Current perspectives on the management and prevention of antiretroviral-associated lipoatrophy

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Lipoatrophy (LA) is a common and now well-recognized complication of highly active antiretroviral therapy (HAART). Over the last decade as knowledge of the mechanisms behind LA has developed, several antiretroviral drugs, in particular, have emerged as the likely agents responsible for this complication. This has been supported by studies comparing alternative HAART regimens and by those in which HAART regimens have been modified with a resulting impact on LA. In this article, we review the evidence underlying the current perspectives on the development of LA and the strategies employed to manage or avoid it.

Keywords: lipoatrophy, lipodystrophy, HAART, HIV, antiretrovirals

Introduction

Highly active antiretroviral therapy (HAART) has markedly reduced the morbidity and mortality of those infected with the human immunodeficiency virus (HIV), transforming the infection into a chronic disease. However, with more patients surviving on antiretroviral (ARV) medications, long-term toxicities of these medications have become prominent issues for HIV management in the developed world.¹ Lipoatrophy (LA), initially described alongside visceral fat accumulation, insulin resistance and dyslipidaemia as the lipodystrophy syndrome, is one such complication that has even been a cause for caution over early initiation of HAART. Mild LA may manifest as increased muscle definition and venous prominence in the limbs or face. Severe LA can cause facial disfigurement or pain as fat cushioning is lost from bony prominences, e.g. the buttocks. Facial LA is particularly stigmatizing because for some it discloses their HIV status. LA may contribute to failure in adherence to ARVs or delay initiation of ARVs in those needing to start them.

Mechanism of LA

Initially, protease inhibitors (PIs) were associated with the metabolic disturbances of the ‘lipodystrophy syndrome’ and implicated in all aspects of lipodystrophy. However, substantial evidence has accumulated implicating nucleoside reverse transcriptase inhibitors (NRTIs), particularly the thymidine analogues (tNRTIs), as those responsible for LA.²–⁵ Recent studies disregard PIs in the aetiology of LA, e.g. Moyle et al.⁶ demonstrated little benefit in removing PIs from a HAART regimen compared with the greater benefit from removing tNRTIs. A growing body of evidence from larger ‘switch studies’ (Table 1) where a tNRTI is replaced by another ARV endorses the role of tNRTIs in LA.²–⁷⁵

NRTIs inhibit mitochondrial γ-DNA polymerase thereby reducing replication of mitochondrial DNA (mtDNA).¹⁶,¹⁷ Reduction of mtDNA has been demonstrated in adipocytes of patients with LA, suggesting an organ-specific disturbance of mtDNA.⁹,¹⁸ Cohorts taking the tNRTI stavudine have consistently reported a high incidence of LA and since stavudine is a potent inhibitor of γ-DNA polymerase in vitro, mitochondrial toxicity has gained credibility as the mechanism behind LA. In vitro γ-DNA polymerase is also inhibited by didanosine and zidovudine, while lamivudine, emtricitabine, tenofovir disoproxil fumarate and abacavir show little inhibition. This is the rationale for examining NRTI switching to resolve or prevent LA. Although zidovudine is a relatively weak inhibitor of γ-DNA polymerase, it is converted into stavudine-triphosphate in some human cells and is well correlated with LA.¹⁸–²⁰

For established LA, management involves switching ARV drugs, using non-ARV pharmacological agents or employing reconstructive-cosmetic techniques. The majority of this article outlines the basis behind each of these approaches.

Measurement and interpretation of intervention studies on LA

Data on LA can appear to be confusing. LA improvements with an ARV switch in one study may appear contradicted by another. The methods by which LA is evaluated may be partly...
Table 1. An overview of the major trials that have studied the association of particular ARVs with LA

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Acronym and year</th>
<th>Study design</th>
<th>Follow-up in weeks</th>
<th>Discontinuations</th>
<th>Measurement modality</th>
<th>Outcome</th>
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| 8    | MITOX 2004       | randomized, open, switch; patients on AZT or d4T regimen randomized to:  
• continue AZT or d4T (n = 57) or  
• switch AZT/d4T for ABC (n = 54) | 104 | 14 in AZT/d4T group  
12 in ABC group | DEXA (n = 77) | AZT/d4T group mean limb fat gain: 490 ± 1380 g  
switch to ABC group mean limb fat gain: 1260 ± 2020 g |
| 9    | TARHEEL 2004     | randomized, open, switch; patients on HAART had d4T switched for:  
• ABC (n = 86) or  
• AZT (n = 32) | 48 | 25 in total, groups not specified | DEXA | median % change in arm fat (range):  
ABC group: 38 (−37 to 174)  
AZT group: 17 (−46 to 132) |
| 11   | RAVE 2006        | randomized, open, switch; 105 patients on d4T or AZT regimen with LA switched to:  
• TDF (n = 52) or  
• ABC (n = 53) regimen | 48 | 1 in TDF group  
3 in ABC group | DEXA | limb fat gain:  
TDF group: 329 g  
ABC group: 483 g |
| 14   | ABCDE 2007       | randomized, open; 237 patients HAART-naive started either:  
• ABC-3TC-EFV (n = 115) or  
• d4T-3TC-EFV (n = 122) | 96 | 40 in ABC group  
59 in d4T group | anthropometric DEXA (n = 57) | ‘moderate to severe’ LA reported:  
ABC group 4.8%, d4T group 39.2%  
mean change in limb fat:  
ABC group: +913 g (gain)  
d4T group: −1579 g (loss) |
| 15   | BICOMBO substudy 2007 | randomized, open, switch; 333 patients on 3TC-based HAART switched to:  
• TDF-FTC (166) or  
• ABC-3TC (167) | 48 | 22 of 166 from TDF-FTC group  
32 of 167 from ABC-3TC group | DEXA substudy (47 of total 333): TDF-FTC = 24  
ABC-3TC = 23 | mean limb fat gain from baseline:  
TDF-FTC: 164 g  
ABC-3TC: 132 g |
| 21   | SWEET substudy 2007 | randomized, open, switch; 234 patients on AZT-3TC-EFV:  
• continue regimen (n = 117) or  
• switch to TDF-FTC-EFV (n = 117) | 48 | NA | DEXA (n = 74) intention to treat analysis | median change in limb fat from baseline:  
TDF-FTC-EFV: +261 g  
AZT-3TC-EFV: −187 g |
| 26   | GS934 2007       | randomized, open; 509 patients HAART-naive started either:  
• TDF-FTC-EFV (n = 255) or  
• AZT-3TC-EFV (n = 254) | 144 week DEXA data not available: TDF-FTC = 207  
AZT-3TC = 216 | DEXA (n = 86) | median actual limb fat (for those with 48 week data):  
TDF group: 8.3 kg  
AZT group: 4.9 kg |

AZT, zidovudine; 3TC, lamivudine; FTC, emtricitabine; d4T, stavudine; ABC, abacavir; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; open, open-label study; naive, all entrants ARV-naive at baseline; switch, all entrants on ARVs at baseline; NA, not available.
to blame. Some studies report subjective improvements in LA by patient report or physician assessment, although many trials now use objective measures, e.g., dual energy X-ray absorptiometry (DEXA). This allows accurate and consistent quantitative assessments of subcutaneous fat. However, the detection of fat changes to the nearest gram may be unaccompanied by subjective improvements in LA, which is the purpose of intervention. Mean limb fat for a man is ~8 kg. Severe LA can reduce this by half, so with annual fat restoration at 0.4–0.7 kg, return to pre-morbid composition may take several years using switch strategies alone. So even after the withdrawal of ARVs associated with LA, recovery may take a long time and therefore the length of trial follow-up is important.

Similarly, measurable improvement in LA depends on the severity of LA prior to intervention, which, in turn, depends on the duration of time for which an offending drug is taken. In the SWEET study (summarized in Table 1) median limb fat increased at 48 weeks in subjects switching to tenofovir disoproxil fumarate/emtricitabine (Truvada) by 0.5, 0.2, 0.1 and <0.05 kg in subjects with a total exposure to zidovudine/lamivudine (Combivir) of <1.5, 1.5–3.0, 3.0–4.5 and 4.5–10 years, respectively, suggesting that recovery is likely to be better in subjects with a short exposure to zidovudine/lamivudine. This is compounded by the greater amount of limb fat at baseline in those with shorter zidovudine/lamivudine exposure: median limb fat in the respective groups was 5.69, 6.38, 3.75 and 3.57 kg, respectively.

Finally, infection and AIDS-related diseases themselves bring about ill-health and wasting. This may take time to halt and reverse despite initiation of HAART. So in early treatment, fat loss may continue despite the use of non-LA-associated drugs. Conversely, as health and nutrition improves on treatment, there can be a short-term gain in body fat compared with the pre-morbid state of relative cachexia, despite taking drugs associated with later onset LA.

### Switching ARV therapy

From the time stavudine became implicated in the aetiology of LA, small cohort studies emerged, in which patients replaced stavudine with another ARV resulting in improvement in LA. Then followed several large randomized ‘switch studies’ (Table 1) substituting stavudine and also zidovudine with other ARVs allowing restoration of limb fat while maintaining virological control, further supporting the role of tNRTIs in LA.

The TARHEEL study demonstrated improvement in LA even in patients replacing stavudine with zidovudine, another tNRTI (n = 32). This apparent contradiction may be explained by recognizing that the 86 patients switched to the non-tNRTI abacavir experienced significantly greater subjective and objective improvements in LA than patients in the zidovudine group. This does not exonerate zidovudine as cause of LA but suggests that stavudine is a more potent toxin. Furthermore, we do not know whether these patients may have just improved to a new set point of less severe LA compared with those continuing to take stavudine. It is more likely that these data support the hierarchy of potency of tNRTIs in causing LA over other NRTIs that do not. While earlier studies used abacavir, results from RAVE and long-term data from GS934 have shown tenofovir disoproxil fumarate to be just as adequate a substitute to tNRTIs. The time required for LA to improve is variable and depends on the tNRTI and severity of LA at entry to the study as well as the LA assessment method (described above).

Some investigators have reported subjective benefit as early as 24 weeks following ARV switching, whereas others found only objective improvements by week 48. In MITOX, it took 104 weeks before significant subjective benefits were reported in the switch group.

### NRTI sparing

Several groups have investigated the effects of complete NRTI sparing. In M03-613, following 24 weeks of induction with zidovudine-lamivudine-efavirenz, 74 patients switched to the PI lopinavir (boosted with ritonavir). At 96 weeks, this group had 2.3 kg greater limb fat compared with those continuing on zidovudine-lamivudine-efavirenz. ANRS 108 randomized 100 lipoatrophic patients on NRTI-based HAART. Fifty switched to a non-NRTI (NNRTI) + PI and 50 continued on their original regimen. At week 48, significant improvements in limb fat were found, yet limited to those switching away from a tNRTI at baseline; viral suppression was maintained in all groups. With a similar 1:1 switch, ACTG-A5116 randomized 236 treatment-experienced patients but found high rates of virological failure and treatment discontinuations due to toxicity in the NNRTI + PI group. Since patients with established LA are likely to have prior exposure and a degree of resistance to the NNRTI and PI drug classes, NRTI-sparing HAART may be risky or non-viable options better suited to treatment-naive patients.

A step further could involve complete cessation of HAART. Histological markers of LA have been shown to improve by 6 months following HAART cessation; however, no subjective improvements in LA were seen. A 25% gain in limb fat by week 48 (n = 16) was shown on a 1-week-on–1-week-off HAART schedule (containing zidovudine or stavudine), but a third of cases failed virologically. Ultimately, studies such as SMART, demonstrating excess morbidity and mortality in subjects undergoing structured treatment interruptions, render such strategies unacceptably hazardous.

### Non-ARV pharmacological interventions

Modifying HAART regimens can risk virological escape or drug toxicity. ARV options for drug-experienced patients or those in a resource-poor setting may be limited, and some patients, satisfied with virological efficacy, wish to remain on their ARV regimens. Furthermore, subjective improvement in LA following ARV switching can take years. Therefore, other therapies have been investigated to be administered alongside or instead of ARV switching. There are controversial results over the benefits of thiazolidinediones or statins, showing no or modest improvements in LA confined to those stopping offending drugs. Some have shown significant improvement in LA using recombinant human growth hormone (rhGH) after 12 weeks of therapy, but limb fat returned to baseline levels shortly after rhGH discontinuation. Uridine is thought to counteract pyrimidine depletion caused by tNRTI inhibition of γ-DNA polymerase. One randomized controlled trial has shown an average 900 g increase in limb fat after 12 weeks of uridine supplementation in patients taking tNRTIs.
Reconstructive-cosmetic techniques

Cosmetic approaches to LA involve injection of natural or synthetic compounds into areas of fat loss. Permanent fillers last up to 5 years but demand considerable technical skill and can give an unnatural look as the facial contour changes with age. The semi-permanent agent poly-1-lactic acid (Newfill) lasts ~2 years and is the only FDA-licensed agent for the treatment of facial LA. Confirmed safety and efficacy, along with ease of use has made it the leading cosmetic treatment for facial LA in the UK.

Preventing LA

What about patients yet to experience LA, either being ARV-naive or on HAART with as yet no apparent features of LA: should we avoid or pre-emptively switch away from ARVs implicated in LA? With the now minimal use of stavudine in the developed world, the real question is: are we so certain LA is inevitable with zidovudine that we should avoid it? Despite all the evidence discussed in favour of this, prominent studies still emerge, which appear not to support the central role of tNRTIs in the pathogenesis of LA. However, the methodology of these studies makes it difficult to draw valid conclusions. ACTG 5005s, a substudy of ACTG 384, reported no LA in the zidovudine-lamivudine-efavirenz group at week 144. This was a censored on-treatment subanalysis of a study whose primary aim was not to evaluate the development of LA. This type of analysis disregards dropouts (in this case up to 40%) leaving comparison of small subgroups. The population was biased to those remaining on the initial regimen and so ignored many subjects who had been exposed to zidovudine. The apparent lack of significant LA in the remaining small groups could be partly (as previously discussed) down to the relative fat gain as a result of improvements in general health following initiation of HAART. ACTG 5142 showed LA to be associated with NNRTI (efavirenz) use compared with a PI (lopinavir) and in some even on a non-tNRTI backbone. However, regimen switching was allowed in ACTG 5142 and analysis was intention-to-treat, i.e. subjects were grouped for analysis according to the drug they were assigned at week 0. Exposure to zidovudine will have occurred even in some subjects stated as commencing with non-tNRTI regimens explaining why LA was reported in these groups. One final comment regards the differential rates of reported LA in NNRTI versus PI groups even after controlling for tNRTI usage. A reasonable conclusion is that while tNRTIs are central in the aetiology of LA, the modulating effect of PIs and NNRTIs has not been elucidated fully. Ultimately, a randomized study relating LA to cumulative exposure of ARVs is required. Study GS934 meets this purpose: the tenofovir disoproxil fumarate group had normal limb fat (8.3 kg) at week 144 compared with almost 50% lower levels (4.9 kg) in the zidovudine group (Figure 1), strongly associating zidovudine with LA.

Conclusions

Data are convincing that newer non-tNRTIs do not lead to LA and that switching away from tNRTIs associated with LA leads to a slow recovery of fat loss. In the developing world where tNRTIs play a major role in the limited ARV repertoire, we can at least aim to opt for less toxic INRTIs while anticipating wider access to new generic drugs. In the developed world, where options to switch ARVs are available, it is better to pre-empt than await the clinical manifestations of LA. Even for those with resistant virus, the availability of new ARV agents means that tNRTIs are now rarely essential to achieve virological suppression and can be avoided. The data from GS934 and switch studies are compelling; we cannot justify continuing to put patients at very high risk of developing potentially irreversible LA by the continued use of tNRTIs.

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Leading article


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