You asked: 1. The Abstract needs to be revised, please add strong background knowledge.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

Cardiovascular disease (CVD) has become one of the commonest causes of comorbidity and mortality among People living with HIV (PLWH) on antiretroviral therapy (ART). Nearly 50% of PLWH are likely to have an increased risk of developing CVD, including coronary heart disease, cerebrovascular disease, peripheral artery disease and aortic atherosclerosis. Aside from the common risk factors, HIV infection itself and side effects of antiretroviral therapy contribute ~~in~~to the pathophysiology of this entity. Potential non-pharmacological therapies are currently being tested worldwide for this purpose, including eating patterns such as Intermittent fasting (InF). InF~~Intermittent fasting~~ is a widespread practice gaining high level of interest in the scientific community due to its potential benefits such as improvement in serum lipids and lipoproteins, blood pressure (BP), platelet-derived growth factor AB (PDGF-AB), and carotid artery intima-media thickness (IMT) among others~~and~~ cardiovascular benefits. This review will focus on exploring the potential role of intermittent fasting as a non-pharmacological and cost-effective strategy in decreasing the burden of cardiovascular diseases among HIV patients on ART due to its intrinsic properties improving the main cardiovascular risk factors and modulating inflammatory pathways related to endothelial dysfunction, lipid peroxidation and aging. Intermittent fasting regimens need to be tested in clinical trials as an important, cost-effective, and revolutionary coadjutant of ART in the fight against the increased prevalence of cardiovascular disease in PLWH.

You asked: 2. Page 3: "Intermittent Fasting is a widespread practice…" Intermittent fasting of how many hours/days?

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

Core Tip: Intermittent Fasting of 14-18 hours/day (Time Restrictive) or 2-days fast/5-day fed (Alternate Day) is a widespread practice that has aroused great interest in the scientific community. Many reviews have postulated the potential benefits of intermittent fasting in different diseases. It has been shown to improve weight loss, cardiovascular effects, and glucose metabolism. It consists of periods of strict caloric restriction alternating with variable feeding schedules. Hence, we aimed to present the first literature review regarding the role of intermittent fasting as a potential nonpharmacological and cost-effective strategy in decreasing the burden of cardiovascular disease among HIV patients on antiretroviral therapy.

You asked: 3. Page 4: "The 2019 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) reported that 48 percent of persons ≥ 20 years of age in the United States have some form of Cardiovascular Disease (CVD)." Please enlist few types of CVD that are most abundant in the USA.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

The 2019 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) reported that 48 percent of persons ≥ 20 years of age in the United States have some form of Cardiovascular Disease (CVD)[1]. In USA, roughly 16.3 million of people have Coronary Heart Disease (CHD), secondly with approximately 7 million of Americans had at least one episode of stroke. Moreover, almost 82.6 million US citizens present at least one or more forms of CVD, which encompasses four major areas: ~~coronary heart disease (~~CHD~~)~~, cerebrovascular disease, peripheral artery disease and aortic atherosclerosis as well as thoracic or abdominal aortic aneurysm[1].

You asked: 4. Page 4: It is recommended to add updated epidemiology of CVD in the united stated.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

-.Current data suggest that every 36 seconds Americans die from CVD, accounting for 1 in 4 deaths in the country. Furthermore, this illness i~~I~~t is characterized as a chronic low grade inflammatory condition that has atherosclerosis as its most common pathological substrate. In People living with HIV (PLWH), CVD risk has been shown to be 50% higher than in uninfected individuals[2]. Aside from the well-known risk factors for CVD such as smoking, changes in lipid profile and insulin resistance; HIV infection itself and some side effects of antiretroviral therapy (ART), especially protease inhibitors, are further contributing factors among this population[3-5]. In that sense, Cardiovascular disease (CVD) has become one of the commonest causes of death in the PLWH under treatment with virological and immunological control[6].

You asked: 5. Page 4: "Intermittent fasting (IF), consisting of periods of strict calorie restriction (CR)..." On which counts IF is the optimal choice because some drugs also showed good results.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

It is important to remark that intermittent fasting does not necessarily involve limiting the total number of daily calories as in a typical caloric restriction regimen; therefore, it may be implemented in pathologies that do not require a reduction in the number of calories ingested. We agree with this suggestion, however there is not broad data available in the literature.

You asked: 6. Page 4, The whole introduction section is general. Authors are advised to revise the introduction section carefully and add more data to make an association between each paragraph to support the problem statement. It is advised to add literature in the introduction section to create a research gap.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

Intermittent fasting (IF), consisting of periods of strict calorie restriction (CR) alternating with variable feeding schedules, is a widespread practice gaining high level of interest in the scientific community and the media followed by millions of people around the globe[7,

8]. Different regimens of intermittent fasting have been reported in the literature with two of them being the most notorious: Time Restrictive Feeding (TRF), where the fasting period is about 14-18 hours/day, and Alternate Day Fasting, traditionally 2 day fast/5 day fed[7, 9, 10]. It is important to remark that intermittent fasting does not necessarily involve limiting the total number of daily calories as in a typical caloric restriction regimen; therefore, it may be implemented in pathologies that do not require a reduction in the number of calories ingested[10]. Multiple potential benefits of IF have been described such as improvement in glucose metabolism and insulin sensitivity, weight loss, delayed aging, beneficial neurocognitive effects and cardiovascular benefits[10,11]. Additional metabolic benefits are still being investigated with promising paths for future research[10]. To the best of our knowledge, there is a large literature on the benefits of InF in cardiovascular disease, but none on the particular case of PLWH. Therefore, w~~W~~e aimed to explore the potential role of intermittent fasting as a non-pharmacological and cost-effective strategy in decreasing the burden of cardiovascular diseases among HIV patients on ART due to its intrinsic properties improving the main CVD risk factors and modulating the systemic inflammatory state.

You asked: 7. Page 5: What is the novelty of the present study?

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes (red) :

To the best of our knowledge, there is a large literature on the benefits of InF in cardiovascular disease, but none on the particular case of PLWH. →This is the novelty of our study.

You asked: 8. Page 5: "High blood pressure, hyperlipidemia, metabolic syndrome, diabetes, obesity, and smoking are some of the clinical characteristics of HIV patients with or without ART that contribute to these rates." This is a repeated data, already present in the introduction section.

Answer to the reviewer: We agree with the reviewer's comment. Therefore, we decided to move out the repeated sentence.

People living with HIV are almost 38 million distributed throughout all the continents[12]. PLWH on ART are disproportionately affected by an increase in the incidence of CVD compared with age-matched HIV-negative controls[2]. To date, it is known that people living with HIV present more than twice increased risk of cardiovascular disease in general[2,12]. ~~High blood pressure, hyperlipidemia, metabolic syndrome, diabetes, obesity, and smoking are some of the clinical characteristics of HIV patients with or without ART that contribute to these rates.~~ Lately, there has been an increase prevalence of smoking in the HIV population

which could be explained by a variety of factors including anxiety and other mental illnesses, alcohol and illicit drug use, sociodemographic stressors due to social discrimination, increased risk-taking behaviors and impulsiveness, or false perception of smoking risks[13, 14].

You asked: 9. Page 5: "Epidemiology" This heading is not well explained, no countrywide epidemiology is presented. Authors are advised to revise this section and add a figure/table of the epidemiology of CVD and HIV.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes:

People living with HIV are almost 38 million distributed throughout all the continents[12]. PLWH on ART are disproportionately affected by an increase in the incidence of CVD compared with age-matched HIV-negative controls[2]. To date, it is known that people living with HIV present more than twice increased risk of cardiovascular disease in general[2,12]. For instance, from 1999 to 2013 the rate of deaths in the US caused by CVD in PLWH increased from 2% to almost 5%. Furthermore, CVD is one of the main non-AIDS- related complications, since between 9% and 20% of PLWH in developed countries are at moderate to high risk of suffering a myocardial infarction (MI). Lately, there has been an increase prevalence of smoking in the HIV population which could be explained by a variety of factors including anxiety and other mental illnesses, alcohol and illicit drug use, sociodemographic stressors due to social discrimination, increased risk-taking behaviors and impulsiveness, or false perception of smoking risks[13, 14]. It was seen in a Danish study that HIV smokers had a higher relative risk of suffering a Myocardial infarction (MI) compared to negative controls[15]. Furthermore, some of the ART regimens that include protease inhibitors (PIs) can also contribute to the increase in the incidence of CVD[5]. On a different note, the fact that the Framingham Score underestimates the MI risk in PLWH, which was clearly observed in a cohort study, complicates even more the early detection and treatment[16]. The intensity of CVD in HIV patients (measured objectively as Intimal Media Thickness = IMT) may also be directly related to the HIV duration, meaning that the arterial damage is most likely accumulative over the years[17]. The accelerated atherosclerosis formation is thought to be independent of viral replication (at least in plasma) and multifactorial[18-22] being the microbial translocation at the level of the Gut-mucosa one of the main culprits and generators of chronic inflammation[17, 23-26].

You asked: 10. It is recommended to add data in tabular form for the best representation of the effect of IF on CVD with HIV. (e.g., Study type, No. of patients, clinical effect, mechanism, etc.).

Answer to the reviewer: We agree with this suggestion, nonetheless there is a scarce of these types of studies. To the best of our knowledge, there are no previous clinical trials and cohort's studies that demonstrated the potential clinical effects of IF on CVD in PLWH.

You asked: 11. It is recommended to add the mechanistic figures of IF on CVD both in direct and indirect mechanisms that how IF help to reduce CVD and what is the main mechanism behind it.

Answer to the reviewer: We agree with the reviewer's comment, and we have added a new figure to explain a little bit more about its potential mechanisms.

You asked: 12. The conclusion section lacks future recommendations and should be revised critically.

Answer to the reviewer: We agree with the reviewer's comment, and we have added the beneath track changes:

: The burden of cardiovascular diseases among HIV patients on ART is continuously growing. Intermittent fasting, through direct and indirect mechanisms, could play a role in the management and prevention of CVD among PLWH on ART. If these concepts are proven to be true in future clinical trials, IF could be considered as an extremely important, cost-effective, and revolutionary coadjutant of ART in the fight against the increased prevalence of CVD in PLWH which could, in turn, improve survival, decrease CV clinical events, and improve quality of life. Therefore, we recommend further longitudinal and experimental studies to ensure the safety, efficacy and effectiveness of IF on CVD among PLWH.

You asked: 13. Authors are advised to proofread the whole manuscript to overcome grammatical mistakes.

Answer to the reviewer: We agree with the reviewer's comment, therefore

the manuscript will be sent to a native speaker for proofreading.

You asked: 14. Authors are advised to add a list of abbreviations

Answer to the reviewer: We agree with the reviewer's comment,

an Appendix with the list of abbreviations will be and uploaded to the journal.

You asked: 15. The figures need proper interpretation and appropriate captions.

Answer to the reviewer: We agree with the reviewer's comment, therefore

the figures were rearranged according to this suggestion.

You asked: 16. The headings and subheadings need to be revised.

Answer to the reviewer:

We partially agree with this suggestion, but we find convenient to not change the heading and subheadings.

You asked: 17. Most of the references are old and not from prestigious journals, please revise them.

Answer to the reviewer: We agree with the reviewer's comment, therefore

new references have been add from prestigious journals.