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Resuppression of Virus Load after Interruption in Treatment with Nevirapine and 2 Nucleoside Reverse-Transcriptase Inhibitors

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This retrospective chart review evaluated the effectiveness of reinitiation of treatment with nevirapine and dual nucleoside-analogue reverse-transcriptase inhibitors (NRTIs) after an interruption in antiretroviral therapy in 135 patients with human immunodeficiency virus type 1 RNA levels of <400 copies/mL who were receiving the same regimen. Reinitiation of a nevirapine regimen resulted in resuppression of virus load to <400 copies/mL in most patients who adhered to the regimen. Direct interruption of a non-NRTI regimen could lead to easier and more efficient structured protocols for treatment interruption.

Despite significant advances in the development of antiretroviral drugs, effective treatment of HIV type 1 (HIV-1) infection remains a challenging goal, requiring long-term adherence rates of >95% in the face of significant toxicity [1]. Therefore, continuous use of highly active antiretroviral therapy (HAART) may not be practical for some HIV-1–infected patients. In view of these concerns, there is a recognized need for new and innovative treatment strategies that use currently available agents. One approach that has recently received considerable attention is structured treatment interruption (STI), a treatment strategy in which patients alternately do and do not receive HAART, which uses laboratory parameters and physician guidance to determine the length of each interruption. One rationale for the use of STI is that it will boost HIV-1–specific immune response in both acutely and chronically infected patients [2, 3] and, subsequently, reduce the virus load set point [4, 5]. The boosted immune response may lead to maintenance of a lower plasma HIV-1 RNA level once therapy is discontinued, and/or it may increase the rate of clearance of virus during subsequent drug therapy. An additional rationale would be to repopulate the host with wild-type virus [2]. Finally, by giving patients a respite from therapy, STI may lead to diminished toxicity and increased compliance without loss of long-term viral suppression [1]. Although little has been proven about the safety and theorized possible induction of viral suppression, a few studies have shown that STI rarely leads to resistance-conferring mutations [6, 7]. Furthermore, treatment efficacy is not reduced after STI in patients treated with protease inhibitor (PI)–based regimens [7, 8].

Nonnucleoside reverse-transcriptase inhibitors (NNRTIs) have been demonstrated to be effective as alternatives to PIs in HAART [9–11]. The NNRTIs nevirapine and efavirenz can be given just once or twice per day. Thus, the combination of an NNRTI plus 2 nucleoside reverse-transcriptase inhibitors (NRTIs) would represent an effective yet simple treatment regimen, with a longer dosing interval and fewer pills. Because of the long half-life of NNRTIs and the possibility of development of resistance, protocols that use NNRTIs before and after treatment interruptions have not yet been included in the designs of STI trials. Therefore, the objective of this retrospective study was to determine the impact of an STI, performed for the purpose of diminishing drug toxicity, on nevirapine-based regimens in patients with HIV RNA levels that are less than the level of quantitation.

Patients and methods. We conducted a retrospective chart review of 536 patients with laboratory evidence of HIV-1 infection who were treated from September 1996 through April 2000 at Bornemann Internal Medicine, an urban HIV clinic in Reading, Pennsylvania. The term “interruption in antiretroviral therapy” was used instead of “STI” because of the retrospective nature of the study and the variability in the duration of treatment interruption. An “interruption in antiretroviral therapy” was defined as simultaneous cessation of the entire antiretroviral regimen for >7 days. Most treatment interruptions were not planned, but had been the result of adverse events and other factors.

Patients were selected for detailed analysis if they had received treatment with an antiretroviral regimen that consisted of nevirapine plus 2 NRTIs, if they had an interruption in antiretroviral therapy, and if they subsequently restarted the same regimen. The charts of study patients were reviewed for
and physician questioning. The regimen was assessed by means of nursing medicine review of HIV-1 GenotypR PLUS (Specialty Labs). Compliance with antiretroviral therapy was conducted by Specialty Laboratories by use of HIV-1 Monitor (RNA; Roche Diagnostics). Genotypic resistance testing was performed by Amplicor RNA copies/mL was available for only some patients. HIV-1 viral therapy interrupted, after which they restarted the same regimen. The mean age of these 17 patients was 36 years. Ten patients (59%) were male and 7 (41%) were female. Eight patients (47%) were Hispanic, 7 (41%) were black, 1 (6%) was Asian, and 1 (6%) was white. The mean baseline HIV-1 RNA level was 108,276 copies/mL, and the median baseline HIV-1 RNA level was 39,000 copies/mL. The mean CD4+ cell count was 263 cells/mm³.

As shown in table 1, all patients in the study were treated with nevirapine plus 2 NRTIs (zidovudine plus lamivudine, stavudine plus lamivudine, or didanosine plus lamivudine). The mean duration of antiretroviral therapy was 193 days (range, 26–528 days), and the mean duration of the interruption in antiretroviral therapy was 58 days (range, 7–162 days).

Table 2 presents the HIV-1 RNA levels recorded before and during the interruption in antiretroviral therapy and after HAART reinitiation. The mean baseline HIV-1 RNA level in study patients was 108,276 copies/mL (range, 2487–367,481 copies/mL). The mean CD4+ cell count nadir for these patients was 263 cells/mm³. Before the interruption in antiretroviral therapy, the HIV-1 RNA level was below the limit of quantitation (<50 copies/mL or <400 copies/mL, depending on the threshold limit of quantitation in the assay used) in all study patients. The mean HIV-1 RNA level during the interruption in antiretroviral therapy was 16,830 copies/mL (range, <50–66,699 copies/mL). Five (29.4%) of 17 patients had HIV-1 RNA levels that were greater than the baseline levels during treatment interruption. In 15 (88.2%) of 17 study patients, the HIV-1 RNA level returned to <50 copies/mL or <400 copies/mL after the interruption in antiretroviral therapy. Four subjects had >1 interruption in antiretroviral therapy (2 subjects had 2 interruptions, and 2 subjects had 3 interruptions). All of these patients achieved HIV-1 RNA levels of <50 copies/mL or <400 copies/mL after each interruption. Of the 2 patients in whom viral suppression was not regained, one patient (patient 10) was noncompliant with antiretroviral therapy, and the other (patient 17) was found to have serum virus isolates that contained the I184V and Y181C mutations after HAART reinitiation. Genotypic testing was performed for patient 17 after viral suppression did not occur after the reinitiation of HAART. Results were not available for patient 10, because testing was not performed for this patient. Coincidentally, both patients 10 and 17 also had high baseline HIV-1 RNA levels (96,177 copies/mL and 351,288 copies/mL, respectively).

Discussion. On the basis of a retrospective analysis of 17 HIV-1–infected patients treated during a 3.5-year period with an NNRTI (nevirapine) plus 2 NRTIs (zidovudine plus lamivudine, stavudine plus lamivudine, or didanosine plus lamivudine), we determined that the efficacy of antiretroviral therapy was not reduced after reintroduction of antiretroviral therapy following treatment interruption. In the majority of patients, the nevirapine-containing HAART regimen reduced the following information: baseline and demographic characteristics, specific antiretroviral regimen, treatment duration, HIV-1 RNA level before and during antiretroviral therapy interruption, duration of the interruption in antiretroviral therapy, and HIV-1 RNA level after reinitiation of the same nevirapine-containing antiretroviral regimen. The HIV-1 RNA level was considered less than the limit of quantitation if it was <400 copies/mL of plasma. Because of the retrospective nature of this study, analysis using a limit of quantitation of <50 HIV-1 RNA copies/mL was available for only some patients. HIV-1 RNA levels were measured by PCR that used the Amplicor HIV-1 Monitor (RNA; Roche Diagnostics). Genotypic resistance testing was conducted by Specialty Laboratories by use of HIV-1 GenotypR PLUS (Specialty Labs). Compliance with the regimen was assessed by means of nursing medicine review and physician questioning.

Results. Seventeen (3.2%) of the 536 HIV-1–infected patients received treatment with an antiretroviral regimen that consisted of nevirapine plus 2 NRTIs and had their antiretroviral therapy interrupted, after which they restarted the same regimen. The mean age of these 17 patients was 36 years. Ten patients (59%) were male and 7 (41%) were female. Eight patients (47%) were Hispanic, 7 (41%) were black, 1 (6%) was Asian, and 1 (6%) was white. The mean baseline HIV-1 RNA level was 108,276 copies/mL, and the median baseline HIV-1 RNA level was 39,000 copies/mL. The mean CD4+ cell count was 263 cells/mm³.

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a Mean duration of ART, 193 days; mean duration of ART-i, 58 days.
the HIV-1 RNA level to undetectable levels after treatment reinitiation. This observation is consistent with other studies that have demonstrated reassertion of viral suppression after an STI [6, 7].

In our study, treatment failure after reintroduction of antiretroviral therapy was observed in only 2 (11.8%) of 17 patients. The treatment failure in the first patient could be attributed to reported noncompliance (no information on the genotype was available). A second patient, who experienced treatment failure with the Y181C and I184V mutations, had an impeccable history of compliance and reported good compliance after HAART reinitiation. Therefore, treatment interruption cannot be ruled out as a contributing factor to the selection of the strains with Y181C and I184V mutations in this patient. De novo development of NNRTI resistance (K103N mutation) after an interruption of therapy that contains efavirenz has been reported elsewhere [12]. Both patients who did not have resuppression of HIV-1 RNA after HAART reinitiation had high baseline HIV-1 RNA levels (96,177 copies/mL and 351,288 copies/mL). However, 3 (75%) of 4 patients with baseline HIV-1 RNA levels of >100,000 copies/mL did experience resuppression of HIV-1 RNA after reinitiation of HAART.

It is important to note that patients in the present study stopped receiving all medications simultaneously. It is possible that a strategy of sequential interruption (stopping use of NRTIs 48 h after stopping use of NNRTIs) may prevent HIV from being exposed to NNRTIs alone, which may lead to development of resistance.

Interruptions in antiretroviral therapy have been a common part of clinical practice since the development of PIs; in different reports, 36.2%–45.9% of patients in the study or clinic population experience treatment interruption [5, 13]. As the need for long-term antiretroviral therapy becomes more evident, we should study the effects of STI. STI may be able to provide long-term virologic control while offering temporary relief from adverse events and daunting adherence requirements. STI may have other benefits, such as decreasing resistance or improving cellular immunity, although evidence for this is mixed. The present retrospective study showed, for the first time, that viral resuppression occurred in patients receiving a regimen containing nevirapine that was interrupted and subsequently restarted. Because studies of STI have been conducted primarily in patients who receive PI-containing HAART, additional large-scale, prospective studies of STI in patients who receive regimens that contain nevirapine are warranted.

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References


