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Evaluation of the Virological and Metabolic Effects of Switching Protease Inhibitor Combination Antiretroviral Therapy to Nevirapine-Based Therapy for the Treatment of HIV Infection

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ABSTRACT

In spite of indisputable benefits, the use of antiretroviral therapy is associated with multiple metabolic complications. Switching to simpler regimens might maintain viral suppression, improve metabolic side effects, and provide insight into the pathogenesis of these complications. Our objective was to carefully characterize the virological and metabolic effects of switching from a successful protease inhibitor (PI)-based antiretroviral regimen to a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen with nevirapine (NVP). Forty patients, taking their first successful (less than 40 HIV RNA copies/ml) PI-based regimen, switched their PI to NVP. If patients did not tolerate NVP, substitution with efavirenz was allowed. The duration of the study was 48 weeks. At 12 weeks intervals subjects had multiple virological and metabolic parameters including glucose, insulin, C-peptide, glucagon, proinsulin, blood lipids, and lipoproteins. A subgroup of 18 patients also had body composition evaluations with DEXA scans and MRIs of the abdomen and the thighs as well as insulin tolerance tests. Ninety-five percent of the patients maintained viral suppression (95% CI 88–100%); only one patient failed and another developed hepatitis. There were improvements in glucose (decreased fasting glucose, insulin, and improved insulin tolerance) and lipid metabolism (decreased triglycerides and increased HDL), but no changes in body composition and bone mineral density. Our study supports a pathogenic role for PIs in the development of hypertriglyceridemia and insulin resistance, but a more limited role in the fat redistribution syndrome.

INTRODUCTION

THE CLINICAL BENEFITS IN TERMS OF MORBIDITY AND MORTALITY of antiretroviral therapy are incontrovertible. However, the use of potent antiretroviral therapy is associated with multiple long-term complications. These include the development of insulin resistance and occasionally diabetes,¹ lipid abnormalities including increases in serum cholesterol and triglyceride levels, abnormalities in the distribution of fat, including visceral fat accumulation and peripheral fat atrophy, lactic acidemia or lactic acidosis, and osteopenia and osteoporosis. Although most of these side effects were initially linked to the use of protease inhibitors (PIs), it has become apparent that

many factors associated with treatment contribute to the development of these problems.² The specific contribution of each component of potent antiretroviral regimens is unknown. Furthermore, individual drugs within the same class may be associated with different long-term toxicities, as suggested by studies of single PIs given to HIV-negative subjects.^{3,4}

One possible strategy to maximize the benefits of potent antiretroviral therapy while minimizing the side effects would be to use certain drug regimens initially, and after a period of time, when the HIV viral replication is completely suppressed, to switch to a simpler regimen that might maintain viral suppression with less metabolic side effects. The original trials using this approach failed because the “stepping down” regimens

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were not fully suppressive.^{5,6} Short-term studies have demonstrated the maintenance of virological suppression when more aggressive regimens are used. These have been popularly termed “switch” studies.⁷ Initial reports focused on the virological safety of the strategy. However, careful characterization of the effects of switching on fasting metabolic parameters and objective evaluations of body composition is less common. The purpose of this nonrandomized longitudinal trial, therefore, was to carefully characterize the virological and metabolic effects of switching from a successful PI-based antiretroviral regimen to a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen with nevirapine (NVP).

MATERIALS AND METHODS

Patients

Eligible patients included those taking their first successful induction potent antiretroviral therapy with a combination regimen that included any of the approved protease inhibitors, and who had maintained an undetectable plasma HIV RNA viral load (<400 HIV RNA copies/ml) for at least 6 months. Patients had to have a viral load <40 HIV RNA copies/ml at the time of the switch, but were not required to have a metabolic abnormality. The study was approved by the IRBs at Washington University and Regions Hospital. All patients provided written informed consent.

Objectives

The objectives of the trial were to evaluate the proportion of subjects who maintained suppression of plasma HIV RNA at 48 weeks after the substitution of the PI in a potent antiretroviral combination with NVP and to carefully evaluate the metabolic changes, if any, associated with this substitution.

Study design

All patients discontinued the current PI and started NVP 200 mg/day for 7 days and then 400 mg in two divided doses. Prednisone 40 mg qd was given prophylactically for a week because of anecdotal reports of decreased frequency of rash in subjects receiving prednisone. Patients maintained the nucleoside regimen they were taking before enrollment in this pilot study. If patients did not tolerate NVP, substitution with efavirenz (EFV) was allowed. The anticipated duration of the study was 48 weeks.

Virological/immunological studies

Plasma samples were obtained at the time of the switch and then every 4 weeks for 48 weeks. Plasma was processed and assayed in “real time” for HIV RNA using the Roche ultrasensitive assay at the Washington University Retrovirology lab. The limit of quantification of this assay is 40 HIV RNA copies per ml. CD4⁺ lymphocyte count was monitored every 4 weeks.

Metabolic studies

At baseline, and at 12-week intervals after the switch, patients had the following fasting endocrine and metabolic parameters as-

ayed: glucose, insulin, C-peptide, glucagon, proinsulin, blood lipids, and lipoproteins. Metabolic parameters were performed in batches at a central laboratory (Washington University).

A subset of 18 patients at Washington University also had whole-body DEXA scans and ¹H-MRIs of the abdomen and thighs at baseline and at 48 weeks to assess body fat distribution. The MRI images of the abdomen and the lower extremities were collected in a Siemens 1.5-Tesla whole-body imager. Adipose tissue area was measured in these images using NIH Image 1.62c for MacOS. Within a region, fat and muscle tissue were identified by their different pixel intensities. Fat and muscle areas were quantified by converting their respective pixel numbers to surface area (cm²). A skilled technician processed each image to minimize inter- and intrameasurement variability. Five transverse T1-weighted images of the abdomen (8 mm thick) at the level of L4 were obtained. Intraabdominal (visceral) and subcutaneous (SAT) adipose tissue areas were measured in each of the five images. The results for each image were averaged and expressed as intraabdominal adipose area to total abdominal adipose area [VAT/(VAT + SAT)]. A T1-weighted scan was used to acquire eight serial cross-sectional images of both right and left thighs at a position 10 cm proximal to the lateral condyle of the right tibia. Each cross-sectional image was 5 mm thick and 5 mm separated each image. NIH Image 1.62c was used to quantify adipose tissue and muscle cross-sectional area in the right and left thighs. The bone (femur) cross-sectional area was deleted from the area measurements. The average adipose tissue areas in the eight images of the right and left thighs are reported separately as [fat area/(fat + muscle area)] × 100.

An Hologic QDR-2000 enhanced-array whole-body DEXA scanner and software (v5.71A) (Hologic, Waltham, MA) were used to measure whole-body lean, adipose and bone mass. Central to peripheral adipose tissue ratio was calculated as trunk fat/(right and left arm and leg fat) as previously described.⁸ Regional array software (v4.74A:1) was used to determine bone mineral density (BMD) of the whole-body, lumbar spine (L1–L4), and proximal femur. Each scan was acquired and processed by a Hologic-certified radiology technologist.

The subjects at the Washington University site also underwent a 15 min insulin tolerance test every 12 weeks, according to the previously published method.⁹ In summary, after an overnight fast, patients were given an intravenous bolus of 0.05 IU/kg of human insulin (Insulin Actrapid HM, Novo Nordisk, Mainz, Germany). Blood samples were taken before (0 min), and at 5, 8, 9, 10, 11, 12, 13, 14, and 15 min after the administration of insulin for glucose analysis. An index of peripheral insulin sensitivity was determined from the slope of the decline in plasma glucose levels from 5 to 15 min (linear regression analysis). A slope with absolute value <95 μmol/liter/min was an indication of peripheral insulin resistance.

Statistical analysis

Comparisons between categorical groups were done with the Chi square and the Fisher exact test when appropriate. Mean values ± SE are presented for continuous variables. Paired Student's *t* test was used to compare continuous variables. All *p* values are two tailed. The data were analyzed using the SPSS software package (SPSS/Sysat, Chicago, IL).

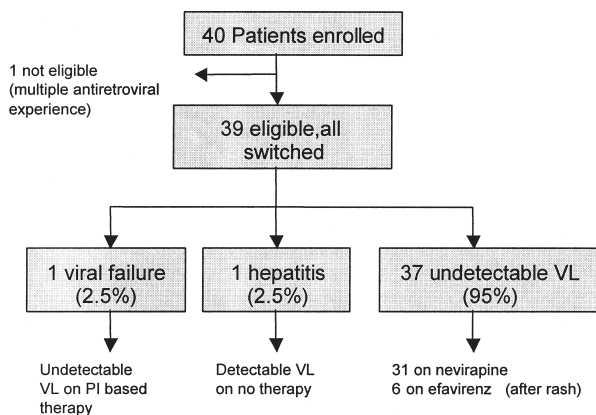


FIG. 1. Trial profile. Virology/toxicity endpoints. By intent-to-treat analysis of eligible subjects, the virological success rate of this switch strategy at 48 weeks (defined as <40 copies/ml) was 95% (95% CI 88–100%) while the on-treatment success rate was 97.5% (95% CI 95–100%).

RESULTS

Baseline characteristics and virology

Figure 1 shows the trial profile and the situation of all patients at week 48 of the study. Forty patients were enrolled; one patient was in fact not eligible due to having multiple protease experience and was excluded from further analysis.

Ninety percent of the patients were men, with a median CD4 cell count at baseline of 511 cells/mm³ (range 140–1329 cells/mm³). The mean baseline body mass index was 26 ± 0.7 kg/m².

Ninety two percent of the patients were on lamivudine (3TC)-containing regimens, 46% on zidovudine (ZDV), 46% on stavudine (D4T), 10% on didanosine (DDI), and only 2% on abacavir or zalcitabine (DDC). Indinavir (IDV) was the most common protease (59%), followed by ritonavir/saquinavir (RTV/SQV) (15%), nelfinavir (NFV) (13%), RTV alone (10%), and NFV/SQV (2%) in combination.

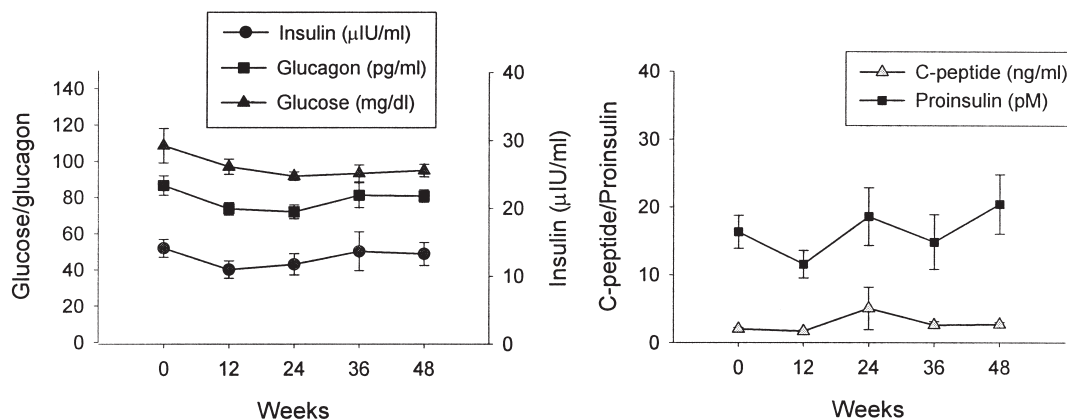


FIG. 2. Effects of switching to NVP on fasting glucose metabolism (mean \pm SE). There was a trend toward lower glucose and lower insulin levels at all time points, although it did not reach statistical significance.

In general, NVP was well tolerated; six patients (15%) developed severe rash and switched to EFV. Severe rash was more frequent among female (3/4, 75%) than in males (3/35, 9%) ($p = 0.008$). One patient dropped out of the study because of drug-related hepatitis at week 8. By intent-to-treat analysis of eligible subjects, the virological success rate of this switch strategy at 48 weeks (defined as <40 copies/ml) was 95% (95% CI 88–100%) while the on-treatment success rate was 97.5% (95% CI 95–100%). There was one virological failure at week 24 in a patient whose undetectable viral load was restored after switching back to a PI-containing regimen.

CD4⁺ T cell counts increased significantly during the duration of the study from a median count at baseline of 518 cells/mm³ to 608 cells per mm³ ($p < 0.01$).

Metabolic effects of the switch

Glucose metabolism. The average baseline insulin levels were elevated above 15 µIU/ml in 30% of the patients. After the switch to NVP, there was a decrease in the fasting levels of glucose, insulin, C-peptide, and glucagon with a trend toward gradual normalization of these values by week 12 (Fig. 2). Fasting glucose tended to decline from 103 ± 9 mg/dl at baseline to 94 ± 4 mg/dl at week 48, although this difference did not reach statistical significance ($p = 0.18$). Four of the 15 subjects who underwent an insulin tolerance test at baseline had evidence of insulin resistance (slope < 92 µmol/liter/min). All four of these patients normalized their insulin sensitivity by week 48 (Fig. 3). One patient who was not insulin resistant at baseline became insulin resistant during the study. Together these changes suggest that insulin resistance, one of the hallmarks of antiretroviral-associated hyperglycemia, improved after the switch to NVP.

Lipid metabolism. There were no significant changes in total cholesterol, but the median baseline cholesterol levels were below 200 mg/dl at baseline. Twenty percent of the subjects had cholesterol levels above 240 mg/dl at baseline, a proportion that did not change at week 48 (17%). HDL cholesterol increased from 34 ± 2 mg/dl at baseline to 42 ± 2 mg/dl at week 48 ($p < 0.0001$). There was an average decrease in serum

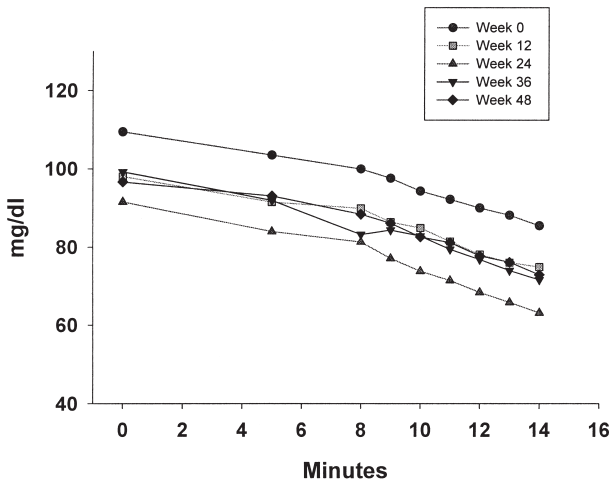


FIG. 3. The effects of switching to NVP on glucose levels during an intravenous insulin tolerance test ($n = 15$).

triglycerides (TG) of approximately 80 mg/dl for the whole group between baseline and week 48. However, the proportion of individuals with high or very high TG levels (>200 mg/dl) only tended to decrease, from 40% of the cohort at baseline to 37% at week 48 (Fig. 4).

Fat distribution. We did not observe clinically significant changes in total fat, total lean mass, or central to peripheral fat ratio measured by DEXA after the switch to NVP (Fig. 5). Percent body fat measured by whole-body DEXA remained stable after the switch ($22 \pm 2\%$ vs. $21 \pm 2\%$). The T:A ratio measured with DEXA at baseline (1.58 ± 0.12) did not improve after the switch (1.59 ± 0.14). Abdominal fat mass was not changed significantly (12 ± 1.8 kg at baseline vs. 12 ± 1.3 kg at week 48). There was a trend toward peripheral fat loss (-7%) over the 48 week follow-up: from 8.3 ± 1.5 kg to 7.6 ± 1.3 kg (paired t test = 0.07). The mean percentage of thigh fat

area/(fat + muscle area) measured by MRI was right thigh = $30 \pm 4\%$; left thigh = $33 \pm 4\%$ at baseline and right thigh = $33 \pm 4\%$; left thigh = $33 \pm 4\%$ at week 48 (NS). In the abdomen the visceral adipose tissue/total adipose tissue ratio (VAT:TAT) was $53 \pm 4\%$ at baseline vs. $53 \pm 5\%$ at week 48 (paired t test, $p = 0.16$). Lean body mass increased 2 kg during the 48 weeks from 56 ± 2 kg to 58 ± 2 kg (paired t test = 0.23). Baseline leptin levels ($n = 17$, mean level 3.8 ± 0.6 ng/ml) correlated with appendicular ($r = 0.84$; $p < 0.0001$), trunk ($r = 0.81$; $p < 0.0001$), and whole-body fat mass ($r = 0.86$; $p < 0.0001$). However, leptin levels did not change significantly after the switch (mean level after the change 4.0 ± 0.8 ng/ml), reflecting the lack of change in total fat mass.

Bone mineral density (BMD). In agreement with previously published cohort studies there was a high prevalence of osteopenia/osteoporosis in this cohort: 50% had t scores of the lumbar spine lower than -1 . No clear improvements in whole-body and lumbar spine BMD occurred after 48 weeks of follow-up (BMD in the lumbar spine was 1.00 ± 0.03 g/cm² at baseline and 1.02 ± 0.03 g/cm² after 48 weeks, $p = 0.14$).

DISCUSSION

Potent antiretroviral therapy regimens containing protease inhibitors have contributed to declining mortality and morbidity from HIV-associated immune dysfunction.¹⁰ However, in general PI-containing regimens are complex, and have been associated with several metabolic toxicities.¹¹ This has led to a desire to simplify treatment. NNRTI-containing regimens and the use of three nucleosides have been shown to be potent in studies of previously untreated patients. More recently, several studies have also shown that agents such as efavirenz, nevirapine, and abacavir can effectively replace protease inhibitors in patients in whom virological suppression is achieved using a PI-based regimen.⁷ Our study confirms these observations and shows that nevirapine can be successfully used in place of protease inhibi-

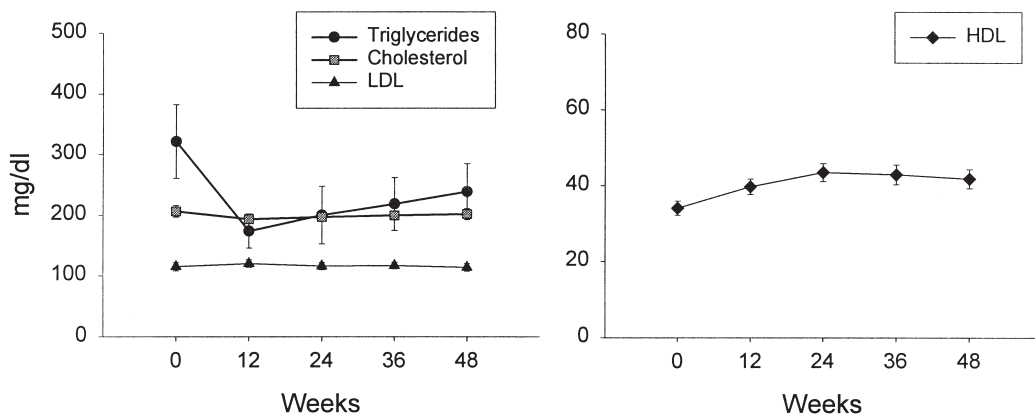


FIG. 4. Effects of switching to NVP on serum lipid levels (mean \pm SE). There were significant reductions in triglyceride levels at all time points ($p < 0.05$), as well as significant increases in HDL cholesterol ($p < 0.001$). Total cholesterol and LDL cholesterol did not change significantly over the 48 week follow-up.

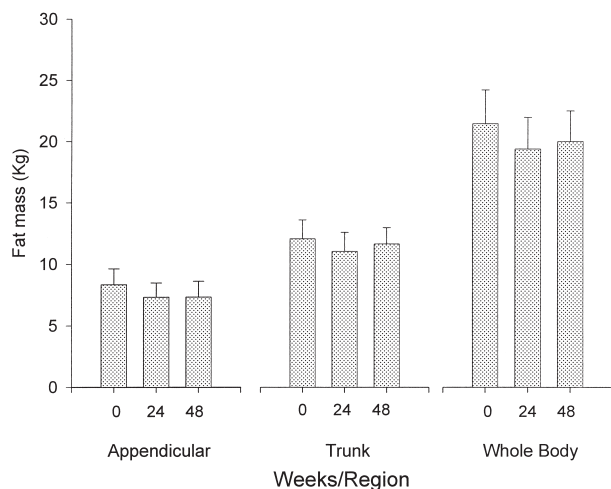


FIG. 5. Total, central, and peripheral fat mass measured by DEXA. There were no significant changes in trunk and whole-body fat mass. A trend towards peripheral lipoatrophy was noted: 7% of the peripheral fat was lost ($p = 0.07$).

tors in patients for whom the PI-based regimen was the first potent regimen and who have had plasma HIV RNA levels below the limit of detection for at least 6 months prior to the switch.

Nevirapine was well tolerated in our study, although we had an unusually high occurrence of rash. Two different factors probably contributed to this. The first is the short induction phase with nevirapine probably led to a greater likelihood of rash. We originally opted for this 1 week induction instead of the classic 2 weeks, because of our concerns about low levels of nevirapine immediately after the discontinuation of protease inhibitor therapy. Second we added prednisone to prevent the development of rash. At the time of the design of this study there were data from nonrandomized cohort studies that suggested a decreased risk of rash in patients taking prednisone during the initiation of nevirapine therapy.¹² Subsequent randomized trials have proven that in fact prednisone increases the risk of nevirapine-associated rash.^{13–15} Rash was more frequent among females, a phenomenon that has already been reported.¹⁶ Further studies are needed to understand the mechanism for the gender-associated differences in nevirapine-associated rash.

Observational studies have suggested that PIs may contribute to the metabolic abnormalities seen in treated patients, including insulin resistance, dyslipidemia, lipoatrophy, central adiposity, and bone demineralization.^{1,17,18} We carefully assessed these factors at baseline and during the time on nevirapine and showed that switching from a PI to nevirapine was associated with an improvement in glucose metabolism, a lowering of serum triglycerides, an increase in HDL cholesterol, but no change in total serum cholesterol levels. It should be noted that only a minority of the current patients had abnormal metabolic parameters at baseline, and this may have reduced our ability to demonstrate significant improvements in these biochemical parameters. Furthermore, switching to nevirapine did not reduce visceral fat content or increase thigh subcutaneous fat content, at least at the 48 week time point. Lumbar spine and proximal femur bone mineral densities were not in-

creased at 48 weeks. Improvements in these anthropomorphic parameters may require a longer period of time. Alternatively, the PI to NVP switch did not eliminate the factors responsible for these anthropomorphic complications.

Studies such as this do allow some insights into the potential role of protease inhibitors in the pathogenesis of these metabolic abnormalities. Abnormalities in glucose metabolism have been reported in HIV-negative subjects who received indinavir,⁴ and suggest a primary role for this PI in the development of insulin resistance and hyperglycemia. Reversal of abnormalities in glucose metabolism when the PI is replaced with NVP (and viremia remains undetectable) supports this conclusion. In a similar manner, ritonavir has been shown to increase cholesterol and triglyceride levels in HIV-negative subjects.³ Our findings suggest that switching to nevirapine reduces triglyceride levels and increases HDL-cholesterol levels, but 35–40% of the subjects did not achieve “normal” triglyceride or HDL cholesterol levels by week 48. Furthermore, in agreement with others^{7,19} we found no reduction in total cholesterol after the switch to NVP. Our findings, combined with observations that HIV infection itself alters lipid metabolism, suggest that the lipid abnormalities seen in treated patients have a complex pathogenesis, and treatment will therefore be difficult. The improvement in HDL cholesterol with NVP is interesting and consistent with recent findings from naive subjects enrolled in the Atlantic study²⁰ and the 2NN study,²¹ as well as other switch studies. Taken together, the findings suggest that long-term treatment studies assessing the cardiovascular effects of varying regimens continue to be warranted.

We observed no effect of the switch to NVP on central and peripheral fat distribution. This is consistent with other switch studies that involve discontinuing protease inhibitors⁷ and suggests that the development of either visceral fat gain or peripheral fat loss is a complex one. Although PIs have been associated with these changes in observational studies, the failure to reverse such changes when the PI is discontinued suggests that the PIs are not required to maintain these effects. This may suggest that the PIs do not contribute to the pathogenesis of central fat accumulation or peripheral lipoatrophy. Patients in our study continued their original nucleoside drugs as a group had evidence of ongoing peripheral fat loss. Many studies have implicated nucleosides in the development of lipoatrophy, and several switch studies have shown that substituting thymidine analogues can improve lipoatrophy.²²

In summary, the switch from PI-based regimens to nevirapine is virologically safe and it is associated with improvements in some, but not all, metabolic parameters. Our study supports a pathogenic role for PIs in the development of hypertriglyceridemia and insulin resistance, but perhaps a more limited role in lipoatrophy.

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REFERENCES

1. Powderly WG: Long-term exposure to lifelong therapies. *J Acquir Immune Defic Syndr* 2002;29(Suppl.):S28–40.
2. Carr A and Cooper DA: Adverse effects of antiretroviral therapy. *Lancet* 2000;356:1423–1430.
3. Purnell JQ, Zamban A, Knopp RH, *et al.*: Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* 2000;14:51–57.
4. Noor MA, Lo JC, Mulligan K, *et al.*: Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001;15:F11–18.
5. Havlir DV, Marschner IC, Hirsch MS, *et al.*: Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 team. *N Engl J Med* 1998;339:1261–1268.
6. Pialoux G, Raffi F, Brunvezinet F, *et al.*: A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. *N Engl J Med* 1998;339:1269–1276.
7. Drechsler H and Powderly WG: Switching effective HIV therapy: A review. *Clin Infect Dis* 2002;35:1219–1230.
8. Hadigan C, Miller K, Corcoran C, Anderson E, Basgoz N, and Grinspoon S: Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab* 1999;84:1932–1937.
9. Walli R, Herfort O, Michl GM, *et al.*: Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* 1998;12:F167–F173.
10. Palella FJ Jr, Delaney KM, Moorman AC, *et al.*: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853–860.
11. Safrin S and Grunfeld C: Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999;13:2493–2505.
12. Barreiro P, Soriano V, Casas E, *et al.*: Prevention of nevirapine-associated exanthema using slow dose escalation and/or corticosteroids. *AIDS* 2000;14:2153–2157.
13. Montaner J, Cahn P, Zala C, *et al.*: Randomized, controlled study of the effects of a short course of prednisone on the incidence of rash associated with nevirapine in patients infected with HIV-1. *J Acquir Immune Defic Syndr* 2003;33:41–46.
14. Knobel H, Miro JM, Domingo P, *et al.*: Failure of a short-term prednisone regimen to prevent nevirapine-associated rash: A double-blind placebo-controlled trial: The GESIDA 09/99 Study. *J Acquir Immune Defic Syndr* 2001;28:14–18.
15. Wit FW, Wood R, Horban A, *et al.*: Prednisolone does not prevent hypersensitivity reactions in antiretroviral drug regimens containing abacavir with or without nevirapine. *AIDS* 2001;15:2423–2429.
16. Bersoff-Matcha SJ, Miller WC, Aberg JA, *et al.*: Sex differences in nevirapine rash. *Clin Infect Dis* 2001;32:124–129.
17. Martinez E, Mocroft A, Garcia-Viejo MA, *et al.*: Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: A prospective cohort study. *Lancet* 2001;357:592–598.
18. Schambelan M, Benson CA, Carr A, *et al.*: Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002;31:257–275.
19. Martinez E, Arnaiz JA, Podzamczar D, *et al.*: Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003;349:1036–1046.
20. Van der Valk M, Kastelein JJ, Murphy RL, *et al.*: Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* 2001;15:2407–2414.
21. van Leth F, Phanuphak P, Gazzard B, *et al.*: Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN study). Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, February 10–14, 2003, Boston, MA, abstract 752.
22. Carr A, Workman C, Smith D, *et al.*: Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: A randomized trial. *JAMA* 2002;288:207–215.

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