Research article

Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV Cohort Study

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Background: Blood lipid abnormalities in patients on highly active antiretroviral therapy (HAART) have been associated with exposure to protease inhibitors (PIs), particularly ritonavir. First therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) leads to relatively favourable lipid profiles. We report on medium-term lipid profiles (up to 5 years) for antiretroviral-naive patients starting NNRTI- and PI-based HAART in the Swiss HIV Cohort Study.

Methods: Since April 2000, blood samples taken at visits scheduled every 6 months have been analysed for cholesterol and triglyceride concentrations. For 1065 antiretroviral-naive patients starting HAART after April 2000, we estimated changes in concentration over time using multivariate linear regression with adjustment for baseline covariates, use of lipid-lowering drugs and whether the sample was taken in a fasting state.

Results: Non-high density lipoprotein (HDL) cholesterol levels increase with increasing exposure to either PI- or NNRTI-based therapy, whereas triglyceride levels increase with increasing exposure to PI-based therapy. Between NNRTI-based therapies, there is a slight difference in triglyceride levels, which tend to increase with increasing exposure to efavirenz and to decrease with increasing exposure to nevirapine. Of the three common PI-based therapies, nelfinavir appears to have a relatively favourable lipid profile, with little change with increasing exposure. Of the other two PI therapies, lopinavir with ritonavir has a more favourable profile than indinavir with ritonavir, with smaller increases in both non-HDL cholesterol and triglycerides and an increase in HDL cholesterol. Increasing exposure to abacavir is associated with a decrease in the level of triglycerides.

Conclusion: In general, NNRTI-based therapy is associated with a more favourable lipid profile than PI-based therapy, but different PI-based therapies are associated with very different lipid profiles. Nelfinavir appears to have a relatively favourable lipid profile. Of the two boosted PI therapies, lopinavir appears to have a more favourable lipid profile than indinavir.

Introduction

Changes in blood lipids occur naturally during the course of HIV infection, with decreases early in the infection in both total cholesterol and high density lipoprotein (HDL) cholesterol and increases later in triglycerides [1]. However, highly active antiretroviral therapy (HAART) also leads to lipid changes with increases in both total cholesterol [2] and triglycerides [3]. While increases in total cholesterol on therapy may...
represent a return to pre-infection levels to some degree [2], HAART is associated with an increased risk of myocardial infarction [4].

Changes in blood lipids have been associated with exposure to protease inhibitors (Pis) – particularly ritonavir (RTV) [5,6]. Switching studies suggest that replacing the PI component of therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) improves lipid profiles [7,8]. Additionally, in antiretroviral-naive patients, first therapy with either nevirapine (NVP) [9] or efavirenz (EFV) [10] leads to increases in HDL cholesterol. Yet studies of lipid profiles for first therapy with an NNRTI are either of short duration (less than a year) or based on a small number of patients (less than 100). We report on medium-term lipid profiles (up to 5 years) for antiretroviral-naive patients on PI- and NNRTI-based HAART in the Swiss HIV Cohort Study (SHCS).

Methods

Patients

The SHCS is a prospective cohort with continuing enrolment of HIV-infected adults. Since 1 April 2000, a cardiovascular risk assessment has been part of follow-up visits scheduled every 6 months. Blood is analysed for cholesterol, triglyceride, glucose and lactate concentrations; fat loss or gain, weight, hip and waist measurements are also recorded.

Our population of interest comprised all antiretroviral-naive patients in the SHCS starting HAART after 1 April 2000 with at least one subsequent measurement of a lipid concentration prior to any switch from PI- to NNRTI-based therapy or the reverse. Our sample from this population is those patients with weight, CD4 cell count and plasma HIV RNA (viral load) measured between 6 months before and 3 months after starting HAART. We define HAART as the combination of at least two nucleoside reverse transcriptase inhibitors (NRTIs) with at least one PI or NNRTI.

Statistical analyses

We used SAS version 8.2 for all analyses (SAS Institute Inc, Cary, NC, USA). For an unadjusted descriptive analysis, we present non-parametric regression curves showing lipid profiles over time on HAART. We used a local regression procedure with iterative re-weighting (LOESS) so that the fitted curve is relatively robust to outliers [11].

For an adjusted confirmative analysis, we fitted multivariate linear regression models with the level of a blood lipid as the response and with covariates and exposure to antiretrovirals as predictors. For covariates we used: CD4 cell count, viral load and body mass index (BMI) at baseline, age, gender, family history of cardiovascular disease and intravenous (iv) drug use as the likely mode of transmission – all time-independent, and use of lipid-lowering drugs and whether the sample was taken in a fasting state – both time-dependent. Exposure to a specific drug class or drug is time-dependent and was calculated at each lipid measurement as time to date in units of years.

We estimated model parameters using generalized estimating equations, to allow for correlation between repeated measurements from the same patient. We didn’t use the baseline measurement of the lipid as a covariate, because there was no reason to expect that the correlation between this measurement and others would be different from the correlation between other measurement pairs [12]. We assumed an independent correlation structure: although other correlation structures may be more efficient, this structure ensures unbiased estimates for time-dependent predictors [13]. Two types of statistic are given for each model. The nature of any association between a blood lipid and exposure to therapy is shown by an estimate of the mean change in the lipid level per year of exposure; 95% confidence intervals are given for each estimate, calculated using the empirical standard error. The evidence for different associations under different therapies is assessed by a generalized score test [14].

For each blood lipid, we considered a sequence of three models. Firstly, for patients starting HAART, we compared PI- and NNRTI-based therapy prior to any switch from one therapy to the other. Secondly, for patients starting NNRTI-based therapy, we compared EFV with NVP prior to any switch from one to the other or to a PI. Finally, for patients starting a common PI-based therapy, we compared nelfinavir (NFV), lopinavir (LPV) with RTV and indinavir (IDV) with RTV prior to any switch to another PI or to an NNRTI.

We also adjusted for concomitant NRTI use for those NRTIs that have been linked to changes in blood lipids [15–18]. Firstly, we adjusted separately for time on abacavir (ABC) and time on stavudine (d4T). Then, as a sensitivity analysis, we adjusted separately for time on either ABC or tenofovir (TDF) and for time on either d4T or zidovudine (AZT) (because AZT and d4T have similar effects in vitro [19]). We did not consider TDF separately from ABC because TDF was not yet in common use in this cohort.

Results

Patients

As of 31 January 2005, 1565 antiretroviral-naive patients in the SHCS had started HAART after April 2000. Of these, 1378 patients had at least one blood lipid measurement prior to any switch from PI- to NNRTI-based HAART or the reverse; 1065 (77%) had
also had weight, CD4 cell count and viral load measured between 6 months before and 3 months after starting HAART.

Of these 1065 patients, 32% were female, 71% were Caucasian southern or northern Europeans, 15% were black sub-Saharan Africans, 11% had a family history of cardiovascular disease and 15% were probably infected through iv drug use; when starting HAART, 59% were in CDC group A, the median age was 37 and the median BMI was 22. Of these 1065 patients, 594 and 471 started PI- and NNRTI-based therapy, respectively, and were followed for a median of 18 [interquartile range (IQR) 6.5–33] and 17 (IQR 7.5–29) months from starting HAART until either switching from one therapy to the other or until the last lipid measurement to date. These patients contributed a total of 4134 blood samples, of which 24% were taken in a fasting state. For patients starting PI- and NNRTI-based therapy, 2488 and 1646 samples were available, respectively, and of these, 31% and 13% were taken in a fasting state.

Antiretroviral therapy
The most common PIs were NFV and LPV with RTV, used by 269 (45%) and 292 (49%) patients, respectively, of the 594 using any sort of PI. Ninety-two patients (15%) received other boosted PIs, notably IDV, atazanavir and saquinavir. As first therapy, 554 of these 594 patients (93%) started on either NFV (253, 43%), LPV with RTV (256, 43%), or IDV with RTV (45, 8%). Most NNRTI use was of EFV – this was used by 443 (94%) of the 471 patients using either of the two NNRTIs. As first therapy, 422 of these 471 patients (90%) started on efavirenz. Common NRTIs were lamivudine and AZT, used by 1025 (96%) and 903 (85%) patients, respectively. d4T, ABC and TDF were used by 157 (15%), 178 (17%), and 133 (12%) patients, respectively, with median exposures of 11 (IQR 4.7–20), 14 (IQR 4.5–26) and 6.2 (IQR 1.7–11) months.

Lipid profiles
Using the same smoothing function for each lipid, unadjusted descriptive analyses suggest early changes in both HDL and non-HDL cholesterol (that is, total cholesterol minus HDL cholesterol). The levels of both increased within the first year, with a greater increase in HDL cholesterol for patients on NNRTI-based therapy (Figure 1). Triglyceride levels were higher for those starting PI-based therapy compared with those starting NNRTI-based therapy. Triglyceride levels decreased with time on either therapy – a result not confirmed by subsequent adjusted analyses.

Adjusted analyses suggest similar increases in non-HDL cholesterol with increasing exposure to either PI- or NNRTI-based therapy [0.15 (95% CI: 0.07, 0.24) and 0.11 (95% CI: 0.02, 0.20) mmol/l per year, respectively; see Table 1]. However, with increasing exposure to NNRTI-based therapy, HDL cholesterol levels increased and triglyceride levels decreased; whereas with increasing exposure to PI-based therapy, triglyceride levels increased.

Between NNRTI-based therapies, the only difference was in triglyceride levels, which tended to increase with increasing exposure to EFV and to decrease with increasing exposure to NVP. Between the common PI-based therapies, differences were the rule rather than the exception. In comparison with other PIs and NNRTIs, increasing exposure to NFV was associated with the smallest increase in non-HDL cholesterol and the greatest decrease in triglycerides. HDL cholesterol increased with increasing exposure to LPV with RTV, but otherwise RTV-boosted regimens were associated with the least favourable lipid profiles because the highest increases in both non-HDL cholesterol and triglycerides were seen with increasing exposure to either of the two boosted PIs.

Increasing exposure to ABC was consistently associated in all analyses with a decrease in triglyceride levels. Increasing exposure to ABC was also associated with a decrease in non-HDL cholesterol but only within NNRTI-based therapy [–0.29 (–0.47, –0.11) mmol/l per year] and not within PI-based therapy [0.07 (–0.16, 0.31) mmol/l per year].

We carried out three sensitivity analyses. Firstly, the sample included patients with viral load measured up to 3 months after starting HAART, so that fewer patients were excluded from our analyses. However, viral load can change rapidly after starting HAART. If we repeated our analyses without baseline viral load as a covariate, the results in Table 1 were essentially the same. Secondly, only 35 patients (3.3%) in this sample used lipid-lowering drugs, so estimates of the association between lipid levels and exposure to such drugs are not precise. The results in Table 1 are essentially the same when we remove all observations made after starting a lipid-lowering drug. Thirdly, as an alternative adjustment for concomitant NRTI use, we adjusted separately for time on either ABC or TDF and for time on either d4T or AZT. This increases point estimates in Table 1 for the effect of each class and for the effect of each individual PI and NNRTI. This confounding occurs because so many patients received AZT that time on AZT is correlated with time on other components of therapy. However, the ranking of the two different classes and of different drugs within each class is robust to this alternative adjustment. Even cross-class comparisons between specific PIs and NNRTIs seem relatively robust to this alternative adjustment, although one should be cautious about such comparisons as many involve at least one relatively small patient subgroup.
Discussion

Similar increases in non-HDL cholesterol are seen with increasing exposure to either PI- or NNRTI-based therapy. Increases in HDL cholesterol and decreases in triglycerides are seen with increasing exposure to NNRTI-based therapy; whereas increases in triglycerides are seen with increasing exposure to PI-based therapy. Comparing NNRTIs, triglyceride levels are slightly higher with increasing exposure to EFV than with increasing exposure to NVP. Increasing exposure to boosted PI therapies leads to higher levels of both...
Abnormalities are due to RTV or to the other PI or to NVP, the only difference in lipid profiles was a higher profile. In a randomized trial comparing NFV with NVP appears to have a relatively favourable lipid profile. Improvements in lipid abnormalities are not always seen when d4T is replaced by ABC in HAART. The increase seen in this study in HDL cholesterol with increasing exposure to boosted LPV is consistent with an increase in HDL cholesterol when boosted LPV is used as salvage therapy [28]. ABC is associated with lower triglyceride levels, in both within- and within-class analyses. ABC is also associated with lower non-HDL cholesterol levels but only within NNRTI-based therapy. There could be between-class differences in the effect of ABC on lipid profiles. Improvements in lipid abnormalities are not always seen when d4T is replaced by ABC in HAART. In one study where improvements were seen, roughly 80% of patients were on NNRTI-based therapy [17]; whereas in a study where no improvements were seen [18], only around 50% of patients were on NNRTI-based therapy [29].

### Table 1. Associations between time on antiretroviral therapy and change in blood lipid concentrations

<table>
<thead>
<tr>
<th>Antiretroviral therapy</th>
<th>Mean change in lipid concentration per year of use [95% confidence interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cholesterol, mmol/l</td>
</tr>
<tr>
<td>Between classes§</td>
<td>n=1064 P=0.50</td>
</tr>
<tr>
<td>PI</td>
<td>0.18 [0.09, 0.28]</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.21 [0.11, 0.30]</td>
</tr>
<tr>
<td>d4T</td>
<td>-0.10 [-0.26, 0.06]</td>
</tr>
<tr>
<td>ABC</td>
<td>-0.11 [-0.24, 0.03]</td>
</tr>
<tr>
<td>Between NNRTIs†</td>
<td>n=457 P=0.61</td>
</tr>
<tr>
<td>EFV</td>
<td>0.23 [0.14, 0.33]</td>
</tr>
<tr>
<td>NVP</td>
<td>0.30 [0.05, 0.55]</td>
</tr>
<tr>
<td>d4T</td>
<td>-0.01 [-0.20, 0.19]</td>
</tr>
<tr>
<td>ABC</td>
<td>-0.34 [-0.56, -0.13]</td>
</tr>
<tr>
<td>Between PIs§</td>
<td>n=533 P=0.01</td>
</tr>
<tr>
<td>NFV</td>
<td>0.07 [-0.04, 0.19]</td>
</tr>
<tr>
<td>LPV/r</td>
<td>0.31 [0.16, 0.47]</td>
</tr>
<tr>
<td>IDV/r</td>
<td>0.66 [0.32, 0.99]</td>
</tr>
<tr>
<td>d4T</td>
<td>-0.05 [-0.26, 0.16]</td>
</tr>
<tr>
<td>ABC</td>
<td>0.08 [-0.15, 0.31]</td>
</tr>
</tbody>
</table>

*For between-class analyses, therapy is represented by four predictors: time on any PI, any NNRTI, stavudine and abacavir. For within-class analyses (between NNRTIs or between PIs), therapy is represented by time on each of the (four or five) predictors listed. All analyses are adjusted for gender, family history of cardiovascular disease, transmission probably by iv drug use; baseline age, BMI, log viral load and CD4 cell count; measurement known to be made in fast ing state; and use of lipid lowering drugs. †Excludes measurements made after a patient has taken both PI- and NNRTI-based therapies (P value is the result of a score test for a difference between two NNRTIs). ‡Excludes measurements made after a patient has taken either a PI-based therapy or both EFV and NVP (P value is the result of a score test for a difference between the three PI therapies). BMI, body mass index; iv, intravenous; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ABC, abacavir; d4T, stavudine; EFV, efavirenz; IDV/r, indinavir plus ritonavir; LPV/r, lopinavir plus ritonavir; NFV, nevirapine; NVP, nevirapine.
In conclusion, while in general NNRTI-based therapy is associated with a more favourable lipid profile than PI-based therapy, different PI-based therapies are associated with very different lipid profiles. NFV appears to have a relatively favourable lipid profile. Of the two boosted PI therapies, LPV appears to have a more favourable lipid profile than IDV. Increasing exposure to ABC is associated with a decrease in the level of triglycerides.

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