PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol: Changes in weight, body composition and metabolic parameters after switch to dolutegravir/lamivudine compared to continued treatment with dolutegravir/abacavir/lamivudine for virologically suppressed HIV infection (The AVERTAS trial): A randomized open-label superiority trial in Copenhagen, Denmark
AUTHORS	Pedersen, Karen; Knudsen, Andreas; Møller, Søren; Siebner, Hartwig; Hove, Jens; Gerstoft, Jan; Benfield, Thomas

VERSION 1 – REVIEW

REVIEWER	Cruciani, Mario Center of Community Medicine/HIV Outpatient Clinic
REVIEW RETURNED	04-Jun-2023

GENERAL COMMENTS	The topic is relevant, and the protocol clear and well -written

REVIEWER	Welzen, B.J. van UMC Utrecht
REVIEW RETURNED	06-Jun-2023

GENERAL COMMENTS	This is a study protocol for a RCT to compare metabolic outcomes in PWH continuing DTG/3TC/ABC versus switching to 3TC/DTG. In general, I want to compliment the authors with this comprehensive evaluation of metabolic outcomes in people using ABC. Two minor points came to my mind when reading the study protocol * How do the authors view the potential inter-observer differences when it comes to the imaging outcomes? This also applies for the CAP/Fibroscan, in general these outcomes are highly variable when it comes to the exact numbers (I doubt the reproducibility when it comes to exact numbers, not for classficatiion). * The authors base there sample size on the assumption that DTG/3TC leads to 0 to - 1kg and DTG/ABC/3TC to +2 kg. I would advise to support these statements with literature. Especially the expected weight loss in DTG/3TC is remarkable, as this would insist that participants will gain less weight than the general population annually. As far as I am aware, there are no compelling data that support the anticipated weight change presented here. So, it would be good if the authors provide this in the manuscript.

REVIEWER	Mutagonda, Ritah Muhimbili University of Health and Allied Sciences, Clinical Pharmacy and Pharmacology
REVIEW RETURNED	06-Jun-2023

GENERAL COMMENTS	This is a randomized open-label superiority trial whose aim is to evaluate changes in weight, body composition, and metabolic parameters after the switch to dolutegravir/lamivudine compared to continued treatment with dolutegravir/abacavir/lamivudine for virologically suppressed HIV infection. While it is important to reduce the adverse events/ toxicities related to the use of ART, the primary goal of ART use in HIV patients is to suppress patients' viral load. To my knowledge, most countries are using triple therapy regimens despite the fact that there is current evidence supporting the use of dual therapy. Based on this, in the introduction, it will be more informative to have a paragraph to discuss the use of dual therapy in HIV management and give references to previous studies which have done such work. Or if this is already implemented elsewhere, then a reference is required. Moreover, add information to support why this study prefers to use DTG and 3TC and not other dual ART combinations. More study limitations should be considered, such as loss to follow, suboptimal adherence to the ART regime, and other factors which can cause changes in study variables, including weight which could be non-related to the regime, the complication of non-blinding trials and include the mitigation plans to the limitations. More references are required in support of dual therapy use and studies that support the proposed combination. Cite this study, 'Among NRTIs, abacavir and tenofovir alafenamide (TAF) were associated with more weight gain than tenofovir disoproxil fumarate (TDF) or zidovudine. Is BMI, not an important variable to consider in either enrolling or not? Will you enroll underweight patients? Will you consider recording patients' diet, physical activities, and other variables which could interfere with your outcome of interest? It is indicated that participants will be withdrawn in case of viral rebound or in any other case of compromised participants' safety assessed by the investigator. Add information on how the study will take care of such participants. For those who will have a rebound, what will happen?? Or, in case they get serious adverse events during the study period, how will they be handled besides reporting? There should be clarifications on how the team will take responsibility for referring them for care or managing unforeseen events. In data analysis: Since most variables are collected on weeks 1, 24, and 48, it will also be useful to compare the trend which will be observed between the two groups besides reporting mean/ median change.

REVIEWER	Rusconi, Stefano Universita degli Studi di Milano, DIBIC Luigi Sacco, Infectious Diseases Unit
REVIEW RETURNED	09-Jun-2023

GENERAL COMMENTS	The study protocol is well written and addresses an important clinical question, which is often forgotten in daily practice. The only major concern I have is about the sample size. The abstract indicates 84 subjects who will be randomized 1:2 (28+56) into the 2 study arms. At page 13, the sample size determination is not as specific as in the abstract. I am in favor of keeping the 90% power estimation, which indicates 95 PLWH to be safe, and report it everywhere in the study protocol.

REVIEWER	Assoumou, Lambert INSERM, IPLESP
REVIEW RETURNED	10-Jun-2023

GENERAL COMMENTS	The AVERTAS study is a randomized, open-label, parallel superiority trial designed to demonstrate the superiority of switching to dolutegravir/lamivudine versus continuing dolutegravir/abacavir/lamivudine treatment with regard to changes in weight, body composition and metabolic parameters in virologically suppressed HIV-infected individuals. The study has already been approved by the Danish Capital Region Ethics Committee (H-20011433), its medicines agency (EudraCT No. 2019-004999-19), its regional data protection center (P-2020-207), and registered on clinicaltrials.gov (NCT04904406). However, recruitment for the study has not yet started. The study objectives were clearly presented and the study design and interventions were clearly specified. However, I have a few concerns that need to be addressed. 1. Eligibility criteria. The authors must recruit participants with a BMI≥25kg/m2, the population with a higher risk of metabolic syndrome, diabetes, hypertension and dyslipidemia, and with a risk of CVD, in order to able to see the effect of intervention if it exists. 2. Follow-up visits I suggest using day 0 for the baseline visit, as week 1 is confusing. Participants will be recruited from the infectious disease departments of two Danish hospitals, but follow-up visits and data collection will be carried out at a single hospital. The authors should explain whether this is their usual operation and, if not, why patients cannot be followed up at their recruiting center in this study. 3. Adherence The author stated that « adherence will be monitored by measurements of plasma HIV-RNA viral load at baseline, weeks 4 (2DR group only), 24 and 48. Virological failure defined as two consecutive viral loads > 50 copies/ml with an interval of 14 to 30 days will lead to immediate withdrawal from the study ». It is preferable for viral plasma to have been measured at the same times for all participants in both groups, including at the week 4 visit, so as not to overestimate the rate of virological failure in the 2DR compared with the 3DR group. Furthermore, in case of virological failure, it is preferable not to withdraw participants from the study, but only to change treatment and follow participants until the end of the study in order to collect

	viral load data after the change of treatment to find out whether the viral load has been suppressed again. In addition, in case of virological failure, a drug resistance test should be performed to determine whether participants' viruses have selected drug resistance mutations, and a drug concentration should be performed to assess participants' adherence. 4. CMRI Substudy endpoints In the CMRI substudy, the primary outcome is not a composite endpoint but rather a multiple endpoints, since 4 differents endpoints have been defined. For a multiple endpoints study, the analysis plan should describe how the endpoints are tested, including the order of testing and the alpha level applied to each specific test. For cardiac MRI, it's best to use the same abbreviation throughout the protocol. Sometimes it's CMR, sometimes CMRI. 5. Sample size calculation The authors should explain the assumptions made in calculating the sample size and explain how a 2 kg difference between treatment groups is clinically relevant and how this could lead to a reduction in CVD risk. The authors should replace the term variance by standard deviation. The sample size estimated on the basis of the assumptions made is sufficient to achieve the study objectives. However, given the 2:1 ratio, 96 subjects should be recruited instead of 95. There is a discrepancy with the abstract, which states that 84 PLWH will be recruited. 6. Data collection It is also preferable for safety data to have been collected at the same times for all participants in both groups, including at the week 4 visit, so as not to overestimate the rate adverse events in the 2DR compared with the 3DR group. 7. Cardiac MRI Sub Study It is unclear how randomization will be carried out in the MRI substudy, since randomization will be stratified by center and sex only, and not by substudy participation. Authors should explain how participants will be randomized in the MRI sub-study. The authors must also explain how the 20 HIV-uninfected controls will be selected. I think it's important that controls are matched to HIV-positive patients on sex and age. 8. Statistical analyses The authors must specify that only randomized participants will be included in the intention-to-treat analysis and also indicate how randomized participants who did not receive the study intervention will be analyzed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Mario Cruciani, Center of Community Medicine/HIV Outpatient Clinic
Comments to the Author:
The topic is relevant, and the protocol clear and well -written
Reply: Thank you for your kind words.

Reviewer: 2
Dr. B.J. van Welzen, UMC Utrecht
Comments to the Author:
This is a study protocol for a RCT to compare metabolic outcomes in PWH continuing DTG/3TC/ABC versus switching to 3TC/DTG. In general, I want to compliment the authors with this comprehensive evaluation of metabolic outcomes in people using ABC.

Reply: Thank you very much.

1) Two minor points came to my mind when reading the study protocol
How do the authors view the potential inter-observer differences when it comes to the imaging outcomes? This also applies for the CAP/Fibroscan, in general these outcomes are highly variable when it comes to the exact numbers (I doubt the reproducibility when it comes to exact numbers, not for classification).
Reply: Thank you very much for this comment. We agree that there is a risk of inter- and intra-observer dif-ferences in transient liver elastography/CAP, and for the cIMT, DXA, CT and MRI as well. To minimize this risk, we primarily use the primary investigator as the examiner fibroscan and cIMT. In the absence of the primary investigator, we have two trained study personnel who can replace them. Additionally, all scans including fibroscan, cIMT, DXA, CT and MRI will be performed on the same scanner, which will be calibrated according to the manufacturer's recommendations. MR scans will be read by the PI and Dr. Hove. CT scans will be read blinded by a single radiographer. DXA scans are read by software provided by the manufacturer.
In the data analysis, we will use the baseline transient liver elastography/CAP, DXA, CT and MR findings as a contributor to describe the overall health of the cohort. When examining the follow-up scans, our plan is not to compare numeric changes, but rather to evaluate the number of participants with significant progression or regression from baseline. In terms of elastography/CAP we will evaluate participants crossing the thresh-old for developing fibrosis/steatosis or progressing in existing fibrosis/steatosis from the baseline. We have redefined the outcome: “Development of liver fibrosis or progression of existing liver fibrosis. Significant liver fibrosis as LSM ≥7.6 kPa”, please see manuscript. Line: 174

2) The authors base their sample size on the assumption that DTG/3TC leads to 0 to - 1kg and DTG/ABC/3TC to +2 kg. I would advise to support these statements with literature. Especially the expected weight loss in DTG/3TC is remarkable, as this would insist that participants will gain less weight than the general population annually. As far as I am aware, there are no compelling data that support the anticipated weight change pre-sented here. So, it would be good if the authors provide this in the manuscript.
Reply: Thank you for this comment. The literature on switching to or from abacavir is limited. Our hypothe-sis regarding weight change is based on a meta-analysis that includes pooled weight data from 8 randomized controlled trials (RCTs) conducted on treatment-naïve people living with HIV (PLWH) after initiating an-tiretroviral therapy (ART) (Sax et al. CID 2020:71:1380-89). The analysis indicated that individuals starting ABC gained 2 kg over 48 weeks compared to 3 kg for individuals initiating TAF. The weight gain continued to 96 weeks.
We have added the following sentence to the Sample Size section: The hypothesis on weight change in this study relies on a meta-analysis with pooled weight data from 8 RCTs of treatment naïve PLWH. In the meta-analysis mean weight gain with abacavir (ABC) was 3.08 kg (95% CI, 2.36–3.81) in 96 weeks. In the same meta-analysis dolutegravir lead to a mean weight gain on DTG, 4.07 kg [95% CI, 3.51–4.62] (1).
Since dolutegravir treatment continues in both study arms, we hypothesize the possible contribution from dolutegravir to weight gain will be equal in the groups. We speculate that that the absence of abacavir in the intervention (2DR) group can lead to a small weight loss in. Anticipated annual weight

change in the two groups are: DTG/3TC + 0 to -1 kg and DTG/ABC/3TC +2 kg. Sample size is estimated by Student's unpaired t-test. Patients will be randomized 2:1 to intervention or control. Line 215-229

Reviewer: 3
Dr. Ritah Mutagonda, Muhimbili University of Health and Allied Sciences
Comments to the Author:
This is a randomized open-label superiority trial whose aim is to evaluate changes in weight, body composi-tion, and metabolic parameters after the switch to dolutegravir/lamivudine compared to continued treat-ment with dolutegravir/abacavir/lamivudine for virologically suppressed HIV infection. While it is important to reduce the adverse events/ toxicities related to the use of ART, the primary goal of ART use in HIV patients is to suppress patients' viral load. To my knowledge, most countries are using triple therapy regimens despite the fact that there is current evidence supporting the use of dual therapy.

1) Based on this, in the introduction, it will be more informative to have a paragraph to discuss the use of dual therapy in HIV management and give references to previous studies which have done such work. Or if this is already implemented elsewhere, then a reference is required. Moreover, add information to support why this study prefers to use DTG and 3TC and no other dual ART combinations.
Reply: Thank you for this comment. We have chosen the combination of DTG/3TC because this regimen has been extensively investigated in large randomized controlled trials (RCTs), demonstrating non-inferiority to three-drug regimens. Furthermore, the use of DTG/3TC is recommended in the EACS Guidelines (v11.1) and in the IAS-USA guidelines for treatment-naïve people living with HIV (PLWH) initiating therapy and as a switch option in virally suppressed PLWH (2,3) . Two studies demonstrated ongoing viral suppression comparable to continued 3-drug treatment, without evidence of loss of virologic control (4,5).
By maintaining DTG/3TC in both treatment arms, we can specifically study the effects of abacavir, which is our primary reason for choosing this combination. To address this in more detail, we have added a paragraph to the introduction with relevant references. Line: 80-86

2) More study limitations should be considered, such as loss to follow, suboptimal adherence to the ART regime, and other factors which can cause changes in study variables, including weight which could be non-related to the regime, the complication of non-blinding trials and include the mitigation plans to the limita-tions.
Reply: Thank you for this very relevant perspective. The limitations are elaborated on in a new Limitation section added to the manuscript Line: 423-434, and a section about Loss To Follow-up. Line: 346-349

3) More references are required in support of dual therapy use and studies that support the proposed com-bination.
Reply: I have added references to the new paragraph in the introduction mentioned above. Line: 80-86

4) Cite this study, 'Among NRTIs, abacavir and tenofovir alafenamide (TAF) were associated with more weight gain than tenofovir disoproxil fumarate (TDF) or zidovudine'.
Reply: Thank you for clarifying. I have moved the reference to the end of the sentence mentioned. Line: 93

5. Is BMI, not an important variable to consider in either enrolling or not? Will you enroll underweight pa-tients?

Reply: We have decided to include participants without any restrictions on baseline weight to ensure the generalizability of our results to the broader HIV population. Additionally, it would be interesting to conduct a subgroup analysis during data analysis to examine whether baseline weight influences the primary outcome.

6. Will you consider recording patients' diet, physical activities, and other variables which could interfere with your outcome of interest?
Reply: We have had discussions regarding this matter, but ultimately, we made the decision not to include such recordings to maximize the feasibility of the study for the participants. However, participants do receive a questionnaire at week 24 and week 48, where we inquire about any changes in their dietary habits or activ-ity levels since their last visit. We trust that the randomization process will ensure an equal distribution of these factors between the two study arms.
7. It is indicated that participants will be withdrawn in case of viral rebound or in any other case of compro-mised participants' safety assessed by the investigator. Add information on how the study will take care of such participants. For those who will have a rebound, what will happen?? Or, in case they get serious ad-verse events during the study period, how will they be handled besides reporting? There should be clarifica-tions on how the team will take responsibility for referring them for care or managing unforeseen events.
Reply: Thank you for this comment. Any case of withdrawal will result in an immediate visit, where the study participant will be offered resistance test, and be assigned to a new suppressive HIV regimen. This will be managed by the study team and the participants primary healthcare provider, who will be involved in the decision and further monitoring of viral load and participants. Participants withdrawn from the study will be included in the intention to treat analysis these details have been added to the manuscript. Line: 134-141

8. In data analysis: Since most variables are collected on weeks 1, 24, and 48, it will also be useful to com-pare the trend which will be observed between the two groups besides reporting mean/ median change.
Reply: Thank you for your very useful suggestion. We have discussed this matter with a statistician, who recommended using a linear mixed model that incorporates data from both week 24 and week 48 for the analysis of the primary outcome. This approach allows us to account for the longitudinal nature of the data and maximize the use of available information. We have added this to the Statistical Methods section. Line: 337-341 and in the abstract line 47.

Reviewer: 4
Prof. Stefano Rusconi, Universita degli Studi di Milano
Comments to the Author:
The study protocol is well written and addresses an important clinical question, which is often forgotten in daily practice.
The only major concern I have is about the sample size.
The abstract indicates 84 subjects who will be randomized 1:2 (28+56) into the 2 study arms. At page 13, the sample size determination is not as specific as in the abstract.
I am in favor of keeping the 90% power estimation, which indicates 95 PLWH to be safe, and report it every-where in the study protocol.
Reply: Thank you for bringing up the issue of the sample size discrepancy between the abstract and the manuscript. The study has been powered with 80% based on our decision to close study inclusion. It is im-portant to note that the eligible participant pool for the study is limited due to the relatively small population of people living with HIV (PLWH) in Denmark. Additionally, three centers withdraw their participation in the study due to the COVID-19 pandemic. Despite our efforts, we were unable to recruit additional participants, leading us to make the decision to terminate study inclusion. Line: 215-229

Reviewer: 5
Dr. Lambert Assoumou, INSERM
Comments to the Author:
The AVERTAS study is a randomized, open-label, parallel superiority trial designed to demonstrate the superi-ority of switching to dolutegravir/lamivudine versus continuing dolutegravir/abacavir/lamivudine treatment with regard to changes in weight, body composition and metabolic parameters in virologically suppressed HIV-infected individuals.
The study has already been approved by the Danish Capital Region Ethics Committee (H-20011433), its med-icines agency (EudraCT No. 2019-004999-19), its regional data protection center (P-2020-207), and regis-tered on clinicaltrials.gov (NCT04904406). However, recruitment for the study has not yet started.
The study objectives were clearly presented and the study design and interventions were clearly specified. However, I have a few concerns that need to be addressed.

1. Eligibility criteria.
The authors must recruit participants with a BMI≥25kg/m2, the population with a higher risk of metabolic syndrome, diabetes, hypertension, and dyslipidemia, and with a risk of CVD, to able to see the effect of in-tervention if it exists.
Reply: Thank you for providing this pertinent suggestion. We have decided against making baseline weight an inclusion criterion for several reasons. First, we aim to ensure the generalizability of our results to the broader HIV population, which would be limited if we imposed strict weight criteria. Additionally, implement-ing such criteria could significantly reduce the pool of eligible candidates, potentially hindering our ability to achieve the planned sample size for the study. We know for the COCOMO study that approximately half of individuals on INSTI in the Copenhagen area have a BMI > 25 (6).

2. Follow-up visits
I suggest using day 0 for the baseline visit, as week 1 is confusing.
Reply: I have change “Week1” to Day O as suggested I the manuscript and figure/tables.

Participants will be recruited from the infectious disease departments of two Danish hospitals, but follow-up visits and data collection will be carried out at a single hospital. The authors should explain whether this is their usual operation and, if not, why patients cannot be followed up at their recruiting center in this study.
Reply: We acknowledge that it would have been more convenient for the participants if the study visits could have been conducted at their local hospital, which was initially the plan. However, due to the unavaila-bility of study personnel and the required study equipment (such as DEXA-scan, fibro-scan, CT-scan, etc.) at Rigshospitalet, we were unable to establish the necessary infrastructure at that location.
As both study sites are located within the same area with just a 10 km distance between them, we made the decision to conduct all study visits and examinations at a single study site. One of the advantages of this ap-proach is that it helps limit inter-observer variability, ensuring more consistent and reliable results.

3. Adherence
The author stated that « adherence will be monitored by measurements of plasma HIV-RNA viral load at baseline, weeks 4 (2DR group only), 24 and 48.
Virological failure defined as two consecutive viral loads > 50 copies/ml with an interval of 14 to 30 days will lead to immediate withdrawal from the study ».

It is preferable for viral plasma to have been measured at the same times for all participants in both groups, including at the week 4 visit, so as not to overestimate the rate of virological failure in the 2DR compared with the 3DR group.
Furthermore, in case of virological failure, it is preferable not to withdraw participants from the study, but only to change treatment and follow participants until the end of the study in order to collect viral load data after the change of treatment to find out whether the viral load has been suppressed again. In addition, in case of virological failure, a drug resistance test should be performed to determine whether participants' viruses have selected drug resistance mutations, and a drug concentration should be performed to assess participants' adherence.
Reply: Thank you for your comment. The measurement of HIV-RNA at week 4 in the 2DR group serves as an additional safety measure due to the medication switch in this group. Since the 3DR group continues with their usual treatment regimen, we have decided not to measure HIV-RNA in this group at week 4. This deci-sion is based on the expectation of no risk of virological failure in the 3DR group, and it also allows us to avoid an extra visit for these participants. Cases of virological failure will be calculated at week 48.
Regarding the withdrawal process, we agree with your suggestion. The study will be analyzed according to the intention-to-treat and per-protocol principles. I have provided a detailed description of the procedure in the manuscript. Line: 134-141
4. CMRI Substudy endpoints
In the CMRI substudy, the primary outcome is not a composite endpoint but rather multiple endpoints, since 4 differents endpoints have been defined.
For a multiple endpoints study, the analysis plan should describe how the endpoints are tested, including the order of testing and the alpha level applied to each specific test.
For cardiac MRI, it's best to use the same abbreviation throughout the protocol. Sometimes it's CMR, some-times CMRI.
Reply: The CMRI substudy is an explorative study which is why we haven’t specified the endpoints in more details. The study is inspired by two similar studies who included approximately the same number of subject (7,8). We rephrased the composite primary outcome for CMRI. Line 198-211

5. Sample size calculation
The authors should explain the assumptions made in calculating the sample size and explain how a 2 kg dif-ference between treatment groups is clinically relevant and how this could lead to a reduction in CVD risk. The authors should replace the term variance by standard deviation.
The sample size estimated on the basis of the assumptions made is sufficient to achieve the study objectives. However, given the 2:1 ratio, 96 subjects should be recruited instead of 95. There is a discrepancy with the abstract, which states that 84 PLWH will be recruited.
Reply: Thank you for bringing up the issue of the sample size discrepancy between the abstract and the manuscript. The study has been powered with 80% based on our decision to close study inclusion. It is im-portant to note that the eligible participant pool for the study is limited due to the relatively small population of people living with HIV (PLWH) in Denmark. Despite our efforts, we were unable to recruit additional partic-ipants, leading us to make the decision to terminate study inclusion. We appreciate you pointing out the error in using "variance" instead of "standard deviation." We have cor-rected this in manuscript. Line: 45 and 226

6. Data collection
It is also preferable for safety data to have been collected at the same times for all participants in both groups, including at the week 4 visit, so as not to overestimate the rate adverse events in the 2DR compared with the 3DR group.
Reply: We measure HIV-RNA at week 4 specifically in the 2DR group as an additional safety measurement due to the medication switch in this group. In contrast, the 3DR group continues with their usual treatment regimen, and we have decided not to measure HIV-RNA in this group at week 4. This decision is based on the expectation that there is no significant risk of virological failure in the

3DR group at that time point. Addition-ally, by avoiding the measurement at week 4 in the 3DR group, we can spare them an extra visit. Cases of virological failure will be calculated at week 48 for both study groups.

7. Cardiac MRI Sub Study
It is unclear how randomization will be carried out in the MRI sub-study, since randomization will be strati-fied by center and sex only, and not by sub-study participation. Authors should explain how participants will be randomized in the MRI sub-study. The authors must also explain how the 20 HIV-uninfected controls will be selected. I think it's important that controls are matched to HIV-positive patients on sex and age.
Reply: In the cardiac MRI sub-study, there is no randomization process (specified in line 307). Participants in the AVERTAS study are offered the opportunity to participate in the MRI sub-study after undergoing ran-domization in the AVERTAS study. The decision to offer participation in the MRI sub-study separately is based on several factors. Not all participants may be suitable for MRI due to various reasons, such as contraindica-tions or their willingness/ability to allocate additional time for the scan. Furthermore, access to the scanner is limited to outside normal working hours because the scans are performed at a hospital where clinical scans take place during the daytime. By making MRI suitability an inclusion criterion, it would significantly restrict recruitment for the AVERTAS main study. We aim to recruit 20 participants from each treatment arm for the MRI sub-study. As for the 20 HIV-uninfected controls, they are recruited from a Danish website for voluntary healthy controls and through recruitment posters at the study hospital. The goal is to match these control participants as closely as possi-ble in terms of age and sex.

8. Statistical analyses
The authors must specify that only randomized participants will be included in the intention-to-treat analysis and indicate how randomized participants who did not receive the study intervention will be analyzed.
Reply: Criteria for both intention-to-treat analysis and per-protocol analysis has been specified in the manu-script. Line: 321-330

Reviewer: 1
Competing interests of Reviewer: none to declare

Reviewer: 2
Competing interests of Reviewer: None

Reviewer: 3
Competing interests of Reviewer: None

Reviewer: 4
Competing interests of Reviewer: None.

Reviewer: 5
Competing interests of Reviewer: None to declare

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8. Yan C, Li R, Guo X, Yu H, Li W, Li W, m.fl. Cardiac Involvement in Human Immunodeficiency Virus Infected Patients: An Observational Cardiac Magnetic Resonance Study. Front Cardiovasc Med. 2021;8:756162.

VERSION 2 – REVIEW

REVIEWER	Welzen, B.J. van UMC Utrecht
REVIEW RETURNED	13-Jul-2023

GENERAL COMMENTS	Thank you for your updates, I have no additional comments.

REVIEWER	Rusconi, Stefano Universita degli Studi di Milano, DIBIC Luigi Sacco, Infectious Diseases Unit
REVIEW RETURNED	13-Jul-2023

GENERAL COMMENTS	I understand the difficulties to involve other clinical centers and thus I agree with the decision of keeping the study power at 80%.