Substitution of a Nonnucleoside Reverse Transcriptase Inhibitor for a Protease Inhibitor in the Treatment of Patients with Undetectable Plasma Human Immunodeficiency Virus Type 1 RNA

Seventy-three patients infected with human immunodeficiency virus type 1 (HIV-1) were enrolled in a prospective observational study to investigate the efficacy and tolerance of substituting a nonnucleoside reverse transcriptase inhibitor (NNRTI) for a protease inhibitor (PI) in patients whose plasma viral load (pVL) was controlled by a PI regimen. After a median follow-up of 52 weeks, 63 patients (86.3%) had undetectable pVLS. The incidence of virological breakthrough at 12 months of follow-up was 6.5% (95% confidence interval [CI], 1–20) among patients who had been antiretroviral naive before receiving HAART and 19.2% (95% CI, 6–34) among patients who had been treated with antiretroviral drugs before receiving the PI regimen (P = .10).

Although combination therapy with at least 3 antiretroviral drugs results in a sustained suppression of viral replication in the majority of patients infected with HIV type 1 (HIV-1), to date, attempts to eradicate the virus have not been successful with current therapeutic regimens [1–3]. As a consequence, patients face the likelihood of taking complex antiretroviral drugs for many years, probably for the rest of their lives. Adherence to the regimen is crucial for effective viral suppression and to prevent the emergence of drug-resistant viral strains [3, 4]. Concerns about the risks of developing lipodystrophy, insulin resistance, and cardiovascular disease may reduce adherence [5, 6]. Three studies have evaluated the concept of induction and maintenance in the treatment of HIV disease: the Amsterdam Duration of Antiretroviral Medication (ADAM) study, AIDS Clinical Trials Group (ACTG) 343, and the TRILEGE study [7–9]. Induction with highly active antiretroviral therapy (HAART) for 3 or 6 months was followed by maintenance with a less intensive regimen. Unfortunately, we observed a high rate of failure in these studies: virus rebound was observed within 6–12 weeks of initiation of the maintenance regimen.

Several studies have demonstrated the efficacy of nevirapine, taken either once or twice daily, when administered with 2 nucleoside reverse transcriptase inhibitors (NRTIs) [4, 10–14]. Efavirenz is taken once daily and has potent anti-HIV activity when given in combination with other antiretroviral agents [15]. Nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens are as potent as protease inhibitor (PI)-containing regimens when given as first-line anti-HIV therapy [11, 15]. Their simple dosing schedules and favorable long-term tolerance profiles suggest that they are suitable for use as long-term maintenance therapy [16]. For this reason, we started an observational study to determine whether switching from a PI-containing regimen to a similar, but simpler, non-PI regimen containing an NNRTI maintained viral suppression in patients whose plasma viral loads (pVL) were below the limit of detection of currently available HIV-1 RNA assays.

HIV-1–infected patients were recruited into this prospective observational study if they were NNRTI naive; if they had received a PI-containing regimen for 12 previous months; if they had maintained a pVL of <400 copies/mL for 6 previous months while taking this regimen; and if they had a pVL of <200 copies/mL at enrollment.

Patients substituted an NNRTI for the PI used in their therapy; other components of the regimen were unaltered. Follow-up began at this point. CD4 cell counts, HIV-1 RNA plasma load, and adherence to treatment were assessed at study entry and then every month. Triglycerides and total cholesterol were assessed in most patients at the time of the drug switch and at month 6. pVL was assessed by use of the same technique, either the Amplicor test (Roche Diagnostics, Meylan, France; detection limit, 200 copies/mL) or the ultrasensitive Nuclisens NASBA test (Organon-Teknika, Fresnes, France; detection limit, 80 copies/mL), in each patient. At all times, plasma samples were stored at −80°C. The primary end point of the study was the occurrence of virus rebound, defined as a pVL of ≥200 copies/mL on 2 consecutive occasions, 1 month apart, at a follow-up examination. Factors related to event-free survival were evaluated. Patients who experienced a virus rebound reverted to use of a PI combination, either their previous regimen or an alternative one; use of the NNRTI was discontinued in some, but not all, of these patients.

Seventy-three patients were enrolled in the study (table 1); 31 patients were receiving a PI regimen as first-line anti-HIV therapy (group A), and 42 patients had received other antiretroviral drugs before receiving the PI regimen, which had rendered their pVLS undetectable (group B). All patients were taking 2 NRTIs and 1 or 2 PIs: indinavir (32 patients), nefinavir (15), ritonavir (23), saquinavir (1), and ritonavir + saquinavir (2). The NRTIs that were used were as follows: zidovudine-lamivudine (36 patients); 13 of 36 received Combivir (Glaxo Wellcome, Paris, France), stavudine-lamivudine (26), stavudine-didanosine (7), and zidovudine-didanosine (4). On switching, 63 patients took nevirapine...
Table 1. Patient characteristics at day 0 (the time of the switch from use of a protease inhibitor regimen to a nonnucleoside reverse transcriptase inhibitor regimen), and the study results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (N = 73)</th>
<th>Group A (N = 31)</th>
<th>Group B (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of ART, mo (range)</td>
<td>28 (8-102)</td>
<td>22 (8-36)</td>
<td>43.5 (14-102)</td>
</tr>
<tr>
<td>Receiving successful PI regimen</td>
<td>22 (4-37)</td>
<td>22 (8-36)</td>
<td>26 (4-37)</td>
</tr>
<tr>
<td>With undetectable pVL</td>
<td>19 (1-36)</td>
<td>18 (4-35)</td>
<td>20 (1-36)</td>
</tr>
<tr>
<td>Median CD4 count, cells/µL (range)</td>
<td>149 (1-575)</td>
<td>234 (1-575)</td>
<td>79 (1-511)</td>
</tr>
<tr>
<td>Count at successful PI regimen initiation</td>
<td>206 (1-799)</td>
<td>234 (1-568)</td>
<td>138 (1-799)</td>
</tr>
<tr>
<td>Count at switch</td>
<td>473 (111-1504)</td>
<td>73 (204-1504)</td>
<td>469 (111-917)</td>
</tr>
<tr>
<td>Median pVL, log_{10} copies/mL (range)</td>
<td>4.7 (1.7-6.7)</td>
<td>5 (4-6.7)</td>
<td>4.5 (1.7-6.7)</td>
</tr>
</tbody>
</table>

NOTE: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; PI, protease inhibitor; pVL, plasma virus load. Group A comprised ART-naive, pre-HAART patients. Group B comprised non-ART-naive, pre-HAART patients. HAART was defined as a PI regimen leading to undetectable plasma HIV-1 RNA.

*With the ultrasensitive Roche assay; 69 of 73 baseline plasma samples had an HIV-1 RNA copy value of <50 cells/mL.*

(400 mg/day, either once daily [42 patients] or twice daily [21], after a 2-week lead-in dose of 200 mg/day), and 10 took efavirenz (600 mg/day). Reasons for switching to the NNRTI regimen included ≥1 of the following: lipodystrophy (18 patients), digestive intolerance to PI (17), adherence problems (4), renal colic (4), and a wish to simplify the therapeutic regimen (39). At the time of the regimen switch, the mean CD4 cell count was 487 cells/µL (SD, ±225 cells/µL). The mean time between initiation of antiretroviral therapy and the switch from PI to NNRTI was 37 months. The mean time between initiation of the successful PI regimen and the switch to use of an NNRTI was 22 months. At the time of the switch, the pVL had been <400 copies/mL for a mean of 18 ± 8 months. At the time of the initiation of the PI regimen, patients assigned to group B received 2 new NRTIs (24 of 42 patients), 1 new NNRTI (12 of 42 patients), or no new NRTI—that is, they only added a PI to achieve virological suppression (6 of 42 patients). The mean follow-up after the switch was 52 ± 17 weeks. For 63 patients (86.3%), the pVL was below the limit of detection at the last follow-up visit—that is, <200 copies/mL in 8 and <80 copies/mL in 55 patients (real-time testing).

Ten patients (13.7%) experienced a virus rebound after the switch: 1 patient at 1 month of follow-up, 4 patients at 2 months, 1 patient at 3 months, 2 patients at 5 months, and 2 patients at 6 months. On day 0, stored plasma samples were assayed with the Ultrasensitive Roche test: 69 of 73 samples had a pVL of <50 copies/mL, and the other 4 samples (2 from 10 failing patients) had a pVL of 54–150 copies/mL. The probability of maintaining a pVL below the limit of detection after switching regimens is shown in figure 1. The 95% CI of the incidence rate of virus rebound at 12 months was 3%–25% for the whole population, 1%–20% for patients in group A, and 6%–34% for patients in group B. The 10 treatment failures were moderate; the pVLS were 95–2600 copies/mL (median, 755 copies/mL). In 5 of 10 patients with treatment failure, an intercurrent infection (2 had influenza-like syndrome; 1, herpes outbreak; 1, sinusitis; and 1, acute bronchitis) occurred in the 10–30 days before the virus rebound. Three of the patients with treatment failure showed poor adherence to the drug regimen, missing several doses of antiretroviral drugs in the month preceding virus rebound. The other 7 patients with treatment failure were considered to have adhered to the antiretroviral regimen, as assessed by a medical questionnaire. There was a trend toward a higher risk of treatment failure among patients with a history of antiretroviral therapy before receiving the successful PI regimen (8 of 10 vs. 34 of 63 in nonfailing patients; P = .18). Treatment failure that occurred after therapy was switched was not associated with the total time that patients had received previous antiretroviral therapy (mean, 45 months in patients with treatment failure vs. 34 months in patients with treatment success); the duration of undetectable pVL before the switch (18 months for patients with treatment failure vs. 18.4 months for patients with treatment success); prior AIDS diagnosis (2 of 10 patients with treatment failure vs. 21 of 63 patients with treatment success); CD4 nadir <100 cells/µL (3 of 10 patients with treatment failure vs. 29 of 63 patients with treatment success); or mean CD4 count at switch (481 cells/µL vs. 488 cells/µL). Group B with and without treatment failure did not differ in terms of prior antiretroviral experience; indeed, among the 8 patients with treatment failure in group B, 6 added 2 NRTIs and 1 added 1 new NRTI at the time of initiation of the successful PI regimen.
Kaplan-Meier estimates of subjects with virologic breakthrough. Virologic breakthrough was defined as a plasma HIV-1 RNA (viral load) of \(>200\) copies/mL on 2 consecutive occasions at monthly follow-up. Incidence of viral breakthrough at 12 months was 6.5% (95% CI, 1–20) for patients who had been antiretroviral naive before receiving highly active antiretroviral therapy (group A, naive, solid line) and 19.2% (95% CI, 6–34) for patients who had been treated with antiretroviral therapy before receiving the protease inhibitor regimen (group B, nonnaive, dashed line). For the comparison among the 2 groups, by use of the log-rank test with 1 df.

\[ P = .10 \]

Of follow-up, the mean increase in CD4 cell count from the time of the switch was 82 cells/\(\mu\)L (SD, \(\pm 165\) cells/\(\mu\)L).

Of the 17 patients who had lipodystrophy at the time of the switch in regimens, 7 experienced objective improvements, as assessed by anthropometric measures; none experienced a complete reversal of the syndrome during the follow-up. Furthermore, of the 56 patients with no baseline lipodystrophy, 3 experienced the appearance of a lipoatrophic syndrome, possibly in relation to stavudine therapy, during the follow-up [17]. There was no significant difference in the mean total cholesterol level between month 6 (6.11 mmol/L) and day 0 (6.49 mmol/L) in 25 patients. The mean triglyceride level significantly decreased between day 0 (2.55 mmol/L) and month 6 (1.68 mmol/L) in 44 patients \( (P = .03) \).

The overall tolerance of the NNRTIs was good. Three patients receiving efavirenz experienced significant side effects: 1 patient switched to use of nevirapine on day 3 because of severe vertigo, 1 had mild insomnia and palpitations persisting beyond month 3, and 1 had moderate transient digestive symptoms during month 1. One nevirapine-treated patient developed acute uncomplicated hepatitis A. Of the 63 patients treated with nevirapine, 1 developed a transient cutaneous rash but did not discontinue taking nevirapine. Four patients stopped taking nevirapine (2 at month 7, because of persistent myalgias; 1 at month 10, because of localized cutaneous bullous lesions; and 1 at month 14, because of transaminase elevation. Therefore, 5 patients (1 of 10 patients receiving efavirenz and 4 of 63 of those receiving nevirapine) discontinued taking the study drugs because of adverse effects or intolerance. One 45-year-old patient, who had no history of cardiovascular disease, died of myocardial infarction at month 4. The 10 patients with treatment failure were switched back to the previous PI regimen (5 patients) or to a new PI regimen (5 patients) with the same NRTIs. All patients achieved undetectable pVLs within 2–4 weeks.

Although interest in first-line PI-sparing regimens has grown recently, there is little published information about the efficacy of switching from a PI- to an NNRTI-based regimen in HIV-
1--infected patients whose pVLs have remained undetectable for several months while they were receiving HAART [11]. This strategy has several theoretical advantages, including sparing PIs for future use. The NNRTI regimens are simpler, generally well tolerated, and more convenient for the patient, thus facilitating improved adherence to the drug regimen. The most important characteristic for a simpler regimen is potency. Regimens composed of 1 NNRTI and 2 NRTIs, such as those used in the Maintavir study, have been shown to have equivalent potency to PI-containing regimens [11, 14, 15]. Hence they are suitable candidates for use in patients who have achieved virological suppression with a PI regimen but who wish to change therapies for reasons of toxicity or adherence. We believe that our study demonstrates that an NNRTI regimen can successfully be substituted for a PI regimen in patients who have achieved prolonged viral suppression as a result of HAART. Induction and maintenance trials have demonstrated that switching to a less potent regimen does not control viral replication, with virus rebound occurring 8–12 weeks after initiation of maintenance therapy [7–9]. In the present study, the incidence of viral breakthrough for patients who previously were antiretroviral therapy naive (6.5% at 6 and 12 months) is similar to or lower than the rates observed during maintenance regimens in the ACTG 343 and TRILEGE trials.

Martinez and colleagues [18] have recently reported the results of a small study that investigated whether switching from a PRI to nevirapine reversed the metabolic abnormalities observed among patients treated with PIs. For the 23 patients studied, HIV RNA pVL was <200 copies/mL for a median of 9 months (range, 7–11 months) before the switch to nevirapine. Six months after PRI withdrawal, 22 (96%) of 23 patients still maintained a pVL of <200 copies/mL. Unfortunately, unsensitizing testing was not performed in this study. The low incidence of nevirapine-related rash (1.6%) in our switching study is noteworthy and was unexpected, because rash occurred in 15%–25% of patients starting nevirapine in other trials [4, 12, 16]. Because we did not use preventative antihistamines or steroids for our patients, this low incidence of rash might be related to the good immunovirological condition of our patients at the time of the switch with limited HIV-related immune activation.

The results from our observational study teach us some valuable lessons. First, switching to an NNRTI regimen after a successful PI regimen was successful in the majority of patients who had had pVLs below the limit of detection for a prolonged period and who had experienced an increase of CD4 cells to almost 500 cells/mm^3_. However, switching from the use of PI to NNRTI is probably advisable only if the pVL is <50 copies/mL when real-time testing is used. Second, we must monitor our patients' virological responses regularly and respond to changes in the pVL in an appropriate and proactive manner. Patients who followed the NNRTI regimen and had treatment failure did so mainly within the first 6 months of treatment and could be rescued by rapidly reverting to a PI regimen. Most of the patients who responded well to the NNRTI regimen for the first 3 months were able to maintain virological suppression on a long-term basis (up to 82 weeks for those receiving Maintavir). Intercurrent infections may cause a temporary increase in HIV RNA levels that may not necessarily indicate virological failure [19, 20]. The results of our study mainly apply to patients who have achieved prolonged virological success with their first-line anti-HIV HAART regimen, because patients with previous exposure to antiretroviral drugs or to several suboptimal regimens had a higher rate of viral breakthrough when they switched to an NNRTI regimen. These preliminary results demonstrate that an NNRTI can be substituted for a PI in patients with undetectable pVLs for ≥6 months during first-line treatment with HAART. Although further follow-up analysis and the results of a comparative study are required to confirm these findings, this strategic approach offers HIV-1--infected patients alternative treatment regimens with efficacy similar to those of PI-containing HAART regimens.

Acknowledgments

We thank all of our colleagues who helped conduct the study: colleagues at the Centre d’Information et de Soins de l’Immuno-déficience Humaine (CISIH) and Virology Laboratory of the University Hospital, Nantes, France; those at the Division of Infectious Diseases and the Virology Department of the University Hospital in Limoges, France; and those at La Roche sur Yon Hospital, La Roche sur Yon, France.

François Rafi,1 Bénédicte Bonnet,1 Virginie Ferré,2 Jean-Luc Esnault,1 Philippe Perré,1 Véronique Reliquet,1 Sophie Leautez,1 Christine Boullant,2 Odile Vergnoux,1 and Pierre Weinbreck1

1Department of Internal Medicine, Division of Infectious Diseases and HIV Clinical Research Unit, and 2Virology Laboratory, Biology Institute, University Hospital, Nantes, France; 3Department of Internal Medicine, Centre Hospitalier Departemental, La Roche sur Yon, France; and 4Department of Internal Medicine, Division of Infectious Diseases, University Hospital, Limoges, France

References

Sarcoidosis after Antiretroviral Therapy in a Patient with Acquired Immunodeficiency Syndrome

A 53-year-old man with acquired immunodeficiency syndrome (AIDS) developed clinical and radiological features compatible with sarcoidosis 14 months after starting highly active antiretroviral therapy (HAART). The CD4 lymphocyte count had increased from 5 cells/mm² to 235 cells/mm² with HAART. Transbronchial lung biopsy showed noncrotizing granulomas. All studies for an infectious etiology were negative. His condition improved after treatment with corticosteroids. To our knowledge, this is the fifth case report of sarcoidosis occurring after initiation of antiretroviral therapy for AIDS.

The occurrence of sarcoidosis and HIV infection in the same individual has been infrequently reported, even though both disorders are seen with significant frequency in certain populations, including African Americans living in inner-city areas of large metropolitan centers. Although this could be due to diagnostic failure or underreporting, it also may be due to the divergent immunologic abnormalities in the 2 conditions. In sarcoidosis, disease activity is believed to be related to overactivity of CD4 lymphocytes. With HIV infection, CD4 lymphocytes are primary targets of the virus.

Prior to the introduction of highly active antiretroviral therapy (HAART), 14 cases in which sarcoidosis and HIV occurred in the same individual had been reported [1–10]. In these patients, either sarcoidosis preceded the diagnosis of HIV or CD4 lymphocyte counts were >200 cells/mm³ at the time sarcoidosis was diagnosed. Recently, 4 cases have been reported in which patients developed sarcoidosis or “sarcoid-like” pulmonary disorders after receiving HAART [11–13]. In all 4, CD4 lymphocyte counts exceeded 200 cells/mm³ when sarcoidosis was diagnosed.

We report a case in which a patient developed sarcoidosis 14 months after immunologic reconstitution with HAART and an increase in CD4 lymphocytes from 5 cells/mm³ to 235 cells/mm³. We believe this is the fifth case reported that suggests a relationship between immune restoration after HAART and the development of sarcoidosis.

A 53-year-old white man with HIV infection/AIDS (diagnosed 3 years earlier) was admitted to the hospital in February 1997 because of fever, weakness, and erythema nodosum. He had been enrolled in several clinical trials of antiretroviral

References

5. Murphy RL, Katlama C, Johnson V, et al. The Atlantic Study: a randomized trial of large metropolitan centers. Although this could be due to diagnostic failure or underreporting, it also may be due to the divergent immunologic abnormalities in the 2 conditions. In sarcoidosis, disease activity is believed to be related to overactivity of CD4 lymphocytes. With HIV infection, CD4 lymphocytes are primary targets of the virus.

Prior to the introduction of highly active antiretroviral therapy (HAART), 14 cases in which sarcoidosis and HIV occurred in the same individual had been reported [1–10]. In these patients, either sarcoidosis preceded the diagnosis of HIV or CD4 lymphocyte counts were >200 cells/mm³ at the time sarcoidosis was diagnosed. Recently, 4 cases have been reported in which patients developed sarcoidosis or “sarcoid-like” pulmonary disorders after receiving HAART [11–13]. In all 4, CD4 lymphocyte counts exceeded 200 cells/mm³ when sarcoidosis was diagnosed.

We report a case in which a patient developed sarcoidosis 14 months after immunologic reconstitution with HAART and an increase in CD4 lymphocytes from 5 cells/mm³ to 235 cells/mm³. We believe this is the fifth case reported that suggests a relationship between immune restoration after HAART and the development of sarcoidosis.

A 53-year-old white man with HIV infection/AIDS (diagnosed 3 years earlier) was admitted to the hospital in February 1997 because of fever, weakness, and erythema nodosum. He had been enrolled in several clinical trials of antiretroviral