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Do Non-Nucleoside Reverse Transcriptase Inhibitors Contribute to Lipodystrophy?

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Abstract

Lipodystrophy complications, including lipoatrophy (pathological fat loss) and metabolic complications, have emerged as important long-term toxicities associated with antiretroviral therapy in the current era. The wealth of data that has accumulated over the past 6 years has now clarified the contribution of specific antiretroviral drugs to the risk of these clinical endpoints, with evidence that lipoatrophy is strongly associated with the choice of nucleoside reverse transcriptase inhibitor therapy (specifically, stavudine and to a lesser extent zidovudine). The aetiological basis of metabolic complications of antiretroviral therapy has proven to be complex, in that the risk appears to be modulated by a number of lifestyle factors that have made the metabolic syndrome highly prevalent in the general population, with additional contributions from HIV disease status itself, as well as from individual drugs within the HIV protease inhibitor class. The currently licensed non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs, efavirenz and nevirapine, have been proven to have a favourable safety profile in terms of lipodystrophy complications. However, it must be noted that NNRTI drugs also have individual toxicity profiles that must be accounted for when considering and/or monitoring their use in the treatment of HIV infection.

This review will focus specifically on the topic of non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy and its possible association with lipodystrophy complications in patients with HIV. Given the multifactorial nature of the HIV lipodystrophy syndrome, which encompasses a number of complications including lipoatrophy and visceral and/or localised fat accumulation, as well as metabolic complications, it is gratifying to be able to provide a simple negative answer to the question under review here. In short, NNRTI drugs do not contribute to the risk of any component of lipodystrophy – indeed, nevirapine and efavirenz have emerged as having unexpected beneficial effects on lipid profiles, so that they may have a role in the management of metabolic complications that have arisen in the presence of other antiretroviral drugs.

However, it remains important to consider the factors that do contribute to the various manifestations of HIV lipodystrophy in order to understand the potential benefits that may be expected with NNRTI therapy. For example, the concept of 'switching' from HIV protease inhibitors (PIs) to NNRTI drugs has been advocated for some time as a potential remedy for lipodystrophy complications. Here, we will examine the evidence suggesting that this strategy may be a rational approach to managing metabolic complications, particularly the athero-

genic lipid profile characterised by reduced high-density lipoprotein (HDL)-cholesterol levels, but that lipoatrophy is unlikely to improve in this scenario.

1. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Therapy and Lipoatrophy

Enormous progress has been made in understanding the 'lipodystrophy syndrome' since the earliest published descriptions of changes in body composition and metabolic parameters among highly active antiretroviral therapy (HAART) recipients 6 years ago.[1] In particular, it is now clear that the choice and duration of nucleoside reverse transcriptase inhibitor (NRTI) therapy is the principal risk factor for pathological fat loss – referred to as lipoatrophy – and conversely that NNRTI therapy is exonerated from any association with this stigmatising syndrome.

Lipoatrophy is rare in the general community and is therefore specifically linked to antiretroviral therapy, as demonstrated in the MACS (Multicenter AIDS Cohort Study) of body composition in US adults and HIV-infected individuals receiving such therapy. This study demonstrated lipoatrophy in 1% of HIV-seronegative individuals (n = 314) compared with approximately 20% of HAART recipients (n = 384).[2] Clinical trial data have now confirmed the findings of observational cohort studies,[3] indicating that stavudine therapy is associated with an approximately 2-fold increase in the risk of lipoatrophy compared with zidovudine, so that the risk of clinically apparent lipoatrophy is 10–20% in zidovudine-treated individuals and 40–50% among those treated with stavudine over 30 months.[4-6] However, clinical trials involving alternative NRTI and nucleotide analogue drugs such as abacavir, tenofovir and emtricitabine have shown no association between the use of these drugs and the risk of lipoatrophy, and have also offered definitive evidence for the safety of NNRTI therapy.

For example, 144-week data from the Gilead 903 study involving comparisons of tenofovir and stavudine therapy in antiretroviral naive individuals (combined with lamivudine and efavirenz in both arms), demonstrated that the risk of lipoatrophy is minimal (if it exists at all) with tenofovir therapy over extended follow-up.[7] In this study, 19% of stavudine recipients developed lipoatrophy compared with 3% of patients receiving tenofovir ($p < 0.001$), an outcome that was supported by dual emission x-ray absorptiometry (DEXA) scan data revealing a mean reduction in limb fat of ~50% in the stavudine arm compared with the tenofovir arm ($p < 0.001$). A similar effect was observed in the ABCDE study (n = 237), in which stavudine or abacavir were again combined with lamivudine and efavirenz. In this study, 48-week data demonstrated moderate-to-severe lipoatrophy affecting at least one area in 20% of stavudine recipients and 2.7% of abacavir recipients ($p = 0.001$); this result was supported by DEXA data revealing overall fat gain in the abacavir arm (+1.75kg) and loss in the stavudine arm (−1.15kg) over this time period.[8] Once-daily therapy with emtricitabine also compared favourably with stavudine (combined with enteric-coated didanosine and efavirenz) over 72 weeks in the FTC-301A study (n = 571),[9] with significant differences in waist, hip and chest circumference between the two treatment arms ($p < 0.05$), and average loss of fat only in the stavudine group.

These clinical trials indicate that there is minimal risk of lipoatrophy – if indeed there is any risk at all – associated with antiretroviral therapy combinations that include non-thymidine NRTIs and NNRTIs. But does the use of either NNRTI or PI therapy contribute to lipoatrophy risk in the presence of stavudine or zidovudine? This question has been most clearly addressed in the FRAMS (Fat Redistribution and Metabolic Study) II substudy of the Atlantic study,[10] which compared indinavir (n = 24), nevirapine (n = 24) and lamivudine (n = 33) treatments, each with a backbone combination of stavudine/didanosine. In this study, no differences in the severity of fat loss were detected between the study groups ($p > 0.4$), with reports of clinical lipoatrophy in 25% of patients by week 96 and 39% by week 192. Accordingly, DEXA scan assessments at week 144 demonstrated low body fat (average ~16%) and limb fat (average ~14%) across the study, irrespective of whether the 'third' drug was a HIV PI, NNRTI or NRTI. In contrast, visceral fat accumulation measured by CT scanning was specifically associated with indinavir treatment compared with nevirapine or lamivudine ($p < 0.01$), with

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marked differences in visceral fat area (178cm^2 vs 83cm^2 and 94cm^2, respectively) between the treatment arms.

1.1 Switching Strategies for Lipoatrophy

These observations are also consistent with the results of 'switching' strategies designed to halt or reverse the progression of lipoatrophy. NRTI switching studies have shown that substituting abacavir for stavudine or zidovudine in patients with clinically apparent lipoatrophy[11,12] is associated with statistically significant improvements in fat wasting. However, absolute increases in limb fat are in the order of 1–2% and are often not apparent to either clinicians or patients, so it would seem prudent to focus on prevention of lipoatrophy, as fat restoration appears to be a slow and possibly incomplete process. In contrast, over 30 trials investigating the substitution of NNRTI drugs or triple NRTI regimens in place of HIV PI drugs[13] have failed to demonstrate beneficial effects on fat wasting, although metabolic abnormalities such as dyslipidaemia and insulin resistance have been shown to improve.

2. Metabolic Syndrome-Like Complications and Cardiovascular Risk: Effects of Environment, HIV Infection and Antiretroviral Drugs

There is an increasing appreciation of the complexity that underlies the associations between antiretroviral therapy and metabolic complications such as dyslipidaemia and insulin resistance, although considering specific 'treatment phases' can help to clarify these issues. A central issue is that many of the endpoints that are considered here are common in the general population and are therefore subject to many genetic (non-modifiable) and environmental (potentially modifiable) effects that are not specific to HIV infection or its treatment. This is not to downplay the important role that HIV drugs have in the pathogenesis of metabolic complications, but to place these effects in a broader and perhaps more clinically relevant context.

2.1 Background Risk of Dyslipidaemic Syndromes and the Metabolic Syndrome: Prevalence in the General Community

The MACS cohort body composition study[2] has been instrumental in demonstrating that lipoatrophy is very strongly and specifically associated with antiretroviral treatment for HIV infection, while 'fat accumulation' is a feature that is relatively common in the general population as well as among HAART recipients. These data can be incorporated into a broader context that recognises the increasing prevalence of the metabolic syndrome in populations worldwide. This syndrome incorporates lipid parameters (high triglyceride and low HDL-cholesterol values), abdominal obesity, hypertension and evidence of impaired glucose tolerance into a clinical entity that is present in >30% of adults (both male and female) in population studies.[14-16] As may be expected, a diet high in saturated fat and calories and low in dietary fibre along with a sedentary lifestyle are important risk factors for its development.[17-19] Importantly, a diagnosis of metabolic syndrome is associated with a significantly increased risk of cardiovascular disease, even after adjustment for known cardiovascular risk factors including low-density lipoprotein (LDL)-cholesterol levels.[20-22] Hence, a significant proportion of HIV-infected patients – and particularly those in older age groups – have an inherent risk of the metabolic syndrome irrespective of their HIV status. As discussed in section 2.2, it is also possible that this syndrome may be masked to some extent in the setting of untreated HIV infection, becoming apparent to a treating physician only after treatment is initiated and lipids return to 'pre-HIV' levels.[23]

2.2 The Pre-Treatment Phase: Metabolic Effects of HIV Infection and Traditional Cardiovascular Disease Risk Factors

There is a large body of literature going back more than a decade that demonstrates that advancing HIV disease and immune deficiency are accompanied by changes in lipoprotein metabolism that are characterised by decreased levels of total, LDL and HDL cholesterol as well as decreased apolipoprotein B levels.[24] Progression to AIDS is associated with elevated triglyceride levels,[25] while the other

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metabolic parameters fall in parallel with CD4+ T cell counts.[26] Consistent results were obtained in the recent CPCRA (Community Programs for Clinical Research on AIDS) 065 study, which examined the predictors of low HDL cholesterol levels (<40 mg/dL) among 1028 patients.[27] This study identified that the greatest risk for low HDL cholesterol levels (71%) was among *untreated* individuals with three or more metabolic syndrome components, such as obesity, high triglyceride levels and/or evidence of glucose intolerance.

2.3 The Treatment Phase: NNRTI Therapy and Metabolic Complications

There is now little doubt that nevirapine, and to a lesser extent, efavirenz, stand out as having specific and potentially antiatherogenic effects on HDL cholesterol levels over time.[28] This is perhaps best demonstrated in a study of patients who completed 48 weeks of assigned therapy in the large 2NN trial, which compared efavirenz (n = 289) with nevirapine (n = 417) [both combined with stavudine and lamivudine].[29] Here, nevirapine therapy was associated with a 42.5% increase in HDL cholesterol levels and a decrease in the ratio of total cholesterol to HDL cholesterol of 4.1%, while patients receiving efavirenz had more modest elevations of HDL cholesterol levels (33.7%) and an overall increase in the ratio of total cholesterol to HDL cholesterol (+5.9%). These differences remained, or even increased, after adjusting for changes in HIV-1 RNA levels and CD4+ cell counts, indicating an independent effect of the drugs on lipid levels that could not be explained by suppression of the HIV-1 infection. These results are supported by data from the FRAMS II substudy of the Atlantic study,[10] where average HDL cholesterol levels at 144 weeks were approximately 39 mg/dL in the indinavir and lamivudine arms compared with 50 mg/dL in the nevirapine arm of the study. Significant increases from baseline levels were observed in the nevirapine arm ($p < 0.001$). Hence, in patients with established cardiovascular risk factors, and particularly those with existing cardiovascular disease, NNRTI-containing regimens appear to be a rational treatment choice.

3. Specific Toxicity Profiles of NNRTI Drugs: Efavirenz and Nevirapine

Just as the low risk of lipoatrophy associated with non-thymidine analogue NRTI drugs has prompted increased use of these drugs and increased scrutiny of their specific toxicity profiles, the NNRTI drugs efavirenz and nevirapine have proven to be highly effective anti-HIV drugs that carry a minimal risk of lipodystrophic adverse effects. Moreover, there is evidence that PI-to-NNRTI switching strategies have proven to be more tolerable overall (particularly in relation to gastrointestinal adverse effects) and to also improve patients' metabolic status.[30] Similar trends have been observed for first-line therapy, in that subjects starting NNRTI therapy remained on their initial regimens longer (median time to change 2.1 vs 1.6 years; log rank $p = 0.03$) compared with PI-based therapy.[31] However, such broad statements need to be interpreted with caution, given the individual toxicity profiles of drugs within both the NNRTI and PI drug classes.

3.1 Efavirenz Therapy and CNS Adverse Effects

The lower risks of severe hepatic and skin toxicities associated with nevirapine treatment have led to the adoption of efavirenz as the recommended first-line NNRTI therapy for HIV in the Department of Health and Human Services guidelines (available from URL: http://aidsinfo.nih.gov/guidelines). The most frequent adverse effects relate to cognitive and neuropsychiatric function, as observed in a small observational cohort study of antiretroviral therapy-naive patients receiving the two favoured HAART regimens in the guidelines, which consisted of two NRTIs and either efavirenz (n = 46) or lopinavir/ritonavir (n = 51).[32] In this study, the frequency of treatment interruptions within 1 month were similar in each arm but involved different systems, with gastrointestinal intolerance/diarrhoea events associated with lopinavir therapy (15%) and CNS disturbances associated with efavirenz (14%). Whilst these adverse effects generally resolved in the early stages of treatment, a cohort study conducted in Spain (n = 120) has identified ongoing symptoms over >18 months' average follow-up among patients receiving efavirenz-based (n = 60) versus PI-based

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HAART (n = 60). These included dizziness (22% vs 2.5%, $p < 0.01$), erectile dysfunction (20% vs 2.5%, $p = 0.01$), sadness, irritability, nervousness and mood changes (each >25% vs 10–15%, $p \leq 0.01$), impaired concentration (27% vs 12%, $p = 0.04$) and abnormal dreams (48% vs 1.7%, $p < 0.001$). Although this list would appear to constitute a significant burden of toxicity, it was interesting to note that, on average, patients on these two regimens reported equivalent quality of life, emotional status and adherence to treatment.[33]

3.2 Nevirapine Toxicity Profile

Although quality of life and the overall toxicity burden appear equivalent for efavirenz and nevirapine treatment,[34] the toxicity profile of nevirapine is demonstrably different to efavirenz, as observed in the 2NN trial in which treatment-associated rash and hepatotoxicity emerged as a relatively rare but potentially life-threatening toxicities.[35] On the other hand, CNS disturbances are infrequent with nevirapine use and beneficial effects on lipid profiles appear to be more marked after switching from PI therapy.

Safety data compiled by Boehringer Ingelheim relating to nevirapine therapy have clearly demonstrated that severe (grades 3–4) hepatic and cutaneous events occur during the early phase of treatment (within 12 weeks of treatment initiation) in approximately 5% of nevirapine recipients[36] and that low CD4+ T cell counts are protective against the development of these severe toxicity syndromes.[35] In this context, a recent study in a cohort of 235 nevirapine-exposed individuals in Western Australia has illustrated that a combination of host genetic susceptibility (carriage of *HLA-DRB1**0101) and sufficiently high CD4+ T cell count (>25%) identifies a proportion of patients at high risk for hepatotoxic or multi-system nevirapine hypersensitivity reactions (predictive value = 40%, $p < 0.01$).[37] These data suggest that nevirapine hypersensitivity represents a dose-independent idiosyncratic drug reaction that relies on CD4-dependent T cell function and which also may require the presence of genetic risk factors. The elucidation of clinically relevant risk factors remains an important issue at present and, in their absence, it is important to monitor clinical symptoms as well as liver transaminase level elevations in the early phase of nevirapine treatment.

4. Conclusions

The 'lipodystrophy syndrome' as it was first described is undoubtedly multifactorial, so that breaking this syndrome down into its component features allows for a greater understanding of distinct outcomes such as lipoatrophy and metabolic syndrome-like complications. From a clinical perspective, the body of evidence linking the choice of NRTI therapy – specifically stavudine or zidovudine – to the risk of developing lipoatrophy now provides a rational basis for treatment choices in order to avoid the development of lipoatrophy in individuals commencing HAART regimens, and also allows for appropriate monitoring and assessment of patients who are receiving stavudine- or zidovudine-based therapy. With regard to the metabolic complications of antiretroviral therapy, current evidence supports the possibility that the prescription of NNRTI drugs minimises the risk of dyslipidaemia and insulin resistance in HAART recipients. However, consideration of the metabolic status of HIV-infected individuals needs to be incorporated into a broader framework that acknowledges the contributions of environment (diet, exercise) and HIV status – as well as drug therapy – to these outcomes.

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