after treatment initiation.
- The presence of anemia at ART initiation time will affect the choice of drugs. So, determining anemia at baseline will help to avoid giving drugs that can result in anemia as an adverse effect.

Comment 2. The name has been changed to DEBRE-MARKOS REFERRAL HOSPITAL to Debre-Markos comprehensive specialized hospital, correct it throughout the document.

Author response:

- Thank you for the comment.
- The authors corrected it throughout the document in the revised manuscript.

Abstract:

Comment 3. Spelling and capitalization error

Author response:

- After a through reading and using an online grammar checker, the authors tried to correct the spelling and grammatical errors in the revised manuscript.

Comment 4. Line 22 "ART" makes its long-form.

Author response:

- Thank you, but it is already written in long form at the 'objective' section of the abstract.

Comment 5. page 3 line "had no formal education", if I were you, I prefer to use not attending formal

education over it. Consider it throughout the document.

Author response:

- Thank you, we considered it in the revised manuscript.

Discussion:

The discussion section can be concise more rather than repeat the result.

Author response:

- Thank you. We accepted the comment and tried to make it specific and concise, in the revised manuscript.

Comment 6. The discussion part especially the prevalence should be paraphrased and put the possible justification why the difference happened when it compare to studies conducted in Ethiopia. You didn't reason out why the difference occurred. And also omit unnecessary extra words, Hawassa University Referral Hospital makes it simply South Ethiopia, similarly for others if possible.

Author response:

- We accepted the comment and revised it in the revised manuscript.

Comment 7: Similarly, the current study showed that the odds of being anemic among patients with no formal education was 2.38 times that of college and above educational status (AOR = 2.38; 95% CI: 1.12 - 5.05). Information like this (AOR = 2.38; 95% CI: 1.12 - 5.05) you wrote again in the discussion part, no need of repeating in the discussion once wrote the result part. So, do it for all variables. .

Author response:

- Based on the comments, we removed unnecessary repetitions in the result and discussion section. Comment 8. This information should be cited. "When HIV infection is observed among those with no formal education, the risk of poor nutrition and occurrence of anemia will be double burdened". cite. Line 28, 29.

Author response:

- Ok, we incorporated a citation to this description in the revised manuscript.

Conclusion: would please revise your recommendation based on your finding especially on the modifiable factors also....

Author response:

- Based on the comments, the authors rephrased the conclusion and recommendations based on the findings of this study.

General comment

This literature may offer insights on HIV-infected adults in the study setting. But the following should be addressed before publication.

1. The manuscript is full of grammatical, spelling, and punctuation errors. It should be edited.

Author response:

→ After a thorough reading and using an online grammar checker, the authors corrected the spelling and grammatical errors in the revised manuscript.

2. The discussion part should be paraphrased and possible questions along with citations should be considered.

Author response:

→ Based on the comment, we addressed it in the revised manuscript.

3. Authors should read carefully the author's submission guideline and strictly follow it for all sections of the manuscript.

Author response:

→ Thank you; the authors accepted the recommendation.

VERSION 2 – REVIEW

REVIEWER	Sah, Shiv Purbanchal University, Pharmacy
REVIEW RETURNED	27-Feb-2022

GENERAL COMMENTS	<p>Conclusion: consider including all significant factors associated with anemia, (e.g., baseline CD4, BMI, ambulatory/bedridden)</p> <p>Limitations: the author should acknowledge all limitations with reference to the potential biases in the study.</p> <p>Methods</p> <p>Why did author consider 4% marginal error rather than generally accepted 1% or 5 % or 10%?</p>
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REVIEWER	Bishaw, keralem Debre Markos University, Midwifrey
REVIEW RETURNED	21-Feb-2022

GENERAL COMMENTS	<p>The authors submit a revised and improved version of the manuscript, addressing comments of the reviewers. The responses and corresponding changes are adequate. Additional English language editing would further improve the manuscript.</p> <p>Decision: I accept to be published.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Abstract

Conclusion: consider including all significant factors associated with anemia, (e.g., baseline CD4, BMI, ambulatory/bedridden)

Limitations: the author should acknowledge all limitations with reference to the potential biases in the study.

Authors' response:

- Thank you for the comments.
- The authors included all significant factors associated with anemia in the conclusion section of the abstract.
- The authors tried to list out potential limitations of the study both under the subheading “strength and limitation of the study”, and at the end of the discussion section.

Methods:

Why did the author consider 4% marginal error rather than generally accepted 1% or 5 % or 10%?

Authors' response:

- Actually it is possible to use a marginal error ranging from 1% to 10%, and using a narrow margin of error is advisable. The narrower the margin of error is the larger the sample size will be. But, we didn't use a 1% margin of error in which the sample size became extremely larger that it is costly to collect data from the sample. On the other hand, the acceptable margin of error usually falls between 4% and 8% at the 95% confidence interval. That is why the authors intended to use 4% margin of error.

Reviewer: 2

The authors submit a revised and improved version of the manuscript, addressing the comments of

the reviewers. The responses and corresponding changes are adequate.
Additional English language editing would further improve the manuscript.

Authors' response:

- Thank you for your comments.
- After a repeated reading of the manuscript, the authors corrected a few spelling and editorial problems.