

BMJ Open Lipodystrophy among patients with HIV infection on antiretroviral therapy: a systematic review protocol

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ABSTRACT

Introduction: Lipodystrophy is a frequent and disfiguring adverse effect of antiretroviral therapy (ART) in patients with HIV. It affects the quality of life of the patient and adherence to treatment, and generates new needs for comprehensive healthcare services. The aim of this study will be to conduct a systematic review of the literature from observational studies and describe lipodystrophy among patients with HIV infection 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 that considered lipodystrophy as the primary or secondary outcome and that had enrolled adolescent and adult patients with HIV infection who were on current or previous ART for at least 6 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 HIV infection, are unquestionable. The decrease in 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 stigmatising conditions, affecting the quality of life of patients and their adherence to antiretroviral therapy (ART)^{5 6} thus generating new needs for comprehensive healthcare 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 HIV infection.^{8 9} However, epidemiological studies^{10 11} have demonstrated a strong causal relationship between ART and lipodystrophy. Thus, lipodystrophy is considered an adverse effect of ART, and it is a public health issue of great relevance, since it is associated with insulin resistance, diabetes mellitus and dyslipidaemia—known risk factors for cardiovascular disease.¹² Lipodystrophy is characterised by fat accumulation (hypertrophy) in one or more anatomical sites (eg, abdomen, dorsocervical 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 analogue 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 past few years. Studies indicate that

the prevalence of lipodystrophy in patients with HIV infection 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. Owing 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 the best adherence to ART. In addition, this study will contribute to the improvement of a standardised definition for this important adverse drug reaction which significantly impacts treatment and quality of life of patients who are HIV positive.

OBJECTIVES

Our aim is to describe lipodystrophy among patients with HIV infection 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 patients with HIV infection on different antiretroviral regimens irrespective of the number of participants in each arm.

Types of participants

Adolescent and adult patients with HIV infection on current or previous ART use for at least 6 months.

Types of interventions

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

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, characterised 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;
- ▶ Dorsocervical and suprapubic lipomas.

Lipoatrophy

- ▶ Fat loss in the face;
- ▶ Fat loss in the buttocks;
- ▶ Fat loss from legs;
- ▶ Fat loss in the arms;
- ▶ Disclosure of veins in the muscles of the upper and lower limbs.

Mixed lipodystrophy

- ▶ Combination of lipoatrophy and lipohypertrophy.

Search methods for identification of studies

Electronic searches

A computerised 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 [box 1](#).

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 the 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

Box 1 Search strategy by MEDLINE

MEDLINE (via OVIDsp)

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

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 dyslipidaemia
 - Comorbidity (hepatitis C, tuberculosis, etc)
 - Consumption of alcohol, tobacco and other drugs
- ▶ Characteristics of lipodystrophy
 - Lipodystrophy definitions
 - Diagnostic criteria of lipodystrophy
 - Judgement of causality of lipodystrophy
 - Judgement 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

Owing to the absence of a validated instrument to assess the quality of observational studies of adverse drug reactions, there will be developed a checklist specifically for this review. This tool will be prepared based on the Guideline of the Cochrane Collaboration for non-randomised 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 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 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 with the original author to request the missing data and it will be carried out whenever possible.

Assessment of heterogeneity and sensitivity analysis

These analyses will be performed separately for each type of study design. Heterogeneity in the results will be graphically inspected and evaluated by means of χ^2 test and I^2 test. 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 plot¹⁷ 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 socio-demographic variables. A meta-analysis of the morbidity outcomes will be performed whenever appropriate. If applicable, the following subgroups will be analysed:

- ▶ 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.

DISSEMINATION

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 increasing relevance in the treatment of patients with HIV infection due to the need of maintaining ART indefinitely in order to achieve clinical benefits.¹⁸ Information on the occurrence of lipodystrophy among patients with HIV infection during current or previous use of ART is needed in order to support clinical and informed decision on HIV treatment and the use of ART. Systematic reviews only emphasising 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

Knowledge regarding lipodystrophy among patients with HIV infection has increased since the beginning of the HAART era in the late 1990s. As a result, several randomised 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 has hampered the evaluation of morbidity estimates and risk factors associated with lipodystrophy. It is known that much of the evidence on adverse drug reactions comes from observational epidemiology studies due to the limitations of randomised clinical trials in evaluating this type of outcome. Notably, clinical trials are not adequate for detecting long-term outcomes (such as 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 standardised diagnostic criterion. This being considered, our systematic review will evaluate observational studies investigating different outcome definitions and diagnostic methods. As a consequence, the review will include very heterogeneous studies, resulting in different groups of comparisons and more sophisticated analysis (eg, meta-analysis) may or may 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 this, we believe that this study will contribute to the standardisation 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 is needed and it will ease clinical decisions in relation to healthcare interventions for patients with HIV infection, then contribute to lower morbidity and improve adherence to long-term ART

Contributors LGCL developed the methodological strategies under the guidance of DRGJ and participated in the drafting of the study protocol; DRGJ participated in the planning and drafting of the study protocol; EP participated in the planning and drafting of the study protocol; CMP conceived the study and drafted the study protocol. All the authors read and approved the final version of the study protocol for submission.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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