

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Metabolic syndrome among a Ghanaian cohort living with HIV initiated on dolutegravir in a real-world setting: A prospective study.

Authors

Ganu, Vincent; Adu-Gyamfi, Raphael; Mohammed, Abdul Gafaru; Torpey, Kwasi; Kenu, Ernest; Ayisi Addo, Stephen; Agyabeng, Kofi; Odikro, Magdalene Akos; Lartey, Margaret

VERSION 1 - REVIEW

Reviewer	1
Name	Lima, Kledoaldo
Affiliation	Federal University of Pernambuco
Date	30-Dec-2024
COI	None

Metabolic syndrome among a Ghanaian cohort living with HIV initiated on dolutegravir in a real-world setting: A prospective study.

This study determined the relationship between dolutegravir and metabolic syndrome in a cohort of persons living with HIV (PWH) initiating DTG based regimen in Ghana.

1 – Sometimes the word “antiretroviral” is written this way, sometimes as “anti retroviral”. The first one is correct.

Page 7 Line 31: HIV type or HIV subtypes?

Page 8 line 13: “Patients sat in a straight back chair for 15 minutes before blood pressure (BP) was measured on the left upper arm”. Is there a reference for this methodology, that is, did they follow any guidelines from a national or international cardiology society?

Page 8 line 21: “Fasting blood glucose was measured after 12-hour overnight fast with a OneTouch®”. For the measurement of fasting blood glucose, which guideline did this methodology follow? Same question for Lipids measure.

Table 3: It is not necessary to include the meaning of n and % in the footnotes.

Figure 1a: Include in the figure description that the data correspond to the number of MetS at the end of the study.

Page 14 line 3: put the comma before “low”: ... , low High density lipoprotein”.

Page 14 line 16 “participants with underlying diseases had a higher chance of developing metabolic syndrome”

Authors should specify which comorbidities were analyzed in the methodology. This way, the relationship between the two variables will be clearer.

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<b>Reviewer</b>	<b>2</b>
<b>Name</b>	<b>Kaduka, Lydia</b>
<b>Affiliation Research</b>	<b>Kenya Medical Research Institute, Centre for Public Health</b>
<b>Date</b>	<b>09-Jan-2025</b>
<b>COI</b>	<b>None</b>

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Metabolic syndrome among a Ghanaian cohort living with HIV initiated on dolutegravir in a real-world setting: A prospective study.

The paper reports on the increased risk of cardiometabolic disease among PLWHIV on dolutegravir-based regimen. The associations observed are not new, but the prospective nature of the study is a key strength. Below are few minor comments to strengthen the paper.

Abstract

The conclusion can be strengthened by including a recommendation on the importance of addressing central obesity which carried the highest HR. The last sentence in the conclusion is a repeat of the findings. Kindly revise.

Strengths and limitations

Methodological limitations are well described.

Background

The background can be strengthened by including the policy context highlighting e.g. the CVD and HIV burden and policy focus.

Methods

There is the sentence ‘...patients identified with abnormal clinical outcomes (metabolic syndrome or any components of metabolic syndrome) were provided with the necessary appropriate interventions (lifestyle changes and medications’ on Page 7. What were the outcomes and how do they impact the reported findings?

Page 7: Please provide the right units of measurements for weight.

Page 8: Please provide a justification for the number of BP readings vs the recommended norm. Also provide additional information on biochemical measurements – sample processing, measurements, QC etc.

Page 9: Data analysis – kindly provide the actual cut-offs for overweight.

Page 11: Public and patient involvement – one would expect at the very minimum engagement of local stakeholders. Please elaborate how for instance reporting and dissemination were done without any form of engagement.

## Results

Page 14: Table 3 – Kindly correctly label the MetS components e.g. elevated fasting blood glucose, low HDL etc

Kindly make clear in the abstract, results and discussion section the sex difference observed in risk and hazard of developing MetS.

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<b>Reviewer</b>	<b>3</b>
<b>Name</b>	<b>Abdela, Abdurezak</b>
<b>Affiliation</b>	<b>Addis Ababa University College of Health Sciences,</b>
<b>Internal Medicine</b>	
<b>Date</b>	<b>23-Jan-2025</b>
<b>COI</b>	<b>None</b>

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This is a good work that is showing evidence from SubSaharan Africa on Metabolic Syndrome on PWH. It adds to the scientific evidence on MetS.

The strength of this study is the prospective design and the large sample size to look into the incidence of MetS and associated risk factors.

However, the authors need to address the following:

1. Accuracy, clarity, and word count of the abstract
2. Introduction should show the significance of studying metabolic syndrome among HIV patients and the Lipodystrophy correlation with ART.
3. The methodology should be written in a more clearer form ensuring replicability of this study. I. did the study considered to exclude conditions that could lead to development of MetS by themselves and drugs associated with its development during the study period? II. Did HCV Ab and HBSAg testing considered or planned in this study? if not why? III. how feasible is sitting a study participant for 15 minutes in the clinic to wait for BP measurement? IV. comments on laboratory assessments and calculations as on the attached PDF needs to be addressed. V. How are the centers selected and patients load in the centers.

4. improvements needed on the write-up of the result
5. what is the comorbidity identified, it is not clear
6. Table 4, HIV-2 and Abacavir association with incident MetS in the table and in the discussion does not align. Explain/ revise
7. The discussion should show how does the finding compare to African studies
8. The discussion should show how does doltugravir causes MetS and its components
9. Author need to address comments and editorials on the attached document.

The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

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## VERSION 1 - AUTHOR RESPONSE

### REVIEWER 1 COMMENTS:

#### Comment 1:

Sometimes the word “antiretroviral” is written this way, sometimes as “anti retroviral”. The first one is correct.

**Response:** Thank you. The changes to the word have been effected throughout the document to “antiretroviral” as suggested.

#### Comment 2:

Page 7 Line 31: HIV type or HIV subtypes?

**Response:** Thank you. It is HIV type. The types we stated in this study are the HIV-1 and HIV-2. As this was an observational study, sub typing was not requested.

#### Comment 3:

Page 8 line 13: “Patients sat in a straight back chair for 15 minutes before blood pressure (BP) was measured on the left upper arm”. Is there a reference for this methodology, that is, did they follow any guidelines from a national or international cardiology society?

**Response:** Thank you. The reference has been added on page 7 of the manuscript.

#### Comment 4:

Page 8 line 21: “Fasting blood glucose was measured after 12-hour overnight fast with a OneTouch®”. For the measurement of fasting blood glucose, which guideline did this methodology follow? Same question for Lipids measure.

**Response:** Thank you. The references for the statements have been added on page 7 of the manuscript.

#### Comment 5:

Table 3: It is not necessary to include the meaning of n and % in the footnotes.

**Response:** Thank you. These have been deleted as footnotes under table 3 on page 13 of the manuscript.

#### **Comment 6:**

Figure 1a: Include in the figure description that the data correspond to the number of MetS at the end of the study.

**Response:** Thank you. The figure 1a description has been modified to give clarity that the data corresponds to the end of the study.

#### **Comment 7:**

Page 14 line 3: put the comma before “low”: ... , low High density lipoprotein”.

**Response:** Thank you. This has been done as suggested on page 14 of the manuscript.

#### **Comment 8:**

Page 14 line 16 “participants with underlying diseases had a higher chance of developing metabolic syndrome”

Authors should specify which comorbidities were analyzed in the methodology. This way, the relationship between the two variables will be clearer.

**Response:** Thank you. The co-morbidities have been stated as a footnote under table 1 in the revised manuscript.

### **REVIEWER 2 COMMENTS**

#### **Comment 1:**

Abstract

The conclusion can be strengthened by including a recommendation on the importance of addressing central obesity which carried the highest HR. The last sentence in the conclusion is a repeat of the findings. Kindly revise.

**Response:** Thank you. The conclusion section of the abstract has been revised on page 3 of the manuscript to include recommendation at addressing central obesity and the last sentence deleted.

#### **Comment 2:**

Background

The background can be strengthened by including the policy context highlighting e.g. the CVD and HIV burden and policy focus.

**Response:** Thank you. Additional information has been added to the background to include a policy context.

#### **Comment 3:**

Methods

There is the sentence ‘..patients identified with abnormal clinical outcomes (metabolic syndrome or any components of metabolic syndrome) were provided with the necessary appropriate interventions (lifestyle changes and medications’ on Page 7. What were the outcomes and how do they impact the reported findings?

**Response:** Thank you. For the purpose of the outcome of interest (metabolic syndrome (MetS)) in this manuscript, once a patient is identified to have MetS, follow-up ends for that patient or the data is censored for the study, however, patient continues to receive clinical care by the physicians. The study end was the outcome of interest, interventions were not part of the study.

#### **Comment 4:**

Page 7: Please provide the right units of measurements for weight.

**Response:** Thank you. The unit of measurement for weight has been added on page 7 of the manuscript.

**Comment 5:**

Page 8: Please provide a justification for the number of BP readings vs the recommended norm. Also provide additional information on biochemical measurements – sample processing, measurements, QC etc.

**Response:** Thank you. The reference for the BP measurements has been provided. The sample measurements and cut offs have been stated under the data collection and quality assurance sub-sections under the Methods section

**Comment 6:**

Page 9: Data analysis – kindly provide the actual cut-offs for overweight.

**Response:** Thank you. The cut-offs for the various BMI categories including overweight have been stated on page 8 under the “Data Management and analysis” section.

**Comment 7:**

Page 11: Public and patient involvement – one would expect at the very minimum engagement of local stakeholders. Please elaborate how for instance reporting and dissemination were done without any form of engagement.

**Response:** Thank you. The statement under “Public and patient involvement” has been revised to describe the engagement with local stakeholders and dissemination.

**Comment 8:**

Page 14: Table 3 – Kindly correctly label the MetS components e.g. elevated fasting blood glucose, low HDL etc

**Response:** Thank you. The MetS components have been correctly labelled in table 3 on page 14 of the manuscript as suggested.

**Comment 9:**

Kindly make clear in the abstract, results and discussion section the sex difference observed in risk and hazard of developing MetS.

**Response:** Thank you. The sex difference has been stated in the results section of the abstract, in the main results section and also in the 5<sup>th</sup> paragraph of the discussion section on page 18 of the manuscript.

**REVIEWER 3 COMMENTS**

**Comment 1:**

Introduction should show the significance of studying metabolic syndrome among HIV patients and the Lipodystrophy correlation with ART.

**Response:** Thank you. The introduction has been modified in the last 2 paragraphs on page 4 of the manuscript to show the significance of metabolic syndrome and lipodystrophy correlation with ART.

**Comment 2:**

Did the study considered to exclude conditions that could lead to development of MetS by themselves and drugs associated with its development during the study period?

**Response:** Thank you. The study did not exclude individual conditions that could lead to the development of MetS as it not assured that having an individual condition will result in MetS. But these individual conditions were documented at baseline. These patients were followed up to see who developed MetS and who did not. Patients identified with MetS at baseline were excluded from the study. Patients' antiretroviral drugs and any drugs they were taking were documented at baseline and included in the analysis.

**Comment 3:**

Did HCV Ab and HBSAg testing considered or planned in this study? if not why?

**Response:** Thank you. We did not test for HCV Ab or HBSAg in this study. The aim of the observational study was to identify development of MetS among the patients initiating dolutegravir and the testing of HCV Ab and HBSAg in our patients may not necessarily impact the study outcomes. We however did document hepatitis co-morbidity in our patients if present at baseline.

**Comment 4:**

How feasible is sitting a study participant for 15 minutes in the clinic to wait for BP measurement?

**Response:** Thank you. Due to the high number of patients per clinic day and the desire of each patient to be attended to early, most of our patients report early in the morning to the clinic 3-4 hours prior to the start of the clinic. So, the study team engaged them during this waiting period to feasibly conduct the various study procedures.

**Comment 5:**

How are the centers selected and patients load in the centers.

**Response:** Thank you. Additional information has been added on page 5 of the manuscript to address this comment.

**Comment 6:**

What is the comorbidity identified, it is not clear

**Response:** Thank you. The co-morbidities have been stated as a footnote under table 1 in the revised manuscript. These were identified from talking to patients, patient records and measurements at the study sites.

**Comment 7:**

Table 4, HIV-2 and Abacavir association with incident MetS in the table and in the discussion does not align. Explain/ revise

**Response:** Thank you. These have been revised for the information in the results section to match with that in the discussion

**Comment 8:**

The discussion should show how does the finding compare to African studies

**Response:** Thank you. The discussion has been revised to include African studies.

**Comment 9:**

The discussion should show how does dolutegravir causes MetS and its components

**Response:** Thank you. It has been included in the discussion with references of reports of dolutegravir's association with the individual components of MetS hence increasing the risk of MetS in PLHIV.