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

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A mis padres y abuelos

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Abstract

Introduction: Despite the advances in increasing life expectancy among people living with HIV/AIDS, Highly Active Antiretroviral Treatment (HAART) use and HIV infection itself have been associated with the occurrence of Type 2 Diabetes Mellitus (DM), specifically with the use of protease inhibitors (PIs). The aim of this systematic review was to determine if there is an association between the use of PIs and the incidence of DM in HIV-infected patients.

Methods: A systematic literature search was performed using MEDLINE/PubMed, CENTRAL, LILACS and EMBASE. Included articles were observational studies published on or prior to November 2015 that met the following criteria: 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 were defined in the study and described during follow-up. Studies were selected independently by two investigators. Pooled relative risks (RR) and hazard ratios (HR) were calculated. Heterogeneity was assessed by New Castle Ottawa Scale (NOS) for nonrandomized studies and The Cochrane Collaboration’s Tool for assessing risk of bias for randomized trials.

Results: 13155 HIV patients in 6 studies were included. All studies used HR as association measure and only 1 study used RR. Length of follow-up varied between 3 years to 17 years. No association between the use of PIs and development of DM was found: the HR for the incidence of DM among patients using PIs was 1.23 (95% CI 0.66 to 2.30; p-value: 0.51) and the RR was 1.25 (95% CI 0.99 to 1.58; p-value 0.06).

Conclusion: No evidence of an increased risk of DM was found. However, the length of follow-up could be short to evaluate DM incidence, requiring a longer follow-up in order to detect an association between PI use and onset of DM.

Keywords: HIV, Diabetes Mellitus, Protease Inhibitor, Systematic Review, Meta-analysis, HAART
Introduction

As of 2016 there were 36.7 million people infected with HIV living in the world. About 1.8 million new cases occur annually and 1 million deaths are due to an AIDS-related illness in the same period of time. Nevertheless, the number of deaths has been decreasing each year because of new treatment development and its availability. In 2017, there were 19.5 million people living with HIV/AIDS (PLWHA) that have access to Highly Active Antiretroviral Treatment (HAART), which has been demonstrated to prolong life expectancy of HIV infected patients. Because of therapy advances, there is an increased importance on reducing morbidity and mortality and improving quality of live among PLWHA (1).

HIV and HAART treatment have been associated with various metabolic disorders, specifically Type 2 Diabetes Mellitus (DM) (1-4). According to the American Diabetes Association (ADA), DM is defined as a metabolic disease due to a progressive insulin secretory defect on the background of insulin resistance (5).

One of the principal disorders associated with HAART is raised blood glucose, which is a risk factor for DM (1, 2). In the Multicenter AIDS Cohort Study (MACS), the incidence of DM was of 14% among HIV patients exposed to HAART; this was 4 times higher than among the non-exposed (6). However, this risk does not outweigh the benefits of HAART treatment for the HIV patient (7, 8).

Among the most used antiretroviral drugs in HAART treatment are Protease Inhibitors (PIs) (9). Several studies have reported associations between the use of PIs and the incidence of metabolic disturbances like DM2 (3, 4, 10). Some of the mechanisms by which PIs contribute to the development of metabolic disturbances include the noncompetitive inhibition of GLUT-4 channels in adipose tissue and the decrease of insulin secretion, due to a signaling alteration and to the induction of apoptosis of beta pancreatic cells. Both of these disturbances would generate, in the long term, insulin resistance (11-13). Even with this evidence, other studies have shown no significant association between the use of PIs and the appearance of any metabolic disorder (14-16). Considering the available literature related to the risk of metabolic disorders due to the use
of PIs, this systematic review evaluated the association between the use of PIs in HAART and the appearance of DM in HIV infected, adult (18 years of more) patients.
Methods

We enlisted the systematic review protocol at PROSPERO, the international database for systematic reviews that helps avoid duplication and reduce the possibility of reporting bias (Registration number: CRD42015027223).

Data Sources and Searches

We conducted a search for original studies that discussed the association between the use of PIs and incidence of DM using the following databases: MEDLINE/Pubmed, Cochrane Central Register of Controlled Trials – CENTRAL in The Cochrane Library, LILACS, and EMBASE. We considered all studies presented on or before November 2015. Furthermore, we performed a gray literature search using Web of Science, the references of pertinent articles, abstracts of the International AIDS Society (IAS, 2001-2015) (17), and the Conference on Retroviruses and Opportunistic Infections (CROI, 2014-2015) (18). If data was not available in the original study, we asked for original data to authors, we waited for the response for 2 weeks or otherwise studies were discarded. Additionally, common journals known to publish significant articles within this field were manually inspected. Our search strategy is detailed in Appendix 1.

Study Selection

The exploration for studies was unconditional to their language of origin, taking into consideration: prospective and retrospective cohort studies, case-control studies, and randomized clinical trials. The following inclusion criteria were assessed:

- Patients aged 18 years or older with HIV infection and treated with HAART.
- Patients compared according to their use or not of PIs.
- DM defined by the study.
- The presence of DM described during follow-up.

We omitted case reports, reviews, and cross-sectional studies were excluded. Furthermore, studies that included patients with DM at baseline were also excluded. Finally, the studies with insufficient information about DM or unclear data about PIs treatment were discarded.
Data Extraction and Quality Assessment

Initially, titles, abstracts, and complete texts of potentially relevant articles were reviewed by two separate investigators. Following this, a third investigator decided which studies were included after resolving the differences presented by the formers.

Each investigator carried out individual data extraction, inconsistencies were resolved by consensus. The information extracted from each study was: the year of publication, country, type of study, measure of association, aggregate number of participants, follow-up duration, and the definition of DM.

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of each study. This instrument evaluates the selection process, comparability, and type of study. It is compounded by eight items. There is a subjective tool and has not an assigned score; this is given by the authors (19). Two investigators, separately, assigned a value of one to each item, if the article had fulfilled it. We gave a maximum score of 8 per article. There was not a cut-off point.

Data Synthesis and Analysis

The Cochrane Q test for heterogeneity and the $I^2$ statistic test were used to determine the heterogeneity of the estimated effects (20). From the expected heterogeneity, a random-effects model was chosen.

From the chosen studies, we evaluated the Relative Risk (RR) and Hazard Ratio (HR) and, when possible, calculated the RR from the HR. These analyses were all conducted on 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 111 articles were excluded. We included 6 articles for the quantitative analysis (Table 1). All included studies were cohort studies and all were written in English. Because of this, we solely used NOS for quality assessment. All studies used HR as association measure and only 1 study used RR. Length of follow-up varied between 3 years to 17 years. The results of quality assessment of the studies are described in Appendix 2.

Incidence of Diabetes Mellitus

We evaluated the HR of developing DM after exposure to PIs in three studies: Capeau 2012, Justman 2002 and Wand 2007; the other three studies were not evaluated with HR due to insufficient data. We found considerable estimated effect heterogeneity in the analysis of the pooled HR ($I^2 = 74\%$). The pooled HR for the association between the use of PIs and the appearance of DM was 1.23 (CI 95%, 0.66 to 2.30; p-value: 0.51) (Figure 2a).

We obtained the RR from the HR in three studies: Justman 2002, Riyaten 2015 and Tien 2007. Upon evaluation of the four studies that evaluated the RR of developing DM after the exposure to PIs, we did not find a significant estimated effect heterogeneity in the analysis of the pooled RR ($I^2 = 15\%$). The pooled RR was 1.25 (CI 95%, 0.99 to 1.58; p-value: 0.06) (Figure 2b).
Discussion

There was no association with the development of DM among patients treated with PIs and the heterogeneity between studies was moderate to high in some of the studies evaluating DM.

One study, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group, this has developed an instrument to predict the early risk of DM at 2 and 5 years of antiretroviral initiation (21, 22). In this study, the moderate, high, and very high risks of DM added up to 21% and 46% at 2 and 5 years of antiretroviral treatment, respectively (22).

There are many factors that contribute to develop of DM one of the most known is obesity associated to waist circumference. Hypertension and hypercholesterolemia are risk factors as well and all are components of SM. One systematic review found a relationship between SM and DM. Increased adipose tissue in these patients results in decreased adiponectin production. Adiponectin plays an important role in insulin sensitivity and secretion (23, 24). Furthermore, it has been shown that hyperglycemic periods increase insulin secretion, contributing to impaired fasting glucose. Thus, these factors, if sustained for a certain period, can lead to the development of insulin resistance and, subsequently, the development of DM (25). Many studies show that HIV itself contributes to the appearance of SM components, and the HAART drugs enhance them. Consequently, DM would appear early.

A main limitation of the studies included in this analysis was the short follow-up time. Two out of the six studies we evaluated had a follow-up duration of 10 years or greater. DM is a late onset disease, and therefore requires a longer follow-up period in order to be detected (26). It has been reported that it takes an average of 4 to 7 years, in some cases even decades, from the appearance of insulin resistance to the development of DM (26). Furthermore, there is evidence that HIV-infected patients who receive HAART are at risk of premature morbidity and mortality compared to HIV-uninfected patients (27). This is mainly because of residual immunodeficiency, chronic
inflammation, and the toxicity of antiretroviral drugs (27). For these reasons, studies that evaluate the incidence of DM require longer follow-up times.

Other limitations identified were their population sizes, inadequate information about the initiation of PIs, the absence of other reported risk factors for the studied outcomes, 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.

Unfortunately, the complete HAART regimen was not reported in these patients. This information is important because other antiretroviral drugs such as nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) are also associated to metabolic abnormalities, including lipid metabolism. Future studies should include information about specific drugs due to their different associations with these alterations (28, 29).

As many observational studies, there was not an adequate control of known confounders. Capeau et al, for example, did not perform a multivariate analysis of the use of Nelfinavir and the development of DM. Because DM is multi-factorial, adjustments to the analysis to account for potential unmeasured confounders such as time receiving HAART, family history of DM, Body Mass Index (BMI), and others that may affect the association between PI use and the appearance of DM should be made (30).

Publication bias using Egger’s test nor by the visual inspection of asymmetry in the funnel plot was not performed, because the number of studies included was too small to have an acceptable power for the use of these tests (31, 32).
Conclusions

An association between the use of PIs and the development of DM was not found. We recommend that future studies should have an adequate follow-up duration to account for the typically delayed onset of DM. Future studies should also be adjusted by confounder variables.
Figure 1: PRISMA Flow Diagram for Revised Article

Articles identified through electronic database searching (n = 4612)

Articles after duplicates removed (n = 4203)

Articles screened (n = 4203)

Full-text articles assessed for eligibility (n = 117)

Articles included for qualitative analysis (n = 6)

Articles excluded (n = 4086)

Additional articles identified through other sources (n = 864)

Full-text articles excluded (n = 111)
  - Type of study was not a Cohort, Randomized Clinical Trial or Case-Controlled Study (n = 11)
  - Population younger than 18 years old (n = 7)
  - Population with previous DM (n = 1)
  - Population seronegative for HIV (n = 1)
  - There was not a comparison group for the use of PIs (n = 33)
  - Insufficient information about DM (n = 56)
  - Exposure to PIs not specified (n = 2)

Identification

Screening

Eligibility

Included
## Table 1: Articles that measure Diabetes Mellitus (DM) Incidence

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Associative Measure</th>
<th>Variables for Adjustment</th>
<th>Number of Participants</th>
<th>Number of Participants with PI</th>
<th>Number of Participants without PI</th>
<th>Length of Follow-up</th>
<th>DM</th>
</tr>
</thead>
</table>
| DM-01    | Capeau J.**| 2012 | France  | HR                  | Age, BMI, Abdominal Circumference, Abdominal Circumference-Hip Ratio, BP, Lipoatrophy | 1,046                  | NR                            | NR                              | 10 years          | - FGC ≥7.0 mmol/l  
- OGTT 2-h ≥ 11.1 mmol/l  
- Start of antidiabetic drugs |
| DM-02    | Justman J. | 2002 | USA     | HR                  | DM risk factors, Confounding Factors for HIV as defined by the study | 1,435                  | Pl: 609                       | RTI: 932                        | 3 years or until DM development | - DM specific report  
- General disease report  
- Intake of antidiabetic drugs |
| DM-03    | Riyaten P. | 2015 | Thailand| HR                  | Age, Gender, BMI, Triglycerides | 1,594                  | NR                            | NR                              | 6.9 years          | - FGC ≥126 mg/dL  
- RPG ≥200 mg/dL |
| DM-04    | Tien P.    | 2007 | USA     | HR                  | Age, Race, BMI, Smoking Status, HCV coinfection, Family History of DM, Menopause, CD4 Count | 1,524                  | NR                            | NR                              | 6 years            | - FGC ≥126 mg/dL  
- DM self-report  
- Intake of antidiabetic drugs |
| DM-05    | Tripathi A. | 2014 | USA     | HR, RR              | Age, Gender, Years of follow-up, Race, Dyslipidemia, Obesity, HBV v HCV, CD4 Count, Viral Load | 6,816                  | NR                            | NR                              | 17 years           | - ICD-9 Criteria for DM type 1 and II |
| DM-06    | Wand H.    | 2007 | USA     | HR                  | Age, Gender, Smoking Status | 741                   | Pl: 238                       | NNRTI: 246                      | 3 years            | - FGC ≥7.0 mmol/l  
- RPG ≥11.1 mmol/l |


* All the included studies are Cohort studies

** This study was divided according to the use of Nelfinavir and Indinavir. There was no multivariate analysis for the use of Nelfinavir and the appearance of DM.
Figure 2a: Hazard Ratio for the appearance of DM after PI exposure

Figure 2b: Relative Risk for the appearance of DM after PI exposure
References:

21. The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) Denmark: Center for Health & Infectious Disease Research (CHIP); [Available from: http://www.chip.dk/Ongoing-Studies/DAD/About.
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 "coleccionaSUS"))
Appendix 2. Assessment of Quality using the Newcastle-Ottawa Scale (NCOS).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SELECTION</th>
<th>COMPARABILITY</th>
<th>OUTCOME</th>
<th>NOS Quality Score (Number of Stars)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the Exposed Cohort</td>
<td>Selection of the Non Exposed Cohort</td>
<td>Ascertainment of Exposure</td>
<td>Demonstration that outcome of interest was not present at baseline</td>
</tr>
<tr>
<td>Capeau 2012</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Justman 2002</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Riyaten 2015</td>
<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Tien 2007</td>
<td>1</td>
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<td>Tripathi 2014</td>
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<td>Wand 2007</td>
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