Systematic Review of Antiretroviral-Associated Lipodystrophy: Lipoatrophy, but Not Central Fat Gain, Is an Antiretroviral Adverse Drug Reaction

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Abstract

Background: Lipodystrophy and/or central fat gain are observed frequently in patients on antiretroviral therapy (ART). Both are assumed to be antiretroviral adverse drug reactions.

Methods: We conducted a systematic review to determine whether fat loss or gain was more common in HIV-infected patients on ART than in uninfected controls; was associated with specific antiretrovirals; and would reverse after switching antiretrovirals.

Results: Twenty-seven studies met our inclusion criteria. One cohort study reported more lipoatrophy, less subcutaneous fat gain, but no difference in central fat gain in HIV-infected patients on ART than in controls. Randomised controlled trials (RCTs) showed more limb fat loss (or less fat gain) with the following regimens: stavudine (versus other nucleoside reverse transcriptase inhibitors (NRTIs)); efavirenz (versus protease inhibitors (PIs)); and NRTI-containing (versus NRTI-sparing). RCTs showed increased subcutaneous fat after switching to NRTI-sparing regimens or from stavudine/posingidronate to abacavir/tenofovir. There were no significant between-group differences in trunk and/or visceral fat gain in RCTs of various regimens, but results from efavirenz versus PI regimens were inconsistent. There was no significant between-group differences in central fat gain in RCTs switched to NRTI-sparing regimens, or from PI-containing regimens.

Conclusions: There is clear evidence of a causal relationship between NRTIs (especially thymidine analogues) and lipoatrophy, with concomitant PIs possibly having an ameliorating effect or efavirenz causing additive toxicity. By contrast, central fat gain appears to be a consequence of treating HIV infection, because it is not different from controls, is not linked to any antiretroviral class, and doesn’t improve on switching.

Introduction

Fat redistribution, also called lipodystrophy, is frequently observed in patients on long term antiretroviral therapy (ART) [1]. Some patients develop subcutaneous fat loss, or lipoatrophy; others gain fat, particularly in the breasts, dorsocervical fat pads, and viscerally. Individuals with mixed phenotypes of fat loss and fat gain also occur commonly. Fat redistribution is also associated with metabolic abnormalities, notably dyslipidaemia and insulin resistance, which increase the risk of cardiovascular disease [2].

Lipoatrophy has been associated with exposure to thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) [3]. Central fat gain is also assumed to be an adverse drug reaction [4]. However, there is evidence that visceral abdominal fat in HIV-infected patients on ART is not increased relative to healthy controls [5]. Untreated HIV infection eventually results in wasting, including loss of adipose tissue. Fat gain, which is widely prevalent in the general population and increases with age, may in part be the result of effective ART reversing fat loss due to HIV infection. It is important to determine whether lipodystrophy is an adverse drug reaction to avoid unnecessary drug substitutions which may result in risks of virologic failure, new toxicities, and undermining patient confidence if the lipodystrophy does not improve. Treatment adherence is compromised when patients believe they have lipodystrophy from antiretrovirals [6].

If fat loss and fat gain were adverse antiretroviral drug reactions they would occur more commonly in HIV-infected patients on ART than in HIV-uninfected controls. Second, fat loss and/or fat gain would be associated with specific antiretroviral drugs or drug classes. Third, fat loss and/or fat gain would reverse after switching the identified antiretroviral drugs. We conducted a systematic review to test those three assumptions.

Methods

Eligibility criteria

Types of studies. To answer the question ‘Does fat loss and/or fat gain occur more commonly in patients on ART than in HIV-uninfected controls?’ we included prospective cohort studies...
comparing HIV-infected patients with ART exposure to population controls either known or presumed to be HIV-uninfected. To answer the questions ‘Is fat loss and/or fat gain associated with specific antiretroviral drugs?’ we included randomised controlled trials comparing antiretroviral regimens. To answer the question ‘Is fat loss and/or fat gain reversed after switching antiretroviral drugs?’ we included studies where participants with virologic suppression were randomised to continue their current ART regimen or switch to an alternative regimen.

**Participants.** We included both ART-naïve and ART-experienced HIV-infected patients who were at least 12 years old. For the cohort studies we included control participants who were presumed to be HIV-uninfected. We excluded studies with fewer than 20 participants in any arm.

**Interventions.** We included studies that used any antiretroviral regimens, given for at least 24 weeks, with the exception of those containing hydroxyurea.

**Outcome measures.** We included studies with at least one objective measure of fat distribution done at baseline, and repeated at least once, at a minimum of 24 weeks after baseline. Objective methods of measuring fat distribution included: dual-energy x-ray absorptiometry (DEXA), computerized tomography (CT), or magnetic resonance imaging (MRI). We included measures done both as primary or secondary outcomes, and in the whole study population, or within a sub-study. Specific outcomes included:

- Change from baseline in limb fat
- Change from baseline in subcutaneous adipose tissue (SAT)
- Proportion with ≥20% loss in SAT
- Proportion with ≥20% gain in SAT

To assess fat gain:
- Change from baseline in trunk fat
- Change from baseline in visceral adipose tissue (VAT)
- Proportion with ≥20% gain in trunk fat
- Proportion with ≥20% gain in VAT.

**Search strategies**

We searched two electronic journal databases, PubMed and EMBASE, for articles published between 1 January 1990 and 7 July 2011. We hand-searched electronic databases for the Conferences on Retroviruses and Opportunistic Infections and the International AIDS Society conferences, from 2001. There was no language restriction, provided that an English translation of the abstract was available. The PubMed search strategy terms were as follows:

HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR human immune-deficiency virus[tw] OR (human immun* AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR (acquired immun* AND (deficiency syndrome[tw])) OR “sexually transmitted diseases, viral”[MH:noexp] AND

![Flow diagram of study selection](doi:10.1371/journal.pone.0063623.g001)
| Study | Year published | DEXA/CT/MRI population | n   | ART experience | Lipodystrophy | Age group | Duration of follow up | Primary endpoint(s) |
|-------|----------------|------------------------|-----|----------------|---------------|-----------|----------------------|---------------------|
| [8]   | 2010           | Whole study            | 691 | Experienced    | Patients with and without lipodystrophy included | ≥18 years | 5 years              | SAT, VAT            |
| [3]   | 2011           | Sub-study              | 269 | Naïve          | NA            | ≥16 years | 192 weeks            | Lipatrophy (DEXA)   |
| [9]   | 2011           | Sub-study              | 63  | Naïve          | NA            | NR        | 96 weeks             | Efficacy            |
| [10]  | 2010           | Sub-study              | 112 | Naïve          | NA            | ≥18 years | 96 weeks             | Efficacy            |
| [11]  | 2010           | Sub-study              | 156 | Experienced    | NR            | ≥18 years | 48 weeks             | Efficacy            |
| [4]   | 2009           | Whole study            | 66  | Experienced    | NR            | ≥18 years | 48 weeks             | Mitochondrial changes |
| [12]  | 2009           | Whole study            | 48  | Naïve          | NA            | 18–70     | 24 months            | LF, SAT, VAT        |
| [13]  | 2009           | Whole study            | 757 | Naïve          | NA            | ≥13 years | 96 weeks             | Lipoatrophy (DEXA)  |
| [14]  | 2009           | Sub-study              | 47  | Experienced    | Patients with and without lipodystrophy included | Adult    | 48 weeks             | Efficacy            |
| [15]  | 2009           | Whole study            | 200 | Naïve          | NA            | Adult     | 96 weeks             | Efficacy and safety |
| [32]  | 2009           | Whole study            | 101 | Experienced    | Self-reported lipoatrophy | NR        | 48 weeks             | STF                 |
| [16]  | 2009           | Whole study            | 357 | Experienced    | NR            | ≥18 years | 96 weeks             | Efficacy            |
| [17]  | 2008           | Sub-study              | 140 | Naïve          | NA            | ≥18 years | 48 weeks             | LF                  |
| [18]  | 2008           | Whole study            | 117 | Naïve          | NA            | ≥18 years | 96 weeks             | LF at 96 weeks      |
| [19]  | 2008           | Whole study            | 155 | Naïve          | NA            | ≥18 years | 96 weeks             | Efficacy            |
| [20,33]| 2007           | Sub-study              | 157 | Naïve          | NA            | NR        | 144 weeks            | Changes in glucose and lipid metabolism |
| [21]  | 2007           | Sub-study              | 62  | Experienced    | Patients with and without lipodystrophy included | NR        | ≥96 weeks            | LF                  |
| [22]  | 2007           | Sub-study              | 57  | Naïve          | NA            | Adult     | 96 weeks             | Clinical lipoatrophy |
| [23]  | 2006           | Whole study            | 105 | Experienced    | Lipoatrophy   | ≥18 years | 48 weeks             | LF                  |
| [24]  | 2006           | Sub-study              | 211 | Naïve          | NA            | ≥16 years | 48 weeks             | VAT                 |
| [25]  | 2012           | Whole study            | 200 | Experienced    | Abdominal fat accumulation | ≥18 years | 96 weeks             | TF:LF               |
| [26]  | 2012           | Sub-study              | 74  | Experienced    | NR            | ≥18 years | 48 weeks             | VAT                 |
| [27]  | 2011           | Whole study            | 142 | Experienced    | NR            | Adult     | 48 weeks             | LF                  |
| [28]  | 2009           | Sub-study              | 100 | Experienced    | NR            | ≥18 years | 48 weeks             | Change in haemoglobin |
| [29]  | 2008           | Whole study            | 100 | Experienced    | Self-reported lipoatrophy | ≥18 years | 96 weeks             | STF                 |
| [30]  | 2002           | Whole study            | 106 | Experienced    | Clinical lipoatrophy | >18 years | 24 weeks             | LF                  |
| [31]  | 2001           | Whole study            | 106 | Experienced    | Clinical lipoatrophy | Adult     | 48 weeks             | Efficacy            |

LF: limb fat; NA: not applicable – treatment-naïve patients; NR: not reported; SAT: subcutaneous adipose tissue; STF: subcutaneous thigh fat; TF: trunk fat; VAT: visceral adipose tissue.
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Table 2. Change from baseline in limb fat (LF) on DEXA scan, and subcutaneous thigh fat (STF) and subcutaneous adipose tissue (SAT) on CT scan: NRTI-containing regimens versus NRTI-sparing regimens.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|
| [9]   | LF*     | LPVr+AZT+3TC | −703 g (22) | 0.014 | −1930 g (5) | >0.05 |
|       |         | LPVr monotherapy | −63 g (41) |         | −400 g (8) |         |
| [4]   | Percentage of body fat, 0 & 48 wks² | LPVr+ continue 2NRTIs | 12.2; 13.4 (33⁴) | NR | ND | NA |
|       |         | NVP+LPVr | 11.1; 14.1 (33⁴) | ND |         |         |
| [12]  | Mean (95% CI) g, 0 & 48 wks | AZT+3TC+LPVr | 6360 (5919 to 6801); 6520 (6059 to 6981) (22⁵) | NR | 5980 (5519 to 6441) | NR |
|       |         | NVP+LPVr | 6360 (5968 to 6752); 7030 (6618 to 7442) (26⁵) | 7210 (6789 to 7631) |         |         |
|       | Mean (95% CI) cm², 0 & 48 wks² | SAT* | 118 (107 to 129); 126 (114 to 138) (22⁵) | NR | 123 (111 to 135) | NR |
|       |         | NVP+LPVr | 118 (108 to 128); 132 (121 to 143) (24⁵) | 142 (131 to 153) |         |         |
| [13]  | LF*     | EFV+3TC+(TDF or AZT or D4T) | 8.9%⁸ (188) | NR | 1.4% (171) | <0.001 vs NRTI-sparing |
|       |         | LPVr+3TC+(TDF or AZT or D4T) | 10.1%⁹ (191) | 9.8% (166) | 0.013 vs NRTI-sparing |
|       | EFV+LPVr (NRTI-sparing) | 14.2%⁹ (197) | 17.6% (173) |         |         |
| [32]  | STF*    | ABC+continue other ARVs | 18% (42) | 0.57 | ND | NA |
|       |         | LPVr+NVP | 17% (46) | ND | NA |         |
| [18]  | LF*     | PIr+2NRTIs | 0.37 kg (28) | 0.253 vs NNRTI+PIr | ND | NA |
|       |         | NNRTI+2NRTIs | 0.9 kg (21) | 0.298⁸ vs PIr+2NRTIs | ND | NA |
|       |         | NNRTI+PIr | 0.79 kg (49) | 0.793 vs NNRTI+2NRTIs | ND | NA |
| [21]  | LF*     | EFV+2NRTIs | −242 g (25) | 0.086 | −850 g (25) | 0.002 |
|       |         | LPVr+EFV | 562 g (22) | 782 g (22) | 0.002 |         |
| [11]  | LF*     | DRVr+ continue 2NRTIs | −0.26% (74) | <0.001 | ND | NA |
|       |         | DRVr monotherapy | 8.3% (67) | ND | NA |         |

a. median; b. leg fat; c. absolute values at each time-point (change from baseline not reported); d. n at baseline (n at time-point not reported); e. mean; f. means (corrected for differences in baseline values) and 95% confidence intervals (calculated by the authors of this review) at each time-point (change from baseline not reported); g. values derived from graph; h. calculated by authors of this review; i. DDI+3TC or DDI+AZT or AZT+3TC or D4T+3TC or DDI+D4T; j. at last visit (median 102 weeks).

NA: not applicable; ND: not done; NR: not reported.

Antiretrovirals: 3TC: lamivudine; ABC: abacavir; AZT: zidovudine; D4T: stavudine; DRVr: ritonavir-boosted darunavir; EFV: efavirenz; LPVr: ritonavir-boosted lopinavir; NVP: nevirapine; PIr: ritonavir-boosted PI; TDF: tenofovir.
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Search Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:-NoExp] OR ([anti] AND [hiv[tw]]) OR antiretroviral[tw] OR ([anti] AND [retrovirals[tw]]) OR HAART[tw] OR ([anti] AND [acquired immunodeficiency[tw]]) OR ([anti] AND [acquired immunodeficiency[tw]]) OR ([anti] AND [acquired immuno-deficiency[tw]]) OR ([anti] AND [acquired immuno-deficiency[tw]]) OR ([anti] AND [acquired immun*-AND [deficiency[tw]]) OR [anti] AND [acquired immun*-AND [deficiency[tw]])
OR
Search zalcitabine OR zidovudine OR lamivudine OR stavudine OR didanosine OR tenofovir OR abacavir OR entricitabine OR nevirapine OR efavirenz OR delavirdine OR etravirine OR rifampir OR amprenavir OR atazanavir OR tipranavir OR indinavir OR saquinavir OR lopinavir OR fosamprenavir OR ritonavir OR darunavir OR nelfinavir OR enfuvirtide OR maraviroc OR raltegravir AND
Search Lipodystrophy[mh] OR lipodystrophy[tia] OR hypodystrophy[tia] OR lipodystrophies[tia] OR lipohypertrophy-[tia] OR lipoatrophy[tia] OR body fat distribution[mh] OR fat[tia] OR fats[tia] OR abdominal fat[mh] OR adipose tissue[mh] OR adipose [tia] OR adiposity[tia] OR temporal wasting[tia] OR buffalo hump[tia].
Data collection
Two authors (RdW and KC) independently reviewed all study abstracts identified by the search strategy, using a specially designed eligibility form. We obtained the full articles, conference abstracts or conference posters for all studies that met the inclusion criteria. An independent translator reviewed articles that were published in languages other than English. We resolved disagreements as to study eligibility through consensus and discussion with the third author (GM) if necessary. One author (RdW) extracted data using a data extraction form; another author (KC) checked the extracted data. Two authors (RdW and KC) assessed the risk of bias of all included studies [7].

Results
We identified a total of 27 studies for inclusion in the review: one cohort study comparing HIV-infected patients with controls [8]; 18 randomised controlled trials comparing antiretroviral regimens [3,4,9–24]; seven switching studies [25–31]; and one study that fulfilled the criteria for both randomised controlled trials and switching studies [32]. Our search of PubMed and Embase

Table 3. Change from baseline in limb fat (LF) on DEXA scan and subcutaneous adipose tissue (SAT) on CT scan: PI versus NNRTI.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|
| [3]   | LF^a    | ATVr+(ABC+3TC or TDF+FTC) | 25.2%\(^b\) (105) | NR | 30.4% (94) | 0.01 |
|       |         | EFV+(ABC+3TC or TDF+FTC)  | 17.7%\(^b\) (112) | 16.5% (109) |         |         |
| [13]  | LF^c    | LPV+3TC+(TDF or AZT or D4T) | 10.1%\(^b\) (191) | 9.8% (166) | 0.007 |
|       |         | EFV+3TC+(TDF or AZT or D4T) | 8.9%\(^b\) (188) | NR | 1.4% (171) |         |
| [18]  | LF^a    | NNR TI+2NRTIs | 0.37 g (28) | 0.30\(^d\) | ND | NA |
|       |         | NNR TI+2NRTIs | 0.9 g (21) | ND | NA |         |
| [19]  | LF^c    | LPV+AZT+3TC or LPV monotherapy\(^a\) | 11.8% (NR) | NR | 18.5%\(^b\) (74) | NR |
|       |         | EFV+AZT+3TC | 3.1\(^b\) (20) | NR | −9\(^b\) (32) |         |
| [24]  | SAT^a   | ATV+AZT+3TC | 12.8 cm\(^2\) (62) | 95% CI for difference: −16.8 to 27.5 | NR | ND | NA |
|       |         | EFV+AZT+3TC | 7.6 cm\(^2\) (47) | ND | NA |         |
| [20,33]| LF^c,f  | NFV+(AZT+3TC or DDI+D4T) | −4.7%\(^b\) (23) | NR | −23.7%\(^b\) (11) | NR |
|       |         | EFV+(AZT+3TC or DDI+D4T) | 1.5%\(^b\) (26) | 9.9%\(^b\) (32) |         |         |

\(^a\) mean; \(^b\) values derived from graph; \(^c\) median; \(^d\) calculated by authors of this review; \(e\) if virologically suppressed for 3 months; \(^f\) as-treated analysis.

NA: not applicable; ND: not done; NR: not reported.
Antiretrovirals: 3TC: lamivudine; ABC: abacavir; ATV: atazanavir; ATVr: ritonavir-boosted atazanavir; AZT: zidovudine; D4T: stavudine; DDI: didanosine; EFV: efavirenz; FTC: emtricitabine; LPVr: ritonavir-boosted lopinavir; NFV: nelfinavir; TDF: tenofovir.

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Table 4. Change from baseline in limb fat (LF) on DEXA scan and subcutaneous adipose tissue (SAT) on CT scan: NRTI versus NRTI.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|
| [3]   | LF^a    | ABC+3TC+(ATVr or EFV) | 22.8%\(^c\) (107) | NR | 24.9% (102) | 0.46 |
|       |         | TDF+FTC+(ATVr or EFV) | 19.7%\(^c\) (110) | 20.9% (101) |         |         |
| [14]  | LF^c    | ABC+3TC+continue Pl or NNRTI | 104 g (23) | 0.92 | ND | NA |
|       |         | TDF+FTC+continue Pl or NNRTI | 75 g (24) | ND | NA |         |
| [22]  | LF^a    | ABC+3TC+EFV | 686 g (25) | 0.001 | 913 g (25) | <0.001 |
|       |         | D4T+3TC+EFV | −1164 g (32) | −1578 g (32) |         |         |
| [23]  | LF^a    | ABC+continue other ARVs | 483 g (44) | 0.37 | ND | NA |
|       |         | TDF+continue other ARVs | 329 g (49) | ND | NA |         |
|       | SAT^a   | ABC+continue other ARVs | 8.0 cm\(^2\) (44) | 0.96 | ND | NA |
|       |         | TDF+continue other ARVs | 8.4 cm\(^2\) (49) | ND | NA |         |
| [20,33]| LF^c,d  | DDI+D4T+(EFV or NFV) | −11.9%\(^b\) (42) | NR | −26.4%\(^b\) (22) | NR |
|       |         | AZT+3TC+(EFV or NFV) | 1.6%\(^b\) (39) | 1.7%\(^b\) (24) |         |         |
| [16]  | LF^a    | ABC+3TC+continue NNRTI or PI | 0.3 kg (179°) | 0.4 | 0.53 kg (NR) | 0.46 |
|       |         | TDF+continue NNRTI or PI | 0.19 kg (178°) | 0.42 kg (NR) |         |         |

\(^a\) mean; \(^b\) values derived from graph; \(^c\) median; \(^d\) as-treated analysis; \(e\) n at baseline (n at time-point not reported).

NA: not applicable; ND: not done; NR: not reported.

Antiretrovirals: 3TC: lamivudine; ABC: abacavir; ATV: atazanavir; ATVr: ritonavir-boosted atazanavir; AZT: zidovudine; D4T: stavudine; DDI: didanosine; EFV: efavirenz; FTC: emtricitabine; NFV: nelfinavir; TDF: tenofovir.

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databases identified 3031 potential abstracts. We identified a further 67 articles through conference databases or other sources. After removing duplicate records, we screened 3042 abstracts and excluded 2966 as they did not meet our inclusion criteria. We retrieved and assessed the full text articles for the remaining 76, and excluded 49 that did not meet our inclusion criteria (see Figure 1 and Table S1). We assessed two articles that were published in Spanish through means of a translator. We included the full text articles for five studies that we identified through conference abstracts.

### Characteristics of included studies

Fat distribution measures were done in all participants for 15 studies: one cohort study [8]; nine randomised controlled trials comparing antiretroviral regimens [4,12,13,15,16,18,19,23,32]; and five switching studies [25,27,29–31]. They were done in a subset of participants only in the remaining 12 studies [3,9–11,14,17,21,22,24,26,28,33].

### Tables

#### Table 5. Change from baseline in limb fat (LF) on DEXA scan and subcutaneous adipose tissue (SAT) on CT scan: PI versus PI.

| Study | Measure | Arm                  | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|----------------------|-------------|---------|-------------|---------|
| [15]  | LF      | ATVr+D4T+3TC         | 2% (72)     | NR      | −9% (55)    | >0.05   |
|       |         | ATV+D4T+3TC          | −3% (89)    | NR      | −17% (67)   |         |
|       | SAT     | ATVr+D4T+3TC         | 12% (68)    | NR      | 8% (56)     | >0.05   |
|       |         | ATV+D4T+3TC          | 12% (85)    | NR      | 2% (62)     |         |
| [17]  | LF      | TPVr100+TDF+3TC      | 1.4% (46)   | 0.02 vs LPVr+TDF+3TC | ND | NA |
|       |         | TPVr200+TDF+3TC      | 1.6% (48)   | 0.14 vs LPVr+TDF+3TC | ND | NA |
|       | SAT     | TPVr100+TDF+3TC      | 2.8% (45)   |         | ND | NA |
|       |         | TPVr200+TDF+3TC      | −2.1 cm² (46) | 0.03 vs LPVr+TDF+3TC | ND | NA |
|       |         | LPVr+TDF+3TC         | 4.2 cm² (48) | 0.13 vs LPVr+TDF+3TC | ND | NA |
|       |         | LPVr+TDF+3TC         | 17.6 cm² (45) | ND | NA |

a. mean; b. median.

#### Table 6. Change from baseline in limb fat (LF) on DEXA scan and subcutaneous adipose tissue (SAT) on CT scan: raltegravir versus efavirenz.

| Study | Measure | Arm                  | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|----------------------|-------------|---------|-------------|---------|
| [10]  | LF      | RAL+TDF+FTC          | 18.1% (40)  | 0.95 b  | 18.2% (37)  | 0.88 b  |
|       |         | EFV+TDF+FTC          | 17.7% (46)  | 17.0% (38) |

a. mean; b. p value calculated by authors of this review.

#### Table 7. Proportion of patients with peripheral lipoatrophy on DEXA scan: NRTI-containing regimens versus NRTI-sparing regimens.

| Study | Definition          | Arm                  | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------------------|----------------------|-------------|---------|-------------|---------|
| [9]   | >20% loss of LF     | LPVr+AZT+3TC         | 27.3% (22)  | 0.018   | ND | NA |
|       |                     | LPVr monotherapy     | 4.9% (41)   | ND      |             |         |
|       | OR* LPVr+AZT+3TC vs LPVr monotherapy 7.06. 95% CI 1.11 to 78.69 |
| [13]  | ≥20% loss of LF     | EFV+3TC+(TDF or AZT or D4T) | 21% (188)   | NR      | 32% (171)   | <0.001 vs NRTI-sparing |
|       |                     | LPVr+3TC+(TDF or AZT or D4T) | 10% (191)   | 17% (166) | 0.023 vs NRTI-sparing |
|       |                     | EFV+LPV (NRTI-sparing) | 7% (197)    | 9% (173) |             |         |
| [11]  | >20% loss of LF     | DRVr+ continue 2NRTIs | 10.8% (74)  | 0.035   | ND | NA |
|       |                     | DRVr monotherapy     | 1.5% (67)   | ND      |             |         |

a. adjusted for age and sex.

LF: limb fat; NA: not applicable; ND: not done; OR: odds ratio.

Antiretrovirals: 3TC: lamivudine; AZT: zidovudine; D4T: stavudine; DRVr: ritonavir-boosted darunavir; EFV: efavirenz; LPVr: ritonavir-boosted lopinavir; TDF: tenofovir.

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studies are summarised in Table 1, and risk of bias assessment in Table S2.

### Participants

Twelve randomised controlled trials enrolled antiretroviral-naïve participants [3,9,10,12,13,15,17–19,22,24,33]. The cohort study [8], seven randomised controlled trials [4,11,14,16,21,23,32], and all the switching studies enrolled antiretroviral-experienced participants. The cohort study enrolled participants both with and without lipodystrophy. Two randomised controlled trials enrolled only participants with clinical or self-reported features of lipoatrophy [23,32]; and two enrolled participants both with and without lipoatrophy [14,21]. Three switching studies enrolled only participants with clinical or self-reported lipoatrophy [29–31]; and one enrolled participants with features of abdominal fat accumulation, defined as a waist-to-hip ratio $>0.9$, with a waist circumference $>88.2$ or $>75.3$ cm in men and women respectively [25]. For the remaining studies it was not reported whether or not participants had features of lipodystrophy at baseline.

### Table 8. Proportion of patients with peripheral lipoatrophy on DEXA scan: PI versus NNRTI.

| Study | Definition | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|------------|-----|-------------|---------|-------------|---------|
| [13]  | $\geq 20\%$ loss of LF | LPV+3TC+(TDF or AZT or D4T) | 10% (191) | NR | 17% (166) | 0.003 |
|       |            | EFV+3TC+(TDF or AZT or D4T) | 21% (188) | 32% (171) | OR$^a$ EFV vs LPV 2.63, 95% CI 1.49 to 4.64 | $<0.001$ |
| [19]  | $>20\%$ loss of LF | LPV+AZT+3TC or LPVr monotherapy$^b$ | ND | NA | 5% (74) | $<0.001$ |
|       |            | EFV+AZT+3TC | ND | 34% (32) | |
| [33]  | $>10\%$ loss of LF | NFV+(AZT+3TC or DDI+D4T) | NR | |
|       |            | EFV+(AZT+3TC or DDI+D4T) | NR | ND | NA | |

$^a$ adjusted for NRTI arm, race, sex, baseline extremity fat and baseline CD4 count; $^b$ if virologically suppressed for 3 months; $c$ adjusted for NRTI assignment, age, sex, race, and baseline BMI, HIV RNA and CD4 count.

### Table 9. Proportion of patients with peripheral lipoatrophy on DEXA scan: NRTI versus NRTI.

| Study | Definition | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|------------|-----|-------------|---------|-------------|---------|
| [33]  | $>10\%$ loss of LF | DDI+D4T+(EFV or NFV) | NR | |
|       |            | AZT+3TC+(EFV or NFV) | NR | ND | NA | |

$^a$ adjusted for age, sex, race, and baseline BMI, HIV RNA and CD4 count.

### Table 10. Proportion of patients with peripheral lipoatrophy on DEXA scan: PI versus PI.

| Study | Definition | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|------------|-----|-------------|---------|-------------|---------|
| [15]  | $\geq 20\%$ loss of LF | ATV+D4T+3TC | 21% (72) | 29% (55) | $<0.05$ |
|       |            | ATV+D4T+3TC | 30% (89) | 49% (67) | |

### Table 11. Proportion of patients with peripheral lipoatrophy on DEXA scan: raltegravir versus efavirenz.

| Study | Definition | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|------------|-----|-------------|---------|-------------|---------|
| [10]  | $\geq 20\%$ loss of LF | RAL+TDF+FTC | ND | NA | 8% (37) | 0.62$^a$ |
|       |            | EFV+TDF+FTC | ND | 5% (38) | |

$^a$ p value calculated by the authors of this review.
Interventions

All included studies involved a comparison of different antiretroviral regimens, with the exception of the cohort study that compared HIV-infected people with people who were known or presumed to be HIV-uninfected [8]. Eight randomised controlled trials [4,9,11–13,18,21,32], and two switching studies [29,32] evaluated NRTI-sparing regimens; four randomised controlled trials [3,19,24,33], and one switching study [31] evaluated protease inhibitor (PI) versus non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens; six randomised controlled trials [3,14,16,22,23,33], and five switching studies [27,28,30,32,34] evaluated NRTI versus NRTI regimens; two

Table 12. Change from baseline in trunk fat (TF) on DEXA scan, and visceral adipose tissue (VAT) on CT scan: NRTI-containing regimens versus NRTI-sparing regimens.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|
| [9]   | TFa     | LPVr+AZT+3TC | -211 g (22)  | 0.665   | 346 g (5)   | >0.05   |
|       |         | LPVr monotherapy | -579 g (41) |  | -859 g (8) |  |
| [4]   | Percentage of body fat, 0 & 48 wks. | LPVr+ continue 2NRTIs | 20.6; 22.6 (33) | NR | ND | NA |
|       |         | NVP+LPVr | 22.5; 24.0 (33) |  |  |  |
| [12]  | VATb   | AZT+3TC+LPVr | 100 (88 to 112); 104 (90 to 118) (22) | NR | 122 (108 to 135) | NR |
|       |         | NVP+LPVr | 100 (89 to 111); 109 (96 to 122) (26) |  | 111 (98 to 124) |  |
| [32]  | VATa   | ABC+continue other ARVs | -15% (43) | 0.1 | ND | NA |
|       |         | LPVr+NVP | -4% (47) |  | ND |  |
| [21]  | TFa     | EFV+2NRTIs | 133 g² (25) | >0.05 | -583 g² (25) | >0.05 |
|       |         | LPVr+EFV | -170 g² (22) |  | -206 g² (22) |  |
| [11]  | TFa     | DRV+ continue 2NRTIs | 5.9% (74) | >0.05 | ND | NA |
|       |         | DRVr monotherapy | 7.6% (67) |  | ND |  |

a. median; b. absolute values at each time-point (change from baseline not reported); c. n at baseline (n at time-point not stated); d. mean; e. means (corrected for differences in baseline values) and 95% confidence intervals (calculated by the authors of this review) at each time-point (change from baseline not reported); f. DDI+3TC or DDI+AZT or AZT+3TC or D4T+3TC or DDI+D4T; g. values derived from graph.

Interventions

All included studies involved a comparison of different antiretroviral regimens, with the exception of the cohort study that compared HIV-infected people with people who were known or presumed to be HIV-uninfected [8]. Eight randomised controlled trials [4,9,11–13,18,21,32], and two switching studies [29,32] evaluated NRTI-sparing regimens; four randomised controlled trials [3,19,24,33], and one switching study [31] evaluated protease inhibitor (PI) versus non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens; six randomised controlled trials [3,14,16,22,23,33], and five switching studies [27,28,30,32,34] evaluated NRTI versus NRTI regimens; two

Table 13. Change from baseline in trunk fat (TF) on DEXA scan, and visceral adipose tissue (VAT) on CT scan: PI versus NNRTI.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|
| [3]   | TFa     | ATV+(ABC+3TC or TDF+FTC) | 26.1%² (105) | NR | 36.5% (94) | 0.028 |
|       |         | EFV+(ABC+3TC or TDF+FTC) | 20.4%² (112) |  | 21.1% (109) |  |
|       | VATa    | ATV+(ABC+3TC or TDF+FTC) | NR | NA | LR coefficient⁴ (ATV vs EFV) 11.0 cm² | 0.20 |
|       |         | EFV+(ABC+3TC or TDF+FTC) | NR |  | 95% CI – 5.9 to 27.9 |  |
| [19]  | TFb     | LPVr+AZT+3TC or LPVr’a | 6.9% (NR) | NR | 13.8%² (74) | >0.05 |
|       |         | EFV+AZT+3TC | 15.2% (NR) |  | 14.6%² (32) |  |
| [24]  | VATa    | ATV+AZT+3TC | 15.3 cm² (62); 95% CI for difference: –10.4 to 12.6 | NR | ND | NA |
|       |         | EFV+AZT+3TC | 14.1 cm² (46) |  | ND |  |
| [20,33]| TFc    | NFV+(AZT+3TC or DDI+D4T) | 8.3%⁵ (23) | NR | –6.8%⁵ (11) | NR |
|       |         | EFV+(AZT+3TC or DDI+D4T) | 14.8%⁵ (26) |  | 32.6%⁵ (16) |  |

a. mean; b. values derived from graph; c. adjusted for treatment allocation, sex, age, race, and baseline HIV RNA, CD4 count and BMI; d. median; e. LPVr monotherapy if virologically suppressed for 3 months; f. as treated analysis.

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randomised controlled trials [15,17], and one switching study [25] evaluated PI versus PI regimens; and one randomised controlled trial [10], and one switching study [26] evaluated other antiretroviral categories.

Outcomes
An objective measure of fat distribution was the primary study endpoint in 15 studies [3,8,12,13,17,18,21,23–27,29,30,32]. In the remaining studies, measures of fat distribution were secondary endpoints.

HIV-infected patients compared with healthy controls. The FRAM2 study compared fat distribution in HIV-infected patients with healthy controls, using MRI at two time-points separated by about five years [8]. The control participants were recruited from the Visceral Fat and Metabolic Rate in Young Adults sub-study of the Coronary Artery Risk Development in Young Adults study. They were selected as they had previous experience of fat distribution investigations, and had a similar age and ethnic distribution to most HIV-infected patients in the United States [35]. Although the analyses included HIV-infected patients who had never been on ART (11.8% at baseline and 5.7% at year 5), we included the study as only a small minority were not on ART. Sub-group analyses by ART status were not done.

There was clear evidence of fat loss in HIV-infected people, 53% of whom had lipoatrophy (defined as leg SAT below the 10th percentile of controls) after five years of observation. Longer duration of stavudine use was associated with less leg SAT. After five years there was significantly less SAT at all sites in HIV-infected men, but only in the limbs in HIV-infected women. Multivariable analysis showed that increase in SAT over five years was less in HIV-infected people at all sites except the lower trunk.

Table 14. Change from baseline in trunk fat (TF) on DEXA scan, and visceral adipose tissue (VAT) on CT scan: NRTI versus NRTI.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|------------|---------|------------|---------|
| [3]   | TF*     | ABC+3TC+(ATVr or EFV) | 24.9%b (107) | NR | 29.4%b (102) | 0.76 |
|       |         | TDF+FTC+(ATVr or EFV) | 21.6%b (110) | NR | 27.3%b (101) | 0.52 |
|       | VAT     | ABC+3TC+(ATVr or EFV) | ND | NA | LR coefficient (ABC+3TC vs TDF+FTC) −5.3 cm² | 0.52 |
|       |         | TDF+FTC+(ATVr or EFV) | ND | NA | 95% CI −21.5 to 11.0 |
| [22]  | TF*     | ABC+3TC+EFV | ND | NA | 1225 g (25) | 0.58 |
|       |         | D4T+3TC+EFV | ND | NA | 996 g (32) |
| [23]  | TF*     | Switch AZT/D4T to ABC+cont. other ARVs | 618 g (44) | 0.97 | ND |
|       |         | Switch AZT/D4T to D4T+cont. other ARVs | 607 g (49) | ND |
|       | VAT     | Switch AZT/D4T to ABC+cont. other ARVs | 2 cm² (44) | 0.49 | ND |
|       |         | Switch AZT/D4T to D4T+cont. other ARVs | 6.8 cm² (49) | ND |
| [20,33]| TFd,e  | DDI+D4T+(EFV or NFV) | 9.8%b (42) | NR | −0.7%b (22) | NR |
|       |         | AZT+3TC+(EFV or NFV) | 9.1%b (39) | 13.6%b (24) |

a. mean; b. values derived from graph; c. adjusted for treatment allocation, sex, age, race, and baseline HIV RNA, CD4 count and BMI; d. median; e. as treated analysis. LR: linear regression; NA: not applicable; ND: not done; NR: not reported.

Antiretrovirals: 3TC: lamivudine; ATVr: ritonavir-boosted atazanavir; AZT: zidovudine; D4T: stavudine; DDI: didanosine; EFV: efavirenz; FTC: emtricitabine; NFV: nevirapine; TDF: tenofovir.

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Table 15. Change from baseline in trunk fat (TF) on DEXA scan, and visceral adipose tissue (VAT) on CT scan: PI versus PI.

| Study | Measure | Arm | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|------------|---------|------------|---------|
| [15]  | TF*     | ATVr+D4T+3TC | 12% (72) | NR | 16% (55) | >0.05 |
|       |         | ATVr+D4T+3TC | 15% (89) | 14% (67) |
|       | VAT     | ATVr+D4T+3TC | 28% (68) | NR | 33% (56) | >0.05 |
|       |         | ATVr+D4T+3TC | 34% (85) | 32% (62) |
| [17]  | TFb     | TPVr100+TDF+3TC | −0.8% (46) | 0.005 vs LPVr+TDF+3TC | ND | NA |
|       |         | TPVr200+TDF+3TC | −0.7% (48) | 0.02 vs LPVr+TDF+3TC | ND |
|       |         | LPVr+TDF+3TC | 2.1% (45) | ND |
|       | VATb    | TPVr100+TDF+3TC | −6 cm² (46) | 0.4 vs LPVr+TDF+3TC | ND | NA |
|       |         | TPVr200+TDF+3TC | −9 cm² (48) | 0.04 vs LPVr+TDF+3TC | ND |
|       |         | LPVr+TDF+3TC | −3 cm² (45) | ND |

a. mean; b. median.

NA: not applicable; ND: not done; NR: not reported.

Antiretrovirals: 3TC: lamivudine; ATV: atazanavir; ATVr: ritonavir-boosted atazanavir; D4T: stavudine; LPVr: ritonavir-boosted lopinavir; TDF: tenofovir; TPVr100: tipranavir/ritonavir 500/100 mg twice a day; TPVr200: tipranavir/ritonavir 500/200 mg twice a day.

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By contrast, there was no evidence of regional fat accumulation in HIV-infected people. After five years the amount of trunk SAT and VAT was similar in HIV-infected and control women, while HIV-infected men had less fat at all sites than control men. The gains in VAT over five years were similar in HIV-infected people and controls.

### Fat loss: changes in limb fat and SAT with different antiretroviral regimens.

The changes from baseline in limb fat and SAT are summarised in Tables 2, 3, 4, 5, and 6, and the incidences of peripheral lipoatrophy (defined as ≥20% loss of limb fat) was significantly lower in participants on NRTI-sparing regimens compared with those on NRTI-containing regimens, and in those on PI-containing regimens compared with those on EFV-based regimens [9,11,13,19]. There were no significant differences in average gains in SAT or limb fat over time in the four studies that compared abacavir-with tenofovir-based regimens [3,14,16,23]. One study found that participants who received an abacavir-containing regimen gained limb fat over time, in contrast to participants who received a stavudine-containing regimen who lost limb fat over time (gain of 913 g versus loss of 1578 g, p < 0.001) [22]. Another study found that participants who received a stavudine-lamivudine-containing regimen gained limb fat over time, in contrast to participants who received a stavudine-didanosine-containing regimen who lost limb fat over time (gain of 1.7% versus loss of 26.4%, p value not reported) [33].

Unboosted atazanavir was associated with significant reduction in limb fat at 96 weeks, while there was no significant change in

| Study Measure Arm | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 (n) | p value |
|------------------|------------|---------|------------|---------|------------|---------|
| [31] LF a,b Cont Pi+ 2NRTI | ND | NA | NR (54) | 1.5 (1.3 to 1.8); 1.3 (1.1 to 1.6) | ND | NA |
| Switch to NVP+DDI+D4T | ND | NR (52) | 1.2 (1.1 to 1.4); 1.2 (1.1 to 1.4) | ND | NA |

a. mean; b. leg fat; c. n at baseline (n at time-point not stated); d. means and 95% confidence intervals (calculated by the authors of this review) at each time-point (change from baseline not reported).

NA: not applicable; ND: not done; NR: not reported.
Antiretrovirals: D4T: stavudine; DDI: didanosine; NVP: nevirapine.

doi:10.1371/journal.pone.0063623.t018
| Study | Measure | Arm                  | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 | p value |
|-------|---------|----------------------|-------------|---------|-------------|---------|---------|---------|
| [28]  | LF<sup>a</sup> | Cont AZT+3TC+EFV    | ND          | NA      | 187 g (36)  | 0.024   | ND      | NA      |
|       |         | Switch TDF+FTC+EFV  | ND          | NA      | 261 g (38)  | ND      | ND      |         |
| [32]  | STF<sup>b</sup> | Cont AZT or D4T regimen | −3% (24) | NR      | ND          | ND      | ND      | ND      |
|       |         | Switch AZT/D4T to ABC | 0% (37) | ND      | ND          | ND      |         |         |
| [30]  | LF<sup>a</sup> | Cont AZT or D4T regimen | 0.08 kg (56) | 0.02 | ND          | NA      | ND      | NA      |
|       |         | Switch AZT/D4T to ABC | 0.39 kg (50) | ND      | ND          | ND      |         |         |
|       | STF<sup>a,c</sup> | Cont AZT or D4T regimen | −1.2 cm<sup>2</sup> (56) | 0.01 | ND          | NA      | ND      | NA      |
|       |         | Switch AZT/D4T to ABC | 3.3 cm<sup>2</sup> (50) | ND      | ND          | ND      |         |         |
| [27]  | SAT<sup>b</sup> | Cont AZT+3TC        | −2.7%<sup>d</sup> (NR) | 0.03 | ND          | NA      | ND      | NA      |
|       |         | Switch to TDF+FTC   | 2.1%<sup>d</sup> (NR) | 1.6%<sup>d</sup> (66) | ND      |         |         |         |
|       | LF<sup>b</sup> | Cont AZT+3TC        | 3.2%<sup>d</sup> (NR) | 0.5   | ND          | NA      | ND      | NA      |
|       |         | Switch to TDF+FTC   | 3.9%<sup>d</sup> (NR) | 5.2%<sup>d</sup> (66) | ND      |         |         |         |

<sup>a</sup> mean; <sup>b</sup> median; <sup>c</sup> right thigh; <sup>d</sup> values derived from graph.

NA: not applicable; ND: not done; NR: not reported.

Antiretrovirals: 3TC: lamivudine; ABC: abacavir; AZT: zidovudine; D4T: stavudine; EFV: efavirenz; FTC: emtricitabine; TDF: tenofovir.

doi:10.1371/journal.pone.0063623.t019

| Study | Measure | Arm                  | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 | p value |
|-------|---------|----------------------|-------------|---------|-------------|---------|---------|---------|
| [25]  | LF<sup>a</sup> | Cont PI +2NRTIs      | ND          | NA      | −3.6% (54)  | 0.15    | −6.1% (54) | 0.17 |
|       |         | Switch PI to ATVr    | ND          | NA      | 0.9% (112)  | ND      | 0.8% (112) | ND  |
| [27]  | SAT<sup>a</sup> | Cont PI +2NRTIs      | ND          | NA      | −5.9% (59)  | 0.16    | −9.7% (59) | 0.6  |
|       |         | Switch PI to ATVr    | ND          | NA      | −2.1% (108) | ND      | 3.5% (108) | ND  |

<sup>a</sup> mean.

NA: not applicable; ND: not done.

Antiretrovirals: ATVr: ritonavir-boosted atazanavir; PI: ritonavir-boosted PI.

doi:10.1371/journal.pone.0063623.t020

| Study | Measure | Arm                  | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 | p value |
|-------|---------|----------------------|-------------|---------|-------------|---------|---------|---------|
| [26]  | LF<sup>a</sup> | Cont PI regimen      | ND          | NA      | 171 g (35)  | 0.791   | ND      | NA      |
|       |         | Switch PI to RAL    | ND          | NA      | 32 g (39)   | ND      | ND      | ND      |
|       | SAT<sup>a</sup> | Cont PI regimen      | ND          | NA      | 3.6% (35)   | 0.496   | ND      | NA      |
|       |         | Switch PI to RAL    | ND          | NA      | −1.9% (39)  | ND      | ND      | ND      |

<sup>a</sup> median.

NA: not applicable; ND: not done; RAL: raltegravir.
limb fat in the ritonavir-boosted atazanavir arm (both arms were on stavudine and lamivudine) [15]. The proportion of participants with ≥20% loss in limb fat was significantly greater in the unboosted atazanavir arm at 96 weeks [15]. However, there were no significant between-group differences in absolute change from baseline in SAT or limb fat with ritonavir-boosted versus unboosted atazanavir [15]. There were no significant between-group differences in absolute change from baseline in SAT or limb fat in a study comparing ritonavir-boosted tipranavir (at the registered dose) with ritonavir-boosted lopinavir [17].

In the one study that compared raltegravir with efavirenz, average gains in limb fat over time and the incidence of lipoatrophy were similar in both groups [10].

**Fat gain: changes in trunk fat or VAT with different antiretroviral regimens.** In general, participants randomised to different ART regimens gained similar amounts of trunk fat or VAT over time. The changes from baseline in trunk fat and VAT are summarised in Tables 12, 13, 14, 15, 16.

There were no significant between-group differences in changes from baseline in trunk fat or VAT in the six studies that compared NRTI-sparing and NRTI-containing regimens [4,9,11,21,32], and in the four studies that compared different NRTI-containing regimens [3,22,23,33]. Similarly, there were no significant differences in the incidences of lipohypertrophy (defined as >20% gain in trunk fat) [9,11,19].

The results of studies that compared PIs and NNRTIs were not consistent. One study found that participants who received ritonavir-boosted atazanavir had significantly greater increases in trunk fat at week 96 than those who received efavirenz (36.5% versus 21.1% respectively, p = 0.028) [3]. Another study found no significant changes at week 48 in VAT between those who received unboosted atazanavir compared with those who received efavirenz (15.3 cm$^2$ versus 14.1 cm$^2$ respectively, 95% confidence interval for the difference: −10.4 to 12.6 cm$^2$) [24]. There were no significant between-group differences in changes from baseline in trunk fat, or in incidence of lipohypertrophy in one study that compared ritonavir-boosted lopinavir and efavirenz [19]. One study found that participants who received efavirenz gained more trunk fat over time on average than those who received nefilavir, however it was not reported whether or not the difference was statistically significant [33].

There were no significant between-group changes from baseline in trunk fat or VAT in those who received ritonavir-boosted atazanavir compared with unboosted atazanavir in one study [15]. A study that compared ritonavir-boosted tipranavir and ritonavir-boosted lopinavir found small, but statistically significant between-group differences in changes from baseline in both trunk fat and VAT: those who received ritonavir-boosted tipranavir lost trunk fat over time, while those who received ritonavir-boosted lopinavir gained trunk fat over time [17].

In the one study that compared raltegravir with efavirenz, gains in trunk fat over time were similar in both groups [10].

**Changes in limb fat and SAT after switching antiretroviral regimens.** In general, participants who were switched away from NRTI-containing, or more specifically thymidine analogue-containing, regimens gained limb fat over time, when compared with participants who continued NRTI- or thymidine analogue-containing regimens, who generally lost limb fat [27–30,32,34].

There were no significant between-group differences in changes from baseline in limb fat or SAT in studies that switched to NRTI-containing regimens [31], to ritonavir-boosted atazanavir from other ritonavir-boosted PI regimens [23], or to raltegravir from PI regimens [26].

**Table 22. Switching studies: change from baseline in visceral adipose tissue (VAT) on CT scan: NRTI-containing versus NRTI-sparing regimens.**

| Study | Measure | Arm | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|-------------|---------|
| [29]  | VAT*    | Cont NRTI regimen | ND | NA | 5 cm$^3$ (35) | 0.987 | 17 cm$^3$ (23) | 0.566 |
|       | Switch to PI+NNRTI | ND | 7 cm$^3$ (39) | 6 cm$^3$ (30) |

a. mean.

NA: not applicable; ND: not done.
doi:10.1371/journal.pone.0063623.t022

**Table 23. Switching studies: change from baseline in trunk fat (TF) on DEXA scan: PI versus NNRTI.**

| Study | Measure | Arm | Week 24 | p value | Week 48 | p value | Week 96 | p value |
|-------|---------|-----|---------|---------|---------|---------|---------|---------|
| [31]  | TF      | Cont PI+2NRTIs | ND | NA | NR (54$^b$) | 7.8 (6.9 to 8.7); 8.0 (6.9 to 9.1) | ND | NA |
|       | Switch to NVP+D4T | ND | NR (52$^b$) | 6.3 (5.7 to 6.9); 5.9 (5.2 to 6.7) | ND | |

a. mean; b: n at baseline (n at time-point not stated); c. means and 95% confidence intervals (calculated by the authors of this review) at each time-point (change from baseline not reported).

NA: not applicable; ND: not done; NR: not reported.
Antiretrovirals: D4T: stavudine; DDI: didanosine; NVP: nevirapine.
doi:10.1371/journal.pone.0063623.t023
Changes from baseline in limb fat, subcutaneous thigh fat and SAT are summarized in Tables 17, 18, 19, 20, and 21.

**Changes in trunk fat or VAT after switching antiretroviral regimens.** In general, participants who were switched away from NRTI-containing regimens, or from thymidine analogue-containing regimens, had similar increases in trunk fat over time to those who continued NRTI- or thymidine analogue-containing regimens [29,30].

There were no significant between-group differences in changes from baseline in trunk fat or VAT in studies that switched to NNRTI- from PI-containing regimens [31], to ritonavir-boosted atazanavir from other ritonavir-boosted PI regimens [25], or to raltegravir from PI regimens [26].

Changes from baseline in trunk fat and VAT are summarised in Tables 22, 23, 24, 25, and 26.

**Discussion**

We found overwhelming evidence that lipoatrophy is an antiretroviral adverse drug reaction. Subcutaneous fat volumes are considerably lower in patients on ART than in controls, subcutaneous fat loss progresses on ART, is associated with stavudine and zidovudine use, and partially reverses after switching to abacavir, tenofovir or an NRTI-sparing regimen. By contrast, central fat gain does not appear to be an antiretroviral adverse drug reaction. Visceral and trunk fat volume is no different in women on ART compared with control women, and is less in men on ART than in control men. Visceral fat accumulates at the same rate in patients on ART and controls. Finally, central fat gain generally occurs at similar rates in HIV-infected patients randomised to different ART regimens, is not associated with any specific antiretroviral drug or drug class, and does not reverse on switching antiretrovirals. We believe that this evidence indicates that central fat gain is a consequence of treating HIV infection, which normalizes the concentrations of inflammatory markers such as TNF-α (tumour necrosis factor alpha) that are known to cause wasting [36]. Lipoatrophy occurring together with central fat gain results in an unusual appearance, which may have persuaded clinicians that the fat gain is an antiretroviral adverse drug reaction. The fact that diet and exercise have been shown to improve central fat gain in patients on antiretroviral therapy

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**Table 24.** Switching studies: change from baseline in trunk fat (TF) on DEXA scan and visceral adipose tissue (VAT) on CT scan: NRTI versus NRTI.

| Study | Measure | Arm | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|-------------|---------|
| [28]  | TF*     | Cont AZT+ 3TC+EFV | ND | NA | 358 g | >-0.05 | ND | NA |
|       |         | Switch TDF+ FTC+EFV | ND | NA | 130 g | ND | ND | ND |
| [30]  | TF*     | Cont AZT or D4T regimen | 0.8 kg (56) | 0.31 | ND | NA | ND | NA |
|       |         | Switch AZT/ D4T to ABC | 1.4 kg (50) | ND | NA | ND | ND | ND |

**Table 25.** Switching studies: change from baseline in trunk fat (TF) on DEXA scan and visceral adipose tissue (VAT) on CT scan: PI versus PI.

| Study | Measure | Arm | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|-------------|---------|
| [25]  | TF*     | Continue Plr +2NRTIs | ND | NA | −1.8% (57) | 0.14 | −3.6% (57) | 0.14 |
|       |         | Switch Plr to ATVr | ND | NA | 2.6% (112) | 1.6% (112) |
| VAT*  | Continue Plr +2NRTIs | ND | NA | −0.5% (59) | 0.27 | 1.6% (59) | 0.68 |
|       | Switch Plr to ATVr | ND | NA | 4.6% (108) | 3.4% (108) |

a. mean.
NA: not applicable; ND: not done.
Antiretrovirals: 3TC: lamivudine; ABC: abacavir; AZT: zidovudine; D4T: stavudine; DDI: didanosine; EFV: efavirenz; TDF: tenofovir.
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provides some support for our conclusion that it is a consequence of lifestyle [37–39].

Efavirenz is associated with a higher risk of limb fat loss than PIs when combined with NRTIs that cause fat loss. A possible explanation for this observation is that the anti-apoptotic properties of PIs partially ameliorate the loss of adipocytes by increased apoptosis that is induced by NRTIs [40]. The observation that unboosted atazanavir, which is a non-peptidomimetic PI that does not have anti-apoptotic properties, is associated with more limb fat loss than ritonavir [a peptidomimetic PI]-boosted atazanavir supports this hypothesis. Alternatively, efavirenz may increase the adipocyte toxicity of thymidine analogue NRTIs. Efavirenz has been shown to be more toxic to adipocytes and to release more inflammatory cytokines than lopinavir-ritonavir [41]. Furthermore, efavirenz also displays mitochondrial toxicity in hepatocytes [42]; although we could find no data to support this, it is possible that it has a similar effect on adipocytes. Mitochondrial toxicity is thought to be a key mechanism of thymidine analogue-induced lipoatrophy [3].

Our study has several limitations. First, many of the studies that reported objective measures of fat redistribution by ART regimen were convenience sub-studies of randomised controlled trials, therefore patients undergoing DEXA scan and/or CT scans were not randomised. However, fat distribution sub-studies generally reported that the characteristics of the patients undergoing imaging of fat tissue were not different from the parent trial population. Many RCTs were powered according to efficacy endpoints, and not for objective measures of fat distribution. Second, many studies reported only summary statistics and different outcome measures were reported, which prevented us from pooling data from different studies. Third, some studies did not report statistical analyses of changes in body fat distribution by study arm. Fourth, we were unable to assess the role of older protease inhibitors (other than nelfinavir) or nevirapine in fat redistribution as no studies with those antiretrovirals fulfilled our inclusion criteria. Fifth, we found only one study that compared fat changes over time in patients on ART and HIV-infected controls that was conducted in the United States. This limits our ability to generalise findings to other populations. Finally, we cannot exclude the causative role of specific antiretrovirals in focal forms of fat gain, such as buffalo humps, as the included studies reported trunk or visceral fat changes only.

In conclusion, our systematic review supports the hypothesis that peripheral lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. Lipoatrophy can be avoided and at least partially reversed by avoiding thymidine analogue nucleoside reverse transcriptase inhibitors. Central fat gain appears to be a consequence of treating HIV-infection, and reflects patterns of fat gain seen in the HIV-uninfected population.

### Supporting Information

#### Table S1 Excluded studies.

| Study | Measure | Arm | Week 24 (n) | p value | Week 48 (n) | p value | Week 96 (n) | p value |
|-------|---------|-----|-------------|---------|-------------|---------|-------------|---------|
| [26]  | TF*     | Cont PI regimen | ND | NA | 382 g (35) | 0.729 | ND | NA |
|       |         | Switch PI to RAL | ND | NA | −28 g (39) | ND |         |         |
| VAT*  | Cont PI regimen | ND | NA | 11.9% (35) | 0.936 | ND | NA |
|       |         | Switch PI to RAL | ND | NA | 12.8% (39) | ND |         |         |

a. median.
NA: not applicable; ND: not done; RAL: raltegravir.
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