Lipodystrophy among HIV-infected patients on Highly Active Antiretroviral Therapy: a systematic review of the literature - Protocol

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Lipodystrophy among HIV-infected patients on Highly Active Antiretroviral Therapy: a systematic review of the literature - Protocol

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Keywords: lipodystrophy, HAART, HIV, adverse drug reaction, systematic review.

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ABSTRACT

Introduction: Lipodystrophy is a frequent and disfiguring adverse effect of highly active antiretroviral therapy (HAART) in patients with human immunodeficiency virus (HIV). It affects the quality of life of the patient and adherence to treatment, and generates new needs for comprehensive health care services. The aim of this study will be to conduct a systematic review of the literature from observational studies and describe lipodystrophy among HIV-infected patients during current or previous use of HAART.

Methods and analysis: A systematic review of observational studies published in MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts will be carried out. Citations of included studies will be checked to identify additional studies not identified in the electronic searches. It will include any observational study which considered lipodystrophy as primary or secondary outcomes which enrolled HIV-infected patients adolescents and adults who were under current or previous treatment with HAART. Data extraction and analysis will be performed independently by two reviewers. The extracted data will be discussed, decisions documented and, where necessary, the authors of the studies will be contacted for clarification. Measures of frequency, prevalence and incidence, of lipodystrophy will be stratified according to definition, method of diagnosis and risk factors of the outcome.

Ethics and dissemination: Ethics is not required given this is a protocol for a systematic review. The findings of this study will be widely disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

Protocol registration: PROSPERO - CDR42013005450

INTRODUCTION

The benefits achieved with the highly active antiretroviral therapy (HAART), introduced in the late 1990s for the treatment of human immunodeficiency virus (HIV) infection, are unquestionable. The decrease in acquired immunodeficiency syndrome (AIDS) mortality has been attributed mainly to the reduction in AIDS-related comorbidity and opportunistic infections. However, the increase in non-AIDS-related diagnoses, such as adverse reactions to antiretrovirals, has afforded HIV infection the characteristic of a chronic degenerative disease.[1 - 3]

At the beginning of antiretroviral treatment, adverse events tend to be common and of mild to moderate relevance.[4] During the treatment course, adverse events become less frequent. However, late adverse events are more complex and lead to stigmatizing conditions, affecting the quality of life of patients and their adherence to HAART,[5,6] thus generating new needs for comprehensive health care services.[7]

Morphological alterations caused by abnormalities in body fat distribution (lipodystrophy) have been diagnosed in HIV-infected patients especially among those using antiretroviral regimens. Lipodystrophy is therefore considered an adverse effect of antiretrovirals of the HAART era, and it is a public health issue of great relevance, since it is associated with insulin resistance, diabetes mellitus and dyslipidemia, known risk factors for cardiovascular disease.[8] Lipodystrophy is characterized by fat accumulation (hypertrophy) in one or more anatomical sites (e.g., abdomen, dorso-cervical spine, breasts) or fat loss (atrophy) mainly on the face, buttocks and extremities or mixed lipodystrophy (combination of lipoatrophy and lipohypertrophy).[9] The long term use of HAART, the use of regimens containing a nucleoside analog reverse transcriptase inhibitor (particularly stavudine) and a protease inhibitor, older age, gender and duration of HIV infection have been described as the main risk factors for lipodystrophy.[8, 9]

The number of published observational studies of lipodystrophy has grown markedly in the last few years. Studies indicate that the prevalence of lipodystrophy in HIV-infected patients on HAART ranges from 11 to 83%.[10] Nevertheless, these findings are derived from different definitions of lipodystrophy, as well as distinct selection criteria and follow-up of the study population. Due to this variability, it is important to stratify the information available about estimates of morbidity and risk factors of lipodystrophy

in regard to the different methods and criteria diagnosis employed, population characteristics and types of study designs. A systematic review of published studies may assist in clinical decisions and in public health actions, contributing to best accession to HAART. Additionally, this study will contribute to the improvement of a standardized definition for this important adverse drug reaction which significant impacts treatment and quality of life of patients HIV-positive.

OBJECTIVES

Our aim is to describe lipodystrophy among HIV-infected patients in the current or previous use of HAART through the development of a systematic review of observational studies.

METHODS AND ANALYSIS

This will be a systematic review focused on an adverse drug reaction of HAART. Data collection, analysis, presentation and interpretation of results will be performed based on standard guidelines for systematic review of adverse effect of healthcare interventions.[11, 12]

Criteria for considering studies for this review

Types of studies

Observational studies irrespective of language and publication status.

Types of participants

HIV- infected adolescents and adults on prior or current HAART.

Types of interventions

We will include observational studies investigating the occurrence of lipodystrophy as primary or secondary outcomes.

Types of outcome measures

The diagnosis of lipodystrophy may be performed by clinical evaluation or by self-report of patient, or both, confirmed or not by other techniques and characterized according to one or more of the changes below:[9]

Lipohypertrophy:

- abdominal obesity;
- breast hypertrophy;

- increased fat side of the neck;
- increased fat back of the neck;
- localized or generalized lipomas.

Lipoatrophy:

- fat loss in the face;
- fat loss in the buttocks;
- fat loss from legs;
- fat loss in the arms;
- disclosure of the veins in the muscles of the upper and lower.

Mixed lipodystrophy:

- combination of lipoatrophy and lipohypertrophy.

Search methods for identification of studies

Electronic searches

A computerized search will be conducted of MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts, using a search strategy combining free terms and indexing terms. The search strategy can be found in Table1.

Table 1 Search strategy by MEDLINE

MEDLINE (via OVIDsp)
1. exp Lipid Metabolism Disorders
2. exp Body Fat Distribution
3. lipoatrophy.mp.
4. lipohypertrophy.mp.
5. Lipodystrophy.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp HIV Infection
8. exp Anti-Retroviral Agents
9. Nucleoside Reverse Transcriptase Inhibitors.mp.
10. Non-Nucleoside reverse transcriptase inhibitors.mp.
11. Protease Inhibitors.mp.
12. Integrase Inhibitors.mp.
13. Fusion Inhibitors.mp.
14. Ccr5.mp.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 6 and 15

Searching other resources

Citations of included studies will be checked to identify additional studies not identified in the electronic search.

Data collection and analysis

Selection of studies

The selection of articles to be assessed in this review includes two steps. In a first stage, information from titles and abstracts will be screened for exclusion of non-relevant retrieved papers. The potentially relevant articles will be read in full by two independent reviewers and cases of disagreement will be resolved by consensus. The selection process will be carried out according to the criteria for inclusion mentioned previously.

Data extraction and management

Two reviewers will independently extract data from included trials and cases of disagreement will be resolved by consensus. Extracted data will be discussed, decisions documented, and when necessary, the authors of the studies will be contacted for clarification. The reasons for excluding studies from the review will be documented. The following data will be extracted, checked, and recorded.

- Characteristics of studies

Objective;

Design;

Year and country of study;

Duration of study or follow-up;

Source population;

Sample size;

Number of participants in each group monitoring;

Losses to follow-up and/or reasons for non-participation (if applicable).

- Baseline characteristics of the study population

Age;

Age at the time of HIV infection;

Number of naïve enrolled patients;

Number of non-naïve enrolled patients;

Duration of HIV infection;

HIV risk factors;

Log HIV RNA level;

CD4 – positive lymphocyte count;

AIDS category (A, B, C);

Sex;

Duration of HAART;

Type of current and prior HAART;

Fasting glucose level;

Total cholesterol;

Low density lipoprotein (LDL);

Triglycerides level;

Metabolic syndrome;

Family history of diabetes mellitus, hypertension, cardiovascular events and dyslipidemia;

Co-morbidity (hepatitis C, tuberculosis, etc.);

Consumption of alcohol, tobacco and other drugs.

- Characteristics of lipodystrophy

Lipodystrophy definitions;

Diagnostic criteria of lipodystrophy;

Judgment of causality of lipodystrophy;

Judgment of severity of lipodystrophy;

Number of patients with lipodystrophy;

Age at diagnosis of lipodystrophy;

Occurrence of lipodystrophy according to antiretroviral regimen;

Anthropometric characteristics (height, weight, body mass index, waist circumference, Waist/ hip ratio and percentage of body fat) at diagnosis of lipodystrophy.

Assessment of risk of bias in included studies

Due to the absence of a validated instrument to assess the quality of observational studies of adverse drug reactions, it will be developed a checklist specifically for this review. This tool will be prepared based on the Guideline of The Cochrane Collaboration for non-randomized studies.[12] Two reviewers will assess independently the quality of eligible studies. Disagreements will be resolved by discussion and, when necessary, with the participation of a third reviewer.

Measuring the effect

The primary analysis will measure the frequency of occurrence of lipodystrophy, prevalence and incidence. The extraction of the data of occurrence of the adverse reaction will be carried out in accordance with the study design. Thus, according to the methodological design of the included studies, it will be extracted measures of incidence or prevalence. Moreover, due to the lack of standard diagnostic criteria for this adverse drug reaction, the different outcome measures reported in the included studies will be considered. Data on risk factors associated with lipodystrophy will also be extracted.

Dealing with missing data

Data assumed to be 'missing at random' may not be important and will be ignored. Data assumed to be 'not missing at random' will require contact whit the original author to request the missing data and it will be done whenever possible.

Assessment of heterogeneity and sensitivity analysis

These analyses will be performed separately for each type of study design. The heterogeneity in the results will be graphically inspected and evaluated by means of Chi-squared test and I^2. Sensitivity analysis will be explored through stratification by subgroups defined according to the type of outcome, diagnostic criteria and quality of studies.

Risk assessment of publication bias

The graphical funnel plot [13] will be used to investigate the presence of publication bias in the studies included in the review.

Data synthesis and subgroup analysis

We will present estimates on the occurrence, prevalence and incidence of lipodystrophy, according to study design, diagnosis criteria, type of outcome (lipoatrophy, lipohypertrophy and mixed form) and clinical and sociodemographic variables. A meta-analysis of the morbidity outcomes will be performed whenever appropriate. If applicable, the following subgroups will be analyzed:

- frequency of lipodystrophy according to duration of HIV infection;
- frequency of lipodystrophy according to HAART regimen;
- frequency of lipodystrophy according to duration of HAART;

- frequency of lipodystrophy according to risk factors.

ETHICS AND DISSEMINATION

Ethics is not required given this is a protocol for a systematic review. The findings of this study will be disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

DISCUSSION

The toxicity of HAART is a question of increasingly relevance in the treatment of HIV-infected patients due to the need of maintaining HAART indefinitely in order to achieve clinical benefits.[14] Information on the occurrence of lipodystrophy among HIV-infected patients during current or previous use of HAART are needed in order to support clinical informed decision HIV treatment and the use of HAART. Systematic reviews only emphasizing the benefit of drug therapies contribute to the omission of information on adverse effects of the interventions, thus preventing balanced decisions on benefits and risks.[15]

The knowledge regarding lipodystrophy among HIV-infected patients has increased since the beginning of the HAART era in the late 1990s. As a result, several randomized clinical trials and observational studies have been published worldwide. However, the lack of a precise case definition of lipodystrophy (with reporting of different clinical features and diagnostic methods), and differences in the follow-up time of these studies have hampered the evaluation of morbidity estimates and risk factors associated with lipodystrophy.

It is known that much of the evidence on adverse drug reactions come from observational epidemiology studies due to the limitations of randomized clinical trials in evaluating this type of outcome. Notably, clinical trials are not adequate for detecting long term outcomes (such lipodystrophy), as they are, in general, of limited follow-up length.[15] We expected that the compiled information on morbidity estimates and risk factors according to different groups of patients will ease clinical decisions in relation to health care interventions for HIV-infected patients then contributing to lower morbidity and improve adherence to long term HAART.

AUTHORS' CONTRIBUTIONS

LGCL developed the methodological strategies, with the guidance of DRGJ and participated of the draft of the study protocol; DRGJ participated of the planning and draft of the study protocol; EP participated of the planning and draft of the study protocol; CAMP conceived the study and drafts the study protocol. All authors read and approved the final version of the study protocol for submission.

FUNDING STATEMENT

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	HIV/AIDS, Public health, Pharmacology and therapeutics
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Lipodystrophy among HIV-infected patients on antiretroviral therapy: a systematic review of the literature

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Word count (excluding title page, abstract and references): 1,972 words

ABSTRACT

Introduction: Lipodystrophy is a frequent and disfiguring adverse effect of antiretroviral therapy (ART) in patients with human immunodeficiency virus (HIV). It affects the quality of life of the patient and adherence to treatment, and generates new needs for comprehensive health care services. The aim of this study will be to conduct a systematic review of the literature from observational studies and describe lipodystrophy among HIV-infected patients during current or previous use of ART.

Methods and analysis: A systematic review of observational studies published in MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts will be carried out. Citations of included studies will be checked to identify additional studies not identified in the electronic searches. It will include any observational study which considered lipodystrophy as primary or secondary outcomes which enrolled HIV-infected patients adolescents and adults who were on current or previous ART during at least six months. Data extraction and analysis will be performed independently by two reviewers. The extracted data will be discussed, decisions documented and, where necessary, the authors of the studies will be contacted for clarification. Measures of frequency, prevalence and incidence, of lipodystrophy will be stratified according to definition, method of diagnosis and risk factors of the outcome.

Ethics and dissemination: Ethics is not required given this is a protocol for a systematic review. The findings of this study will be widely disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

Protocol registration: PROSPERO - 42013005450

INTRODUCTION

The benefits achieved with the highly active antiretroviral therapy (HAART), introduced in the late 1990s for the treatment of human immunodeficiency virus (HIV) infection, are unquestionable. The decrease in acquired immunodeficiency syndrome (AIDS) mortality has been attributed mainly to the reduction in AIDS-related comorbidity and opportunistic infections. However, the increase in non-AIDS-related diagnoses, such as adverse reactions to antiretrovirals, has afforded HIV infection the characteristic of a chronic degenerative disease.[1 - 3]

At the beginning of antiretroviral treatment, adverse events tend to be common and of mild to moderate relevance.[4] During the treatment course, adverse events become less frequent. However, late adverse events are more complex and lead to stigmatizing conditions, affecting the quality of life of patients and their adherence to antiretroviral therapy (ART) [5, 6] thus generating new needs for comprehensive health care services.[7]

Morphological alterations caused by abnormalities in body fat distribution (lipodystrophy) are caused by the interaction of multiple factors such as ART, genetic predisposition of the patient, environmental factors and the HIV infection.[8, 9] However, epidemiologic studies [10, 11] have demonstrated a strong causality relationship between ART and lipodystrophy. Thus, lipodystrophy is considered an adverse effect of the ART, and it is a public health issue of great relevance, since it is associated with insulin resistance, diabetes mellitus and dyslipidemia, known risk factors for cardiovascular disease.[12] Lipodystrophy is characterized by fat accumulation (hypertrophy) in one or more anatomical sites (e.g., abdomen, dorso-cervical spine, breasts) or fat loss (atrophy) mainly on the face, buttocks and extremities or mixed lipodystrophy (combination of lipoatrophy and lipohypertrophy).[13] The long term use of ART, the use of regimens containing a nucleoside analog reverse transcriptase inhibitor (particularly stavudine) and a protease inhibitor, older age, gender and duration of HIV infection have been described as the main risk factors for lipodystrophy.[12, 13]

The number of published observational studies of lipodystrophy has grown markedly in the last few years. Studies indicate that the prevalence of lipodystrophy in HIV-infected patients on ART ranges from 11 to 83%.[14] Nevertheless, these findings are derived

from different definitions of lipodystrophy, as well as distinct selection criteria and follow-up of the study population. Due to this variability, it is important to stratify the information available about estimates of morbidity and risk factors of lipodystrophy in regard to the different methods and criteria diagnosis employed, population characteristics and types of study designs. A systematic review of published studies may assist in clinical decisions and in public health actions, contributing to best adherence to ART. Additionally, this study will contribute to the improvement of a standardized definition for this important adverse drug reaction which significant impacts treatment and quality of life of patients HIV-positive.

OBJECTIVES

Our aim is to describe lipodystrophy among HIV-infected patients in the current or previous use of ART through the development of a systematic review of observational studies.

METHODS AND ANALYSIS

This will be a systematic review focused on an adverse drug reaction of ART. Data collection, analysis, presentation and interpretation of results will be performed based on standard guidelines for systematic review of adverse effect of healthcare interventions.[15, 16]

Criteria for considering studies for this review

Types of studies

Observational studies irrespective of language and publication status, comparing HIV-infected patients on different antiretroviral regimens irrespective of the number of participants in each arm.

Types of participants

Adolescents and adults HIV-infected patients on current or previous ART use during at least six months.

Types of interventions

Observational studies investigating the occurrence of lipodystrophy as primary or secondary outcomes.

Types of outcome measures

The diagnosis of lipodystrophy performed by clinical evaluation and/or by self-report of patient, confirmed or not by other techniques, characterized by at least one of the alterations as follows:[13]

Lipohypertrophy:

- abdominal obesity;
- breast hypertrophy in women;
- increased fat side of the neck;
- increased fat back of the neck;
- dorso-cervical and supra-pubic lipomas.

Lipoatrophy:

- fat loss in the face;
- fat loss in the buttocks;
- fat loss from legs;
- fat loss in the arms;
- disclosure of the veins in the muscles of the upper and lower.

Mixed lipodystrophy:

- combination of lipoatrophy and lipohypertrophy.

Search methods for identification of studies

Electronic searches

A computerized search will be conducted of MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts, using a search strategy combining free terms and indexing terms. The search strategy can be found in Table1.

Table 1 Search strategy by MEDLINE

MEDLINE (via OVIDsp)
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5. Lipodystrophy.mp.
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12. Integrase Inhibitors.mp.
13. Fusion Inhibitors.mp.
14. Ccr5.mp.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 6 and 15

Searching other resources

Citations of included studies will be checked to identify additional studies not identified in the electronic search.

Data collection and analysis

Selection of studies

The selection of articles to be assessed in this review includes two steps. In a first stage, information from titles and abstracts will be screened for exclusion of non-relevant retrieved papers. The potentially relevant articles will be read in full by two independent reviewers and cases of disagreement will be resolved by consensus. The selection process will be carried out according to the criteria for inclusion mentioned previously.

Data extraction and management

Two reviewers will independently extract data from included trials and cases of disagreement will be resolved by consensus. Extracted data will be discussed, decisions documented, and when necessary, the authors of the studies will be contacted for clarification. The reasons for excluding studies from the review will be documented. The following data will be extracted, checked, and recorded.

- Characteristics of studies

Objective;

Design;

Year and country of study;

Duration of study or follow-up;

Source population;

Sample size;

Number of participants in each group monitoring;

Losses to follow-up and/or reasons for non-participation (if applicable).

- Baseline characteristics of the study population

Age;

Age at the time of HIV infection;

Number of naïve enrolled patients;

Number of non-naïve enrolled patients;

Duration of HIV infection;

HIV risk factors;

Log HIV RNA level;

CD4 – positive lymphocyte count;

AIDS category (A, B, C);

Sex;

Duration of ART;

Type of current and prior ART;

Fasting glucose level;

Total cholesterol;

Low density lipoprotein (LDL);

Triglycerides level;

Metabolic syndrome;

Family history of diabetes mellitus, hypertension, cardiovascular events and dyslipidemia;

Co-morbidity (hepatitis C, tuberculosis, etc.);

Consumption of alcohol, tobacco and other drugs.

- Characteristics of lipodystrophy

Lipodystrophy definitions;

Diagnostic criteria of lipodystrophy;

Judgment of causality of lipodystrophy;

Judgment of severity of lipodystrophy;

Number of patients with lipodystrophy;

Age at diagnosis of lipodystrophy;

Occurrence of lipodystrophy according to antiretroviral regimen;

Anthropometric characteristics (height, weight, body mass index, waist circumference, Waist/ hip ratio and percentage of body fat) at diagnosis of lipodystrophy.

Assessment of risk of bias in included studies

Due to the absence of a validated instrument to assess the quality of observational studies of adverse drug reactions, it will be developed a checklist specifically for this review. This tool will be prepared based on the Guideline of The Cochrane Collaboration for non-randomized studies.[12] Two reviewers will assess independently the quality of eligible studies. Disagreements will be resolved by discussion and, when necessary, with the participation of a third reviewer.

Measuring the effect

The primary analysis will measure the frequency of occurrence of lipodystrophy, prevalence and incidence. The extraction of the data of occurrence of the adverse reaction will be carried out in accordance with the study design. Thus, according to the methodological design of the included studies, it will be extracted measures of incidence or prevalence. Moreover, due to the lack of standard diagnostic criteria for this adverse drug reaction, the different outcome measures reported in the included studies will be considered. Data on risk factors associated with lipodystrophy will also be extracted.

Dealing with missing data

Data assumed to be 'missing at random' may not be important and will be ignored. Data assumed to be 'not missing at random' will require contact whit the original author to request the missing data and it will be done whenever possible.

Assessment of heterogeneity and sensitivity analysis

These analyses will be performed separately for each type of study design. The heterogeneity in the results will be graphically inspected and evaluated by means of Chi-squared test and I^2. Sensitivity analysis will be explored through stratification by

subgroups defined according to the type of outcome, diagnostic criteria and quality of studies.

Risk assessment of publication bias

The graphical funnel plot [17] will be used to investigate the presence of publication bias in the studies included in the review.

Data synthesis and subgroup analysis

We will present estimates on the occurrence, prevalence and incidence of lipodystrophy, according to study design, diagnosis criteria, type of outcome (lipoatrophy, lipohypertrophy and mixed form) and clinical and sociodemographic variables. A meta-analysis of the morbidity outcomes will be performed whenever appropriate. If applicable, the following subgroups will be analyzed:

- frequency of lipodystrophy according to duration of HIV infection;
- frequency of lipodystrophy according to ART regimen;
- frequency of lipodystrophy according to duration of ART;
- frequency of lipodystrophy according to risk factors.

ETHICS AND DISSEMINATION

Ethics is not required given this is a protocol for a systematic review. The findings of this study will be disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

DISCUSSION

The toxicity of ART is a question of increasingly relevance in the treatment of HIV-infected patients due to the need of maintaining ART indefinitely in order to achieve clinical benefits.[18] Information on the occurrence of lipodystrophy among HIV-infected patients during current or previous use of ART are needed in order to support clinical informed decision HIV treatment and the use of ART. Systematic reviews only emphasizing the benefit of drug therapies contribute to the omission of information on adverse effects of the interventions, thus preventing balanced decisions on benefits and risks.[19]

The knowledge regarding lipodystrophy among HIV-infected patients has increased since the beginning of the HAART era in the late 1990s. As a result, several randomized clinical trials and observational studies focusing on this subject have been published worldwide. However, the lack of a precise case definition of lipodystrophy and differences in the follow-up time of these studies have hampered the evaluation of morbidity estimates and risk factors associated with lipodystrophy. It is known that much of the evidence on adverse drug reactions come from observational epidemiology studies due to the limitations of randomized clinical trials in evaluating this type of outcome. Notably, clinical trials are not adequate for detecting long term outcomes (such lipodystrophy), as they are, in general, of limited follow-up length.[19]

Some potential limitations of the study should be pointed out. Lipodystrophy does not have a precise case definition and a standardized diagnostic criterion. This being considered, our systematic review will evaluate observational studies investigating different outcome definitions and diagnostic methods. As consequence, the review will include very heterogeneous studies, resulting in different groups of comparisons, and more sophisticated analysis (e.g. meta-analysis) may or not be possible. Another potential limitation of our study is that mild to moderate cases of lipodystrophy may be underreported in the eligible studies, which could underestimate the frequency of lipodystrophy. Despite of this, we believe that this study will contribute to the standardization and better report of lipodystrophy related to HIV infection and ART.

In conclusion, compiled information on morbidity estimates and risk factors of lipodystrophy according to different groups of patients are need and it will ease clinical decisions in relation to health care interventions for HIV-infected patients then contributing to lower morbidity and improve adherence to long term ART.

AUTHORS' CONTRIBUTIONS

LGCL developed the methodological strategies, with the guidance of DRGJ and participated of the draft of the study protocol; DRGJ participated of the planning and draft of the study protocol; EP participated of the planning and draft of the study protocol; CAMP conceived the study and drafts the study protocol. All authors read and approved the final version of the study protocol for submission.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

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Lipodystrophy among HIV-infected patients on antiretroviral therapy: a systematic review of the literature

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ABSTRACT

Introduction: Lipodystrophy is a frequent and disfiguring adverse effect of antiretroviral therapy (ART) in patients with human immunodeficiency virus (HIV). It affects the quality of life of the patient and adherence to treatment, and generates new needs for comprehensive health care services. The aim of this study will be to conduct a systematic review of the literature from observational studies and describe lipodystrophy among HIV-infected patients during current or previous use of ART.

Methods and analysis: A systematic review of observational studies published in MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts will be carried out. Citations of included studies will be checked to identify additional studies not identified in the electronic searches. It will include any observational study which considered lipodystrophy as primary or secondary outcomes which enrolled HIV-infected patients adolescents and adults who were on current or previous ART during at least six months. Data extraction and analysis will be performed independently by two reviewers. The extracted data will be discussed, decisions documented and, where necessary, the authors of the studies will be contacted for clarification. Measures of frequency, prevalence and incidence, of lipodystrophy will be stratified according to definition, method of diagnosis and risk factors of the outcome.

Ethics and dissemination: Ethics is not required given this is a protocol for a systematic review. The findings of this study will be widely disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

Protocol registration: PROSPERO - 42013005450

INTRODUCTION

The benefits achieved with the highly active antiretroviral therapy (HAART), introduced in the late 1990s for the treatment of human immunodeficiency virus (HIV) infection, are unquestionable. The decrease in acquired immunodeficiency syndrome (AIDS) mortality has been attributed mainly to the reduction in AIDS-related comorbidity and opportunistic infections. However, the increase in non-AIDS-related diagnoses, such as adverse reactions to antiretrovirals, has afforded HIV infection the characteristic of a chronic degenerative disease.[1 - 3]

At the beginning of antiretroviral treatment, adverse events tend to be common and of mild to moderate relevance.[4] During the treatment course, adverse events become less frequent. However, late adverse events are more complex and lead to stigmatizing conditions, affecting the quality of life of patients and their adherence to antiretroviral therapy (ART) [5, 6] thus generating new needs for comprehensive health care services.[7]

Morphological alterations caused by abnormalities in body fat distribution (lipodystrophy) are caused by the interaction of multiple factors such as ART, genetic predisposition of the patient, environmental factors and the HIV infection.[8, 9] However, epidemiologic studies [10, 11] have demonstrated a strong causality relationship between ART and lipodystrophy. Thus, lipodystrophy is considered an adverse effect of the ART, and it is a public health issue of great relevance, since it is associated with insulin resistance, diabetes mellitus and dyslipidemia, known risk factors for cardiovascular disease.[12] Lipodystrophy is characterized by fat accumulation (hypertrophy) in one or more anatomical sites (e.g., abdomen, dorso-cervical spine, breasts) or fat loss (atrophy) mainly on the face, buttocks and extremities or mixed lipodystrophy (combination of lipoatrophy and lipohypertrophy).[13] The long term use of ART, the use of regimens containing a nucleoside analog reverse transcriptase inhibitor (particularly stavudine) and a protease inhibitor, older age, gender and duration of HIV infection have been described as the main risk factors for lipodystrophy.[12, 13]

The number of published observational studies of lipodystrophy has grown markedly in the last few years. Studies indicate that the prevalence of lipodystrophy in HIV-infected patients on ART ranges from 11 to 83%.[14] Nevertheless, these findings are derived

from different definitions of lipodystrophy, as well as distinct selection criteria and follow-up of the study population. Due to this variability, it is important to stratify the information available about estimates of morbidity and risk factors of lipodystrophy in regard to the different methods and criteria diagnosis employed, population characteristics and types of study designs. A systematic review of published studies may assist in clinical decisions and in public health actions, contributing to best adherence to ART. Additionally, this study will contribute to the improvement of a standardized definition for this important adverse drug reaction which significant impacts treatment and quality of life of patients HIV-positive.

OBJECTIVES

Our aim is to describe lipodystrophy among HIV-infected patients in the current or previous use of ART through the development of a systematic review of observational studies.

METHODS AND ANALYSIS

This will be a systematic review focused on an adverse drug reaction of ART. Data collection, analysis, presentation and interpretation of results will be performed based on standard guidelines for systematic review of adverse effect of healthcare interventions.[15, 16]

Criteria for considering studies for this review

Types of studies

Observational studies irrespective of language and publication status, comparing HIV-infected patients on different antiretroviral regimens irrespective of the number of participants in each arm.

Types of participants

Adolescents and adults HIV-infected patients on current or previous ART use during at least six months.

Types of interventions

Observational studies investigating the occurrence of lipodystrophy as primary or secondary outcomes.

Types of outcome measures

The diagnosis of lipodystrophy performed by clinical evaluation and/or by self-report of patient, confirmed or not by other techniques, characterized by at least one of the alterations as follows:[13]

Lipohypertrophy:

- abdominal obesity;
- breast hypertrophy in women;
- increased fat side of the neck;
- increased fat back of the neck;
- dorso-cervical and supra-pubic lipomas.

Lipoatrophy:

- fat loss in the face;
- fat loss in the buttocks;
- fat loss from legs;
- fat loss in the arms;
- disclosure of the veins in the muscles of the upper and lower.

Mixed lipodystrophy:

- combination of lipoatrophy and lipohypertrophy.

Search methods for identification of studies

Electronic searches

A computerized search will be conducted of MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts, using a search strategy combining free terms and indexing terms. The search strategy can be found in Table1.

Table 1 Search strategy by MEDLINE

MEDLINE (via OVIDsp)
1. exp Lipid Metabolism Disorders
2. exp Body Fat Distribution
3. lipoatrophy.mp.
4. lipohypertrophy.mp.
5. Lipodystrophy.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp HIV Infection
8. exp Anti-Retroviral Agents
9. Nucleoside Reverse Transcriptase Inhibitors.mp.
10. Non-Nucleoside reverse transcriptase inhibitors.mp.
11. Protease Inhibitors.mp.
12. Integrase Inhibitors.mp.
13. Fusion Inhibitors.mp.
14. Ccr5.mp.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 6 and 15

Searching other resources

Citations of included studies will be checked to identify additional studies not identified in the electronic search.

Data collection and analysis

Selection of studies

The selection of articles to be assessed in this review includes two steps. In a first stage, information from titles and abstracts will be screened for exclusion of non-relevant retrieved papers. The potentially relevant articles will be read in full by two independent reviewers and cases of disagreement will be resolved by consensus. The selection process will be carried out according to the criteria for inclusion mentioned previously.

Data extraction and management

Two reviewers will independently extract data from included trials and cases of disagreement will be resolved by consensus. Extracted data will be discussed, decisions documented, and when necessary, the authors of the studies will be contacted for clarification. The reasons for excluding studies from the review will be documented. The following data will be extracted, checked, and recorded.

- Characteristics of studies

Objective;

Design;

Year and country of study;

Duration of study or follow-up;

Source population;

Sample size;

Number of participants in each group monitoring;

Losses to follow-up and/or reasons for non-participation (if applicable).

- Baseline characteristics of the study population

Age;

Age at the time of HIV infection;

Number of naïve enrolled patients;

Number of non-naïve enrolled patients;

Duration of HIV infection;

HIV risk factors;

Log HIV RNA level;

CD4 – positive lymphocyte count;

AIDS category (A, B, C);

Sex;

Duration of ART;

Type of current and prior ART;

Fasting glucose level;

Total cholesterol;

Low density lipoprotein (LDL);

Triglycerides level;

Metabolic syndrome;

Family history of diabetes mellitus, hypertension, cardiovascular events and dyslipidemia;

Co-morbidity (hepatitis C, tuberculosis, etc.);

Consumption of alcohol, tobacco and other drugs.

- Characteristics of lipodystrophy

Lipodystrophy definitions;

Diagnostic criteria of lipodystrophy;

Judgment of causality of lipodystrophy;

Judgment of severity of lipodystrophy;

Number of patients with lipodystrophy;

Age at diagnosis of lipodystrophy;

Occurrence of lipodystrophy according to antiretroviral regimen;

Anthropometric characteristics (height, weight, body mass index, waist circumference, Waist/ hip ratio and percentage of body fat) at diagnosis of lipodystrophy.

Assessment of risk of bias in included studies

Due to the absence of a validated instrument to assess the quality of observational studies of adverse drug reactions, it will be developed a checklist specifically for this review. This tool will be prepared based on the Guideline of The Cochrane Collaboration for non-randomized studies.[12] Two reviewers will assess independently the quality of eligible studies. Disagreements will be resolved by discussion and, when necessary, with the participation of a third reviewer.

Measuring the effect

The primary analysis will measure the frequency of occurrence of lipodystrophy, prevalence and incidence. The extraction of the data of occurrence of the adverse reaction will be carried out in accordance with the study design. Thus, according to the methodological design of the included studies, it will be extracted measures of incidence or prevalence. Moreover, due to the lack of standard diagnostic criteria for this adverse drug reaction, the different outcome measures reported in the included studies will be considered. Data on risk factors associated with lipodystrophy will also be extracted.

Dealing with missing data

Data assumed to be 'missing at random' may not be important and will be ignored. Data assumed to be 'not missing at random' will require contact whit the original author to request the missing data and it will be done whenever possible.

Assessment of heterogeneity and sensitivity analysis

These analyses will be performed separately for each type of study design. The heterogeneity in the results will be graphically inspected and evaluated by means of Chi-squared test and I^2. Sensitivity analysis will be explored through stratification by

subgroups defined according to the type of outcome, diagnostic criteria and quality of studies.

Risk assessment of publication bias

The graphical funnel plot [17] will be used to investigate the presence of publication bias in the studies included in the review.

Data synthesis and subgroup analysis

We will present estimates on the occurrence, prevalence and incidence of lipodystrophy, according to study design, diagnosis criteria, type of outcome (lipoatrophy, lipohypertrophy and mixed form) and clinical and sociodemographic variables. A meta-analysis of the morbidity outcomes will be performed whenever appropriate. If applicable, the following subgroups will be analyzed:

- frequency of lipodystrophy according to duration of HIV infection;
- frequency of lipodystrophy according to ART regimen;
- frequency of lipodystrophy according to duration of ART;
- frequency of lipodystrophy according to risk factors.

ETHICS AND DISSEMINATION

Ethics is not required given this is a protocol for a systematic review. The findings of this study will be disseminated through peer-reviewed publications and conference presentations. Updates of the review will be conducted to inform and guide healthcare practice.

DISCUSSION

The toxicity of ART is a question of increasingly relevance in the treatment of HIV-infected patients due to the need of maintaining ART indefinitely in order to achieve clinical benefits.[18] Information on the occurrence of lipodystrophy among HIV-infected patients during current or previous use of ART are needed in order to support clinical informed decision HIV treatment and the use of ART. Systematic reviews only emphasizing the benefit of drug therapies contribute to the omission of information on adverse effects of the interventions, thus preventing balanced decisions on benefits and risks.[19]

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