**UNIVERSIDAD PERUANA DE CIENCIAS APLICADAS**

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# Association between the use of protease inhibitors in Highly Active Antiretroviral Therapy (HAART) and incidence of metabolic syndrome in HIV-infected patients: A systematic review and meta-analysis

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# Abstract

**Introduction:** Since its introduction, Highly Active Antiretroviral Treatment (HAART) has been shown to prolong the life expectancy of HIV-infected patients. HIV and HAART, especially protease inhibitors (PIs), have been associated with the occurrence of Metabolic Syndrome (MS). The objective of this systematic review and meta-analysis was to determine whether there is an association between the use of PIs and the incidence of MS in HIV-infected patients.

**Methods:** A comprehensive search (including databases such as MEDLINE/PubMed, CENTRAL, LILACS and EMBASE) was performed. Observational studies published until November 2015 were included. Inclusion criteria for primary studies were: study population comprised HIV-infected patients aged 18 years or older and who were receiving HAART; patients assessed according to their use of PIs; DM as defined by the primary study. Heterogeneity was assessed and a pooled analysis was performed using a random-effects model.

**Results:** 3 articles met the inclusion criteria, describing 586 HIV patients. Use of PIs was associated with the development of MS (RR: 2.11; 95% CI 1.28 to 3.48; $Chi^2$:0.04, $I^2$: 0%; p-value 0.003).

**Conclusion:** Use of PIs in HIV-infected patients is associated with an increased risk of MS. These findings are of relevance for future public policy because it will increase the interest in screening and prevention of MS in an expanding population.



**Keywords:** HIV, Metabolic Syndrome, Protease Inhibitor, HAART, Incidence, Systematic Review

# Introduction

Globally, 36.7 million people were living with HIV infection as of 2016 (1). Two million new cases and 1 million deaths from HIV occur annually; and the number of deaths per year is decreasing due to the development and increased availability of new treatments (1-4). Currently, there are 19.5 million people living with HIV/AIDS (PLWHA) who receive Highly Active Antiretroviral Treatment (HAART), which is effective in prolonging life expectancy of HIV infected patients (1, 5, 6). As a result of these advances, there is an increased emphasis on not only decreasing mortality, but also on decreasing morbidity and improving quality of life among PLWHA (1, 5, 6).

HIV and HAART treatment have been associated with metabolic disorders like Metabolic Syndrome (MS). This syndrome is defined as a complex of interrelated risk factors for cardiovascular disease and diabetes by several major organizations in Harmonizing the Metabolic Syndrome as an attempt to unify criteria (7-9). MS is also a risk factor for the development of cardiovascular disease, cerebrovascular disease, and DM (10). It is estimated that one fourth of the world's population has MS and the prevalence ranges from less than 10% up to 84% by country, which happens to be more common in PLWHA (11, 12).

One of the principal disorders associated with HAART is raised blood glucose, which is a component of MS (13, 14). A study by Samaras K, et al. found that the prevalence of MS among seropositive patients that received HAART was between 14% and 18% (12). Nevertheless, this risk does not outweigh the benefits of HAART treatment for the HIV patient (15, 16).

Among the most used antiretroviral drugs in HAART treatment are Protease Inhibitors (PIs) (17). Several studies have reported associations between the use of PIs and the incidence of MS (13, 14, 18). PIs interact with adipose tissue by altering lipid metabolism and generating oxidative stress which modifies the secretion, differentiation, and autophagic activities of adipocytokines (19, 20). Despite these

findings, some studies have shown no association between the use of PIs and the appearance of any metabolic disorder (21-23).

Considering the conflicting literature related to the risk of metabolic disorders resulting from the use of PIs, this systematic review evaluated the association between the use of PIs in HAART and the appearance of MS in HIV infected, adult (18 years of more) patients.

# Methods

The systematic review protocol was registered at PROSPERO, an international database of systematic reviews (Registration number: CRD42015027223).

## Data Sources and Searches

We searched for original studies that describe the association between the use of PIs and incidence of MS using MEDLINE/Pubmed, Cochrane Central Register of Controlled Trials – CENTRAL in The Cochrane Library, LILACS, and EMBASE. All studies published on or before November 2015 were considered. A gray literature search was also performed using Web of Science, the bibliography of relevant articles, abstracts of the International AIDS Society (IAS, 2001-2015) (24), and the Conference on Retroviruses and Opportunistic Infections (CROI, 2014-2015), posteriorly if there was relevant information missing, the authors were addressed giving a 2-week opportunity for reply, otherwise the articles were discarded (25). Finally, a manual search of journals known to publish relevant articles in this field was performed. Our search strategy is further detailed in Appendix 1.

## Study Selection

We performed a literature search unrestricted by language. We included prospective and retrospective cohort studies, case-control studies, and randomized clinical trials. The inclusion criteria were: 1) Patients aged 18 years or older with HIV infection and treated with HAART; 2) Patients compared according to their use of PIs; 3) MS defined by the study; 4) The presence of MS described during follow-up.

Case reports, reviews, and cross-sectional studies were excluded. Additionally, we excluded studies that included patients with MS at baseline. Lastly, we excluded studies with inadequate information about MS, or whether there was no information about PIs usage.

## Data Extraction and Quality Assessment

Two investigators independently checked titles, abstracts, and the full text of potentially relevant articles. Differences were resolved by a third investigator who decided if the study was included.

Data extraction was carried out individually by each investigator and discrepancies were resolved by consensus. For each study, detailed information including the year, country, type of study, measure of association, total number of participants, follow-up duration, and the definition of MS was extracted.

In order to assess the methodological quality of each study, we used the Newcastle-Ottawa Scale (NOS) , which assesses the selection process, comparability, and type of nonrandomized observational studies (cohort studies and case-control studies) (26). For this process two investigators evaluated each study and assigned a value of 1 point for each item of the scale giving a maximum score of 8 points. This tool does not have a consigned cut-off point but is a subjective score given by the authors. The Cochrane Collaboration´s Tool for Assessing Risk of Bias in Randomized Trials was used for the evaluation of randomized clinical trials (27).

## Data Synthesis and Analysis

Heterogeneity of the estimated effects was assessed using the Cochrane Q test for heterogeneity and the $I^2$ statistic test (28). A random-effects model was chosen due to the expected heterogeneity.

We analyzed the Relative Risk (RR) and Hazard Ratio (HR) of the selected studies, and, when possible, calculated the RR from the HR. All analyses were performed using the software programme Review Manager 5.3.

# Results

After eliminating duplicates, we identified and reviewed 4,203 articles by titles and abstracts, of which 4,086 were removed because they did not meet the inclusion criteria or were not relevant to the research topic **(Figure 1)**. The full texts of the remaining 117 articles were reviewed, and 114 articles were excluded. We included 3 articles for the quantitative analysis **(Table 1)**. All included studies were cohort studies and all were written in English. Because of this, the results of quality assessment of the studies were based on the NOS. Although the scores given by this tool were similar in the 3 studies, we consider that heterogeneity exists between them due to differences in the follow-up length and the population sizes. Results are in further detailed in Appendix 2.

## Incidence of Metabolic Syndrome

Within the three studies analyzed to determine the RR of developing MS after exposure to PIs, we found no evidence of an estimated effect heterogeneity in the analysis of the pooled RR ($I^2 = 0$). An association between the use of PIs and developing MS was identified, with a pooled RR of 2.11 (CI 95%, 1.28 to 3.48; p-value 0.003). **(Figure 2)**.

# Discussion

We found a 2.11 times greater risk of the development of MS among HIV-positive patients treated with a PI-containing regimen than those treated with a PI-free HAART regimen. The heterogeneity between studies was low.

The definition of MS was based on the need to predict the risk for cardiovascular disease, cerebrovascular disease, and DM in clinical practice (9, 10). Although there are varying classifications for MS, the IDF criteria is suggested to be most strongly associated with the development of DM (29), which is another public health concern, in addition to cardiovascular disease. Generally, abdominal obesity precedes MS, and it has been shown that with aging and increased obesity, further metabolic risk factors develop until the criteria for MS is reached (30). So far, no study has evaluated the predictive value of MS in the appearance of other metabolic abnormalities among HIV-positive patients receiving antiretroviral treatment (31). The components of MS have a comparatively early onset regard to other chronic diseases (30). This is very important in terms to prevent metabolic and cardiovascular disease in HIV-positive patients with HAART which have higher risk than HIV-negative patients.

A systematic review found a close relationship between MS and the incidence of DM, specially linked to increased waist circumference and impaired fasting glucose (32). Increases in waist circumference are associated with increases in the quantity of adipose tissue, which in turn causes the functions associated with this tissue to be amplified. One of these is the accelerated conversion of cortisone into cortisol, an insulin antagonist, as a consequence they are more likely to develop insulin resistance (33).

One of the main limitations of the studies was the increased sample size of a study (Jacobson 2006, Weight 82.3%) compared to the remaining studies. Other identified limitations of the studies reviewed were incomplete information about PIs usage, the omission of important risk factors associated with MS, the division of the population

into subgroups depending on received treatments, and the analysis of PIs as a group rather than each PI drug individually.

The complete HAART regimen of each study population was not reported, because other antiretroviral drugs such as nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) are also related to metabolic abnormalities, especially those associated with lipid metabolism. Future studies should not only consider pharmacological families but also specific drugs due to their different associations with these alterations (34, 35).

In this study, a subgroup analysis of PIs according to generations was not performed, due to the lack of division of this subject in the included studies. There is evidence that older PIs have an increased association with insulin resistance, hyperglycemia, and diabetes compared to newer PIs (36). In a small study, nine HIV-infected patients with PI-induced insulin resistance were switched to atazanavir, increasing their insulin sensitivity without compromising their viral load (37).

A lack of control of potential confounders was another limitation found in the included studies. For instance, the study by Palacios et al performed just an univariate analysis of the use of PIs and the appearance of MS. Because MS is multi-factorial, adjustments to the analysis to account for potential unmeasured confounders such as time receiving HAART, family history of DM, and others that may affect the association between PI use and the appearance of MS should be made. The main confounders recognized in different studies are: sex, age, mode of HIV-infection, ethnicity, cd4 count, viral load, smoking status, hepatitis B virus coinfection, hepatitis C virus coinfection, ART naivety, and time of previous ART exposure (38).

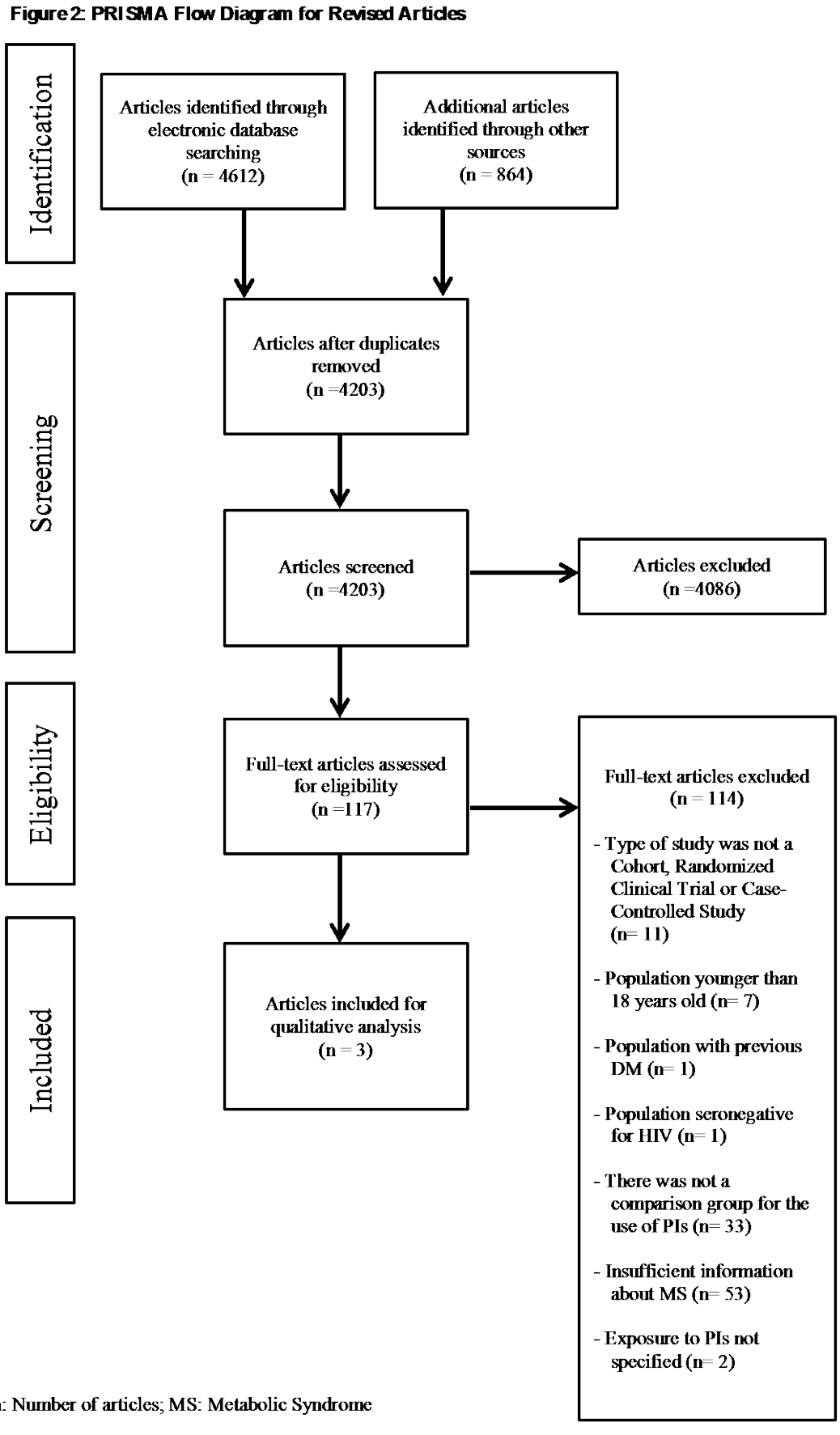
Finally, we did not assess publication bias using Egger’s test nor by the visual inspection of asymmetry in the funnel plot, because the number of studies included was too small to have an acceptable power for the use of these tests (39, 40).

# Conclusions

This study showed that the use of PIs in the treatment of HIV infection is associated with an increased risk of developing MS. A subgroup analysis of PIs by generation could not be performed due to the lack of division in the included studies.

We recommend that future studies consider dividing PIs by generation because of the existing evidence that newer PIs are less associated to metabolic abnormalities. Also, we consider these findings will be of relevance for public policy because it will increase the interest in screening MS in an expanding population and the prevention of its complications.

Figure 1: PRISMA Flow Diagram for Revised Articles




n: Number of articles; MS: Metabolic Syndrome

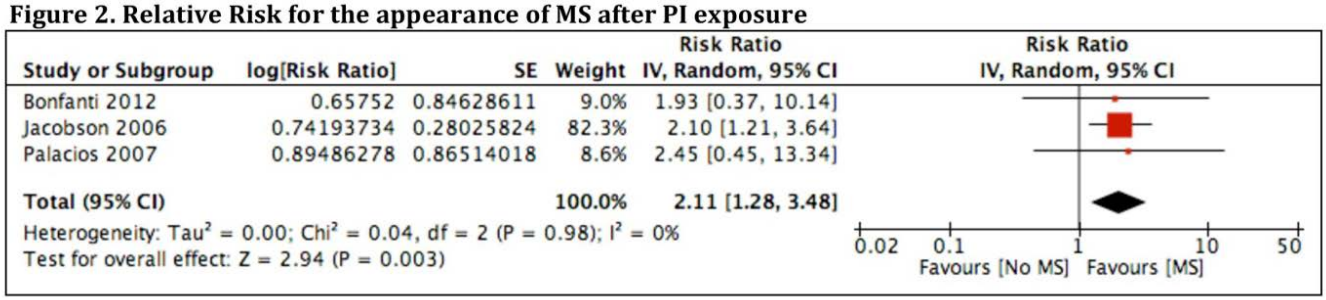
Table 1. Articles that measure Metabolic Syndrome (MS) incidence

| **Table 1. Articles that measure Metabolic Syndrome (MS) incidence** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study ID | Author | Year | Country | Associative Measure | Variables for Adjustment | Number of Participants | PI | No PI | Length of Follow-up | MS |
| SM-01 | Bonfanti P. | 2012 | Italy | RR | Gender<br>Age<br>BMI<br>Physical Activity<br>HCV coinfection | 188 | PI: 60<br>NNRTI: 58 | NR | 3 years or until MS development | ATP III Criteria |
| SM-02 | Jacobson D. | 2006 | USA | RR | Gender<br>Race<br>Age | 338 | PI: 177<br>HAART without PI: 165 | NR | 3 years | ATP III Criteria |
| SM-03 | Palacios R. | 2007 | Spain | RR | NR | 60 | PI: 21<br>NNRTI: 39 | NR | 48 weeks | - Triglycerides > 1.6mmol/l<br>- HDL:<br>Men<br>< 1.04 mmol/L<br>Women<br>< 1.03 mmol/l<br>- BP ≥ 135/85 mmHg<br>- FGC ≥ 6.05 mmol/l<br>- AC:<br>Men<br>> 102 cm.<br>Women<br>> 88 cm.<br>- BMI ≥ 27 kg/$m^2$ |

MS: Metabolic Syndrome; PI: Protease Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; RR: Relative Risk; HCV: Hepatitis C Virus; HDL: High Density Lipoproteins; BP: Blood Pressure; FGC: Fasting Glucose Concentration; AC: Abdominal Circumference; ATP: Adult Treatment Panel; IDF: International Diabetes Federation; NR: Not Reported
* All the included studies are Cohort studies

Figure 2: Relative Risk for the appearance of MS after PI exposure

**Figure 2. Relative Risk for the appearance of MS after PI exposure**



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# Appendix 1. Search Strategy for

PUBMED

((((((((((((((("Diabetes Mellitus"[Mesh]) OR "Diabetes") OR "Hyperglycemia"[Mesh]) OR "Hyperglycaemia") OR "Glucose"[Mesh]) OR "Impaired Glucose Tolerance") OR "IGT") OR "Impaired Fasting Glucose") OR "IFG") OR "Hemoglobin A, Glycosylated"[Mesh]) OR "HbA1c")) OR ((("Insulin Resistance"[Mesh]) OR "Insulin"[Mesh]) OR "Hyperinsulinemia") OR "Hyperinsulinism"[Mesh])) OR ((((("Metabolic Syndrome X"[Mesh]) OR "Metabolic Syndrome") OR "Cardiometabolic") OR "Hypertension"[Mesh]) OR "Sagittal Abdominal Diameter"[Mesh]) OR "Dyslipidemias"[Mesh]))) AND (((((("HIV Infections"[Mesh]) OR HIV[MeSH Terms]) OR “HIV”))) AND ((((((("Anti-Retroviral Agents"[Mesh]) OR "Antiretroviral Therapy, Highly Active"[Mesh]) OR "Protease Inhibitors"[Mesh]) OR "Antiretroviral Therapy") OR "ARV") OR "Anti-Retroviral Therapy")) OR ((((((((((((((((("Saquinavir"[Mesh]) OR "Ritonavir"[Mesh]) OR "Indinavir"[Mesh]) OR "Nelfinavir"[Mesh]) OR "fosamprenavir" [Supplementary Concept]) OR "tipranavir" [Supplementary Concept]) OR "darunavir" [Supplementary Concept]) OR "amprenavir" [Supplementary Concept]) OR "atazanavir" [Supplementary Concept]) OR "Saquinavir") OR "Ritonavir") OR "Indinavir") OR "Nelfinavir") OR "Lopinavir") OR "Fosamprenavir") OR "Tipranavir") OR "Darunavir") OR "Amprenavir") OR "Atazanavir"))))

EMBASE

1. 'human immunodeficiency virus'/exp
2. 'diabetes mellitus'/exp
3. 'metabolic syndrome x'/exp
4. 'highly active antiretroviral therapy'/exp
5. 'proteinase inhibitor'/exp
6. metabolic syndrome

1 AND (2 OR 3)

4 AND (2 OR 3)

(1 AND 5) AND (6 AND 2)

COCHRANE

1. HIV:ti,ab,kw
2. "protease inhibitor":ti,ab,kw
3. metabolic syndrome:ti,ab,kw
4. Diabetes:ti,ab,kw

(1 OR 2) AND (3 or 4)

LILACS

(HIV OR protease inhibitor) AND (diabetes OR metabolic syndrome) AND (instance:"regional") AND (instance:"regional") AND ( db:("LILACS" OR "IBECS" OR "CUMED" OR "MedCarib" OR "SES-SP" OR "DECS" OR "colecionaSUS")

Appendix 2. Assessment of Quality using the Newcastle-Ottawa Scale (NCOS)

| | SELECTION | | | | COMPARABILITY | OUTCOME | | | NOS Quality Score (Number of Stars) |
|---|---|---|---|---|---|---|---|---|---|
| Study ID | Representativeness of the Exposed Cohort | Selection of the Non Exposed Cohort | Ascertainment of Exposure | Demonstration that outcome of interest was not present at baseline | Comparability of Cohorts on the Basis of the Design Analysis | Assesment of Outcome | Adequate Length of Follow-Up | Adequacy of Follow-Up of Cohorts | |
| Bonfanti 2012 | * | * | * | * | * | * | * | | 7 |
| Jacobson 2006 | * | * | | * | * | * | * | | 6 |
| Palacios 2007 | | * | * | * | * | * | | | 5 |