Maintaining Antiretroviral Therapy Reduces the Risk of AIDS-Defining Events in Patients with Uncontrolled Viral Replication and Profound Immunodeficiency

Isabelle Kousignian, Sophie Abgrall, Sophie Grabar, Aba Mahamat, Etina Teicher, Elisabeth Rouveix, Dominique Costagliola, and the Clinical Epidemiology Group of the French Hospital Database on HIV

Background. The benefits of continuing antiretroviral therapy are questionable in human immunodeficiency virus (HIV)–type 1–infected patients with profound immunodeficiency and multiple treatment failure due to viral resistance.

Methods. From the French Hospital Database on HIV, we selected 12,765 patients with a CD4+ cell count <200 cells/mm3 who received a combination antiretroviral therapy (cART) during 2000–2005. Three groups of patients were defined: patients who interrupted cART at least once, patients who had at least 2 consecutive detectable viral loads (VLs) while receiving cART, and patients who had undetectable VL during treatment with cART. Incidence rates and risks of new acquired immunodeficiency syndrome–defining events (ADEs) were assessed among the 3 groups of patients, overall and after CD4+ cell count stratification (<50 and 50–200 cells/mm3).

Results. The estimated incidence rates ± standard deviation of ADEs were 18.5 ± 1.9, 14.5 ± 0.7, and 4.9 ± 0.5, respectively, for patients who interrupted cART, patients who had detectable VL during treatment with cART, and patients who had undetectable VL during treatment with cART. These differences were observed in both CD4+ cell count strata. Overall, after adjustment, risks of a new ADE in patients who had detectable VL and in patients who had undetectable VL during treatment with cART were 22% and 62% lower, respectively, than in patients who stopped cART. Among patients with CD4+ cell count <50 cells/mm3, the risk of a new ADE was 22% lower in patients who continued to receive a failing cART regimen than in patients who stopped treatment with cART. Likewise, among patients with a CD4+ cell count of 50–200 cells/mm3, the risk was 34% lower in patients who continued to receive a failing cART regimen than in those who stopped taking cART.

Conclusions. Even when effective virological control is no longer achievable, cART still reduces the risk of ADEs in profoundly immunodeficient HIV-infected patients.
once more be effective when treatment is resumed. Gigatherapy has proven to be partially effective [3], whereas treatment interruption was found to be beneficial in 1 study [4] but not in others [5–7]. No clinical study assessed clinical outcome of immunosuppressed patients who stop a failing antiretroviral regimen in comparison with patients who continue it. Indeed, when patients are infected with a highly drug-resistant virus because of failed multiple antiretroviral regimens, have developed profound immunosuppression, and have experienced adverse effects associated with antiretroviral medications, clinicians may question the efficacy of maintaining antiretroviral therapy (ART) or have difficulty finding an optimized treatment regimen. Immunological rather than virological factors may be the main determinants of mid- or long-term HIV disease progression, particularly in patients with very advanced HIV disease [8–14]. In deeply immunosuppressed patients, no one really knows whether interruption of ART can be proposed with sufficient safety. With use of the French Hospital Database on HIV (FHDH-ANRS CO4), we analyzed patients with a CD4+ cell count below 200 cells/mm3 during the study period. Our objective was to compare the risk of clinical progression between patients who continued ART and patients who interrupted ART, mainly among the most immunosuppressed of them.

**METHODS**

**Study Population**

**The database.** The FHDH is a large prospective cohort study of HIV-infected patients who are aged ≥15 years and have been treated in a network of 68 French university hospitals. The enrollment criteria are documented HIV-1 or HIV-2 infection and written informed consent. Trained research assistants use French Ministry of Health DMI2 software to collect and record, on standardized forms, clinical and biological data at the time of study inclusion and at each visit or hospital admission for an HIV-related clinical event or a new treatment prescription or at least every 6 months.

**Patients.** To study the impact of maintaining or discontinuing a failing cART regimen on the risk of ADEs, we selected HIV-1-infected patients who were enrolled in the FHDH during 2000–2005 (1 January 2000–31 December 2005) who had a CD4+ cell count <200 cells/mm3, had ≥2 available CD4+ cell count values from follow-up visits, and had received ≥1 cART regimen (≥3 drugs) for ≥6 months while their CD4+ cell count was <200 cells/mm3 during the study period.

Three groups of patients were compared: the “cART interruption group,” which comprised patients with an ARV interruption lasting ≥3 months and spanning ≥2 consecutive follow-up visits; the “detectable VL group,” which comprised patients with at least 2 consecutive VL values ≥500 copies/mL while receiving cART; and the “undetectable VL group,” which comprised patients with at least 2 consecutive VL values <500 copies/mL while receiving cART. A given patient could thus qualify for all 3 study groups. Patients exposed to IL-2 or hydroxyurea were excluded. Patients prescribed regimens containing delavirdine or enfuvirtide were also excluded, because of the small number of patients concerned.

**Statistical Analysis**

**Follow-up data.** For each study group, the baseline was defined as the date of the first recorded CD4+ cell count <200 cells/mm3 after entry into the study group for which the patient qualified. Follow-up data on the cART interruption, detectable VL, and undetectable VL groups were modeled as time-dependent covariates. In each group, all patients’ follow-up durations were summed for the calculation of the entire follow-up of the patient in the considered group. Follow-up data were then censored at (1) the first subsequent CD4+ cell count ≥200 cells/mm3 in patients with ≥2 consecutive CD4+ values ≥200 cells/mm3, (2) death, (3) the last follow-up visit, or (4) 31 December 2005, whichever occurred first.

**Definition of clinical events.** We estimated the incidence of a new ADE in each group of patients, both overall and in different etiological categories (i.e., viral, fungal, protozoal, bacterial, and “other” infections). Viral events comprised cytomegalovirus disease, herpes simplex virus disease, Kaposi sarcoma, and progressive multifocal leukoencephalopathy. Fungal events comprised esophageal candidiasis, extrapulmonary crypttococcosis, and Pneumocystis jirovecii pneumonia. Protozoal events comprised cerebral or disseminated toxoplasmosis, isosporiasis, and cryptosporidiosis. Bacterial events comprised pulmonary and extrapulmonary tuberculosis, recurrent bacterial pneumonia, recurrent Salmonella sepsis, and atypical mycobacteriosis. “Other” events comprised HIV encephalopathy, invasive cervical cancer, non-Hodgkin lymphoma, and primary brain lymphoma.

**Statistical methods.** The incidence rates (IRs) of new ADEs in each group of patients were calculated by dividing the number of patients who had a new ADE during the entire follow-up period as part of the considered group by the number of person-years (PYs) at risk in the considered group, both overall and within the 2 CD4+ cell count strata (<50 and 50–200 cells/mm3). When the occurrence of a new ADE among each group of patients was analyzed, only the first ADE in the patient’s follow-up was considered. When ADE occurrence within each etiological category was analyzed, the first specific event within each category was considered. For instance, a patient who had both cytomegalovirus disease and Kaposi sarcoma during his or her follow-up was considered to have only 1 viral event for the calculation of the IR for viral events, whereas an individual who experienced events in ≥2 different etiologic categories was counted once in each category.

Factors associated with the risk of a new ADE were assessed...
Table 1. Patients’ characteristics at entry into the study group and subsequent follow-up.

<table>
<thead>
<tr>
<th></th>
<th>cART-interruption group (n = 2399)</th>
<th>Detectable VL group (n = 8783)</th>
<th>Undetectable VL group (n = 6548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1671 (69.7)</td>
<td>6342 (72.2)</td>
<td>4773 (72.9)</td>
</tr>
<tr>
<td>Age, median years (IQR)</td>
<td>40.0 (35.4–45.5)</td>
<td>39.6 (35.0–45.4)</td>
<td>41.3 (36.4–48.1)</td>
</tr>
<tr>
<td>HIV transmission group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>657 (27.4)</td>
<td>2455 (28.0)</td>
<td>1727 (26.4)</td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td>644 (26.8)</td>
<td>2002 (22.8)</td>
<td>1355 (20.7)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>893 (37.2)</td>
<td>3518 (40.1)</td>
<td>2723 (41.6)</td>
</tr>
<tr>
<td>Other</td>
<td>205 (8.5)</td>
<td>808 (9.2)</td>
<td>743 (11.3)</td>
</tr>
<tr>
<td>CD4+ cell count, median cells/mm$^3$ (IQR)</td>
<td>112 (46–168)</td>
<td>125 (64–168)</td>
<td>136 (95–171)</td>
</tr>
<tr>
<td>HIV RNA level, median log$_{10}$ copies/mL (IQR)</td>
<td>4.8 (3.9–5.3)</td>
<td>4.6 (3.7–5.2)</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. cART, combination antiretroviral therapy; IQR, interquartile range; PJP, Pneumocystis jirovecii pneumonia; VL, viral load.

Patients could participate in 1 of these groups during their follow-up in 2000–2002.

RESULTS

Baseline Characteristics

During 2000–2005, 12,765 patients (72.2% men) were selected. Table 1 describes the patients’ baseline characteristics at the date of their first qualification in each study group and their subsequent follow-up in the study group.

At baseline, 6703 patients (52.5%) received PI-containing cART, mainly ritonavir-boosted PI (3225 patients), nelfinavir (2047 patients), and indinavir (1501 patients); 3533 patients (27.7%) received a nonnucleoside reverse-transcriptase inhibitor–containing regimen (nevirapine for 1466 patients and efavirenz for 2065 patients); and 2529 (19.8%) received a triple–nucleoside reverse-transcriptase inhibitor regimen only. Each patient could receive 1 regimen during his or her follow-up treatment. The cART-interruption group comprised 2399 patients who had at least 1 cART interruption (of whom 38.7% had a baseline VL $>30,000$ copies/mL). The detectable-VL group comprised 8783 patients (of whom 45.5% had a baseline VL $>30,000$ copies/mL). The undetectable-VL group comprised 6548 patients. Overall, 4351 patients (34.1%) participated in >1 group. On entry to the study period, 44.0% of patients with
cART interruption, 23.0% of patients with detectable VL, and 10.4% of patients with undetectable VL had a CD4+ cell count <50 cells/mm³. Before baseline, 69.9% of patients with cART interruption, 62.9% of patients with detectable VL, and 33.8% of patients with undetectable VL had previously received single- or dual-nucleoside reverse-transcriptase inhibitor therapy; the median numbers of antiretroviral drugs previously received by these patients were, respectively, 9 (interquartile range [IQR], 7–11), 9 (IQR, 8–13), and 7 (IQR, 5–9).

**Clinical Progression**

**Frequency of clinical events.** Table 2 shows the IRs for new ADEs in each group, both overall and according to the CD4+ cell count stratum and the type of event. During the period, 348 patients with cART interruption had an ADE during a total follow-up of 1880 PYs (IR, 18.5 cases per 100 PYs), with 99 ADEs (28.4%) occurring during the first month of cART interruption; 1483 patients with detectable VL had an ADE during a follow-up of 10,263 PYs (IR, 14.5 cases per 100 PYs), with 189 (12.8%) occurring during the first month of inclusion in the detectable group; and 310 patients with undetectable VL had an ADE during a follow-up of 6324 PYs (IR, 4.9 cases per 100 PYs), with 59 (19.0%) occurring during the first month of inclusion in the undetectable group. Overall, the IRs were lower in the detectable VL group than in the cART-interruption group, and were lower still in the undetectable VL group.

Within each group, the IRs for new ADEs were higher in the <50 cells/mm³ CD4+ cell count stratum than in the 50–200 cells/mm³ stratum. Among both CD4+ cell count strata, the ADE IRs were lower in the detectable VL group than in the cART-interruption group and were lower still in the undetectable VL group.

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**Description of clinical events.** The most common events in patients with cART interruption and in patients with detectable VL were esophageal candidiasis (29.9% and 23.3%, respectively), P. jirovecii pneumonia (16.1% and 15.0%, respectively), toxoplasmosis (14.4% and 13.5%, respectively), cytomegalovirus disease (12.4% and 14.1%, respectively), and tuberculosis (13.5% and 9.4%, respectively); in patients with undetectable VL, the most frequent events were tuberculosis (19.0%), Kaposi’s sarcoma (15.2%), non-Hodgkin lymphoma (12.3%), and esophageal candidiasis (10.6%). The most frequent events were fungal infections (38.4% and 32.9%, respectively) in patients with cART interruption and in patients with detectable VL and were bacterial infections (30.4%) in patients with undetectable VL.

Figure 1 shows the IRs of the most frequent ADEs in each group of patients and the associated P values relative to the cART interruption group, in adjusted Cox models. For all events, IRs were significantly lower in patients with detectable VL and in patients with undetectable VL than in patients with cART interruption.

**Risk analyses.** Table 3 shows the estimated risks (i.e., hazard ratios) for a new ADEs, according to the CD4+ cell count stratum and the type of event. During the period, 348 patients with cART interruption had an ADE during a total follow-up of 1880 PYs (IR, 18.5 cases per 100 PYs), with 99 ADEs (28.4%) occurring during the first month of cART interruption; 1483 patients with detectable VL had an ADE during a follow-up of 10,263 PYs (IR, 14.5 cases per 100 PYs), with 189 (12.8%) occurring during the first month of inclusion in the detectable group; and 310 patients with undetectable VL had an ADE during a follow-up of 6324 PYs (IR, 4.9 cases per 100 PYs), with 59 (19.0%) occurring during the first month of inclusion in the undetectable group. Overall, the IRs were lower in the detectable VL group than in the cART-interruption group, and were lower still in the undetectable VL group.

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**Risk analyses.** Table 3 shows the estimated risks (i.e., hazard ratios) for a new ADEs, according to the CD4+ cell count stratum and the type of event.
Table 3. Adjusted hazard ratios and 95% CIs for new AIDS-defining events (ADEs).

<table>
<thead>
<tr>
<th>Patient group, etiology, and CD4+ cell count</th>
<th>Detectable VL (≥500 copies/mL)</th>
<th>cART Interruption</th>
<th>Undetectable VL (≤500 copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New ADE, by CD4+ cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>0.78 (0.60–1.00)</td>
<td>1</td>
<td>0.48 (0.36–0.65)</td>
</tr>
<tr>
<td>50–200 cells/mm³</td>
<td>0.66 (0.57–0.76)</td>
<td>1</td>
<td>0.27 (0.21–0.34)</td>
</tr>
<tr>
<td>Total</td>
<td>0.78 (0.69–0.87)</td>
<td>1</td>
<td>0.38 (0.33–0.45)</td>
</tr>
<tr>
<td>New viral etiology</td>
<td>0.94 (0.74–1.19)</td>
<td>1</td>
<td>0.59 (0.43–0.82)</td>
</tr>
<tr>
<td>New fungal etiology</td>
<td>0.71 (0.60–0.84)</td>
<td>1</td>
<td>0.20 (0.15–0.27)</td>
</tr>
<tr>
<td>New protozoal etiology</td>
<td>0.72 (0.55–0.94)</td>
<td>1</td>
<td>0.23 (0.15–0.36)</td>
</tr>
<tr>
<td>New bacterial etiology</td>
<td>0.85 (0.67–1.07)</td>
<td>1</td>
<td>0.52 (0.38–0.70)</td>
</tr>
<tr>
<td>New other etiology</td>
<td>0.91 (0.66–1.25)</td>
<td>1</td>
<td>0.52 (0.35–0.79)</td>
</tr>
<tr>
<td>Patients with follow-up ≥1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New ADE, by CD4+ cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 cells/mm³</td>
<td>0.90 (0.61–1.07)</td>
<td>1</td>
<td>0.51 (0.37–0.71)</td>
</tr>
<tr>
<td>50–200 cells/mm³</td>
<td>0.69 (0.59–0.80)</td>
<td>1</td>
<td>0.27 (0.21–0.34)</td>
</tr>
<tr>
<td>Total</td>
<td>0.84 (0.74–0.95)</td>
<td>1</td>
<td>0.40 (0.33–0.47)</td>
</tr>
</tbody>
</table>

**NOTE.** Values—calculated using Cox proportional-hazards models with counting process, adjusted for sex, HIV transmission group, prophylaxis against *Pneumocystis jiroveci* pneumonia or toxoplasmosis, the baseline VL stratum, and the calendar period of inclusion—are overall and according to the CD4+ cell count stratum and the etiological category. cART, combination antiretroviral therapy; VL, viral load.

stratum and the type of event, with the cART-interruption group as reference, after adjustment for sex, the HIV transmission group, prophylaxis against *P. jiroveci* pneumonia or toxoplasmosis, the CD4+ cell count, the baseline VL stratum, and the calendar period of inclusion.

Overall, the risk of a new ADE was 22% and 62% lower in patients with detectable VL and in patients with undetectable VL on cART, respectively, than in patients with cART interruption.

Among patients with a CD4+ cell count <50 cells/mm³ and among patients with a CD4+ cell count of 50–200 cells/mm³, the 2 cART-treated groups (detectable and undetectable VL) had a significantly lower risk of new ADEs than did patients with treatment interruption (hazard ratio, 0.78 and 0.48, respectively, for patients with CD4+ cell count <50 cells/mm³; hazard ratio, 0.66 and 0.27, respectively, for patients with a CD4+ cell count of 50–200 cells/mm³). When patients whose follow-up was <1 month in the study group were excluded from the analysis, results were similar (table 3).

**DISCUSSION**

Patients with detectable VL who continued ARV therapy had lower IRs and risks of ADEs of all types than did patients who stopped their treatment, both in the overall population and after CD4+ cell count stratification. The patients with the lowest IRs and risks of ADE were those with undetectable VL while on cART. Several recent studies have examined whether ART can safely be discontinued in patients with a CD4+ cell count ≥350 cells/mm³ [16–19]. A low nadir CD4+ cell count was the best predictor of clinical events (ADEs or death) and the subsequent decrease in the CD4+ cell count [19]. When ART was resumed at a CD4+ cell count <250 cells/mm³, the incidence of clinical events, ADE, or death was significantly increased, and the relative risk of disease progression or death was significantly higher than in patients who continued ART [17–18]. The risk of opportunistic infections increases significantly at CD4+ cell count below the classic threshold of 200 cells/mm³, and such patients require prompt ART plus prophylaxis for *P. jiroveci* pneumonia and toxoplasmosis. ARV withdrawal for 8–24 weeks has been assessed in highly ARV-experienced patients with low CD4+ cell count, but the risk of disease progression or death was higher, and the decrease in the CD4+ cell count was sharper than in patients who continued ART [5–7]. Other cohort studies have suggested that treatment interruption has a negative impact on the prognosis of highly ARV-experienced patients [12, 20–30], particularly among the most immunodeficient patients [21–23], but no study compared clinical outcome of deeply immunosuppressed patients who interrupted with those who continued while the CD4+ cell count was <50 cells/mm³. Our study confirms that interruption of ART has a negative prognostic impact, even in the patients with the most-advanced disease. Patients with low-level viral replication have a lower risk of clinical progression than do patients with a high level of viral...
Figure 1. Incidence rates (per 100 person-years) and 95% CIs for some AIDS-defining events and $P$ values of the comparison of each group with the combination antiretroviral therapy (cART)-interruption group, with use of adjusted Cox models [cytomegalovirus (CMV) disease, esophageal candidiasis, tuberculosis, Kaposi sarcoma, Pneumocystis jirovecii pneumonia, mycobacteriosis, HIV-related encephalopathy, toxoplasmosis, and non-Hodgkin lymphoma].
replication, after adjustment for the CD4+ cell count, AIDS status, and ART [12, 21, 22, 24]. This also argues for the maintenance of ART in such patients.

No resistance data were available in this study, and we did not analyze the reasons for cART interruption. Data on reasons for treatment interruptions are not collected in the FHDH database. Reasons can be in poor compliance because of psychosocial factors, adverse effects of the medications, progressive disease with symptoms of sickness, and weariness of the treatment leading to an interruption of the cART. Analyses of IRs and hazard ratios for new ADE after exclusion of patients with a follow-up <1 month had results similar to those of the analysis of all the study population. Therefore, if some patients in the cART interruption group were sicker than patients in the detectable VL group, in spite of similar CD4+ cell counts, and if they stopped taking their treatment because of progressive disease, indication biases because of such patients were taken into account by these models. Furthermore, multivariable models were adjusted for baseline VL strata and CD4+ cell count strata during follow-up. At the date of inclusion in the groups, ∼25% of the patients had no prophylaxis against *P. jirovecii* pneumonia or toxoplasmosis, despite a CD4+ cell count <200 cells/mm3. This argues for a weariness of the treatment. Prophylaxis at the date of inclusion in each group was not compared among the different groups, but multivariable models were adjusted on prophylaxis against *P. jirovecii* pneumonia or toxoplasmosis during the follow-up as a time-dependant variable, and effect of interruption of prophylaxis on ADE occurrence was taken into account. Because very few patients were receiving atypical mycobacteriosis prophylaxis and because French guidelines recommended a focus on ART and prophylaxis against *P. jirovecii* pneumonia and toxoplasmosis in such patients, during the study period, models were not adjusted for atypical mycobacteriosis prophylaxis. Observational databases like the FHDH, which include substantial numbers of patients managed in numerous hospitals, can explore clinical events that may be too infrequent to assess in clinical trials. Moreover, in profoundly immunodeficient patients, randomized trials of treatment interruption versus treatment continuation may be ethically unacceptable.

Several observations suggest that drug-resistant strains of HIV-1 are less fit than their wild-type counterparts [25]. This might partly explain why reversion to a wild-type quasispecies after treatment interruption appears to be deleterious [25, 26]. Maintenance of a failing drug regimen to which the patient’s HIV quasispecies is resistant may still interfere with viral replication and thereby slow the immunological and clinical deterioration [27]. Furthermore, that antiretroviral treatment might have beneficial effects mediated by mechanisms other than the CD4+ cell increment or the reduction in VL, as previously suggested [12, 21, 28]. Indeed, these surrogate markers do not always accurately predict the clinical efficacy of ART [29–31]. Thus, the predictive value of CD4+ cell count and HIV RNA level may be different in patients off therapy than in patients on therapy [27–32]. Persistently low viral replication (200–10,000 copies/mL) during ART stimulates higher frequencies of HIV-specific CD4+ and CD8+ T cells, compared with full virus suppression or complete ART failure [32]. Some authors have suggested that drug-resistant HIV-1 may be less pathogenic than wild-type virus and that continued use of ART might provide a clinical benefit, despite persistent viremia and drug resistance [33]. Immune defenses against other pathogens are also preserved in patients with persistent low-level HIV replication, because lymphoproliferative responses to recall antigens are similar in patients with low VL and in patients with undetectable VL and are different in patients with high VL [32]. This is supported by our results showing that patients who discontinued cART had a higher incidence of ADEs than did patients with detectable VL on cART. In conclusion, our results suggest that, when profoundly immunodeficient HIV-infected patients have no further treatment options permitting effective viral control, maintaining a failing regimen is preferable to interrupting it.

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