Effect of Antiretroviral Therapy on Viral Load, CD4 Cell Count, and Progression to Acquired Immunodeficiency Syndrome in a Community Human Immunodeficiency Virus–Infected Cohort

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Objective: To examine the effect of different antiretroviral treatment regimens on viral load, CD4 lymphocyte counts, and rates of progression to clinical acquired immunodeficiency syndrome events among treatment-naive human immunodeficiency virus (HIV)–infected patients enrolled in a large community cohort study.

Methods: Based in 7 outpatient clinics, the Swiss HIV Cohort Study is a cohort with national coverage. Virological, immunologic, and clinical results of 755 treatment-naive patients (median age, 36 years; 28.2% female) who initiated antiretroviral therapy between July 1, 1995, and June 30, 1997, were analyzed. Patients started undergoing monotherapy with 1 reverse transcriptase inhibitor (RTI), combination therapy with at least 2 RTIs, or highly active antiretroviral therapy (HAART) with RTIs and protease inhibitors.

Results: Antiretroviral treatment led to a mean reduction of viremia of 1.8 log_{10} copies per milliliter with HAART, 1.2 log_{10} copies per milliliter with RTI combination therapy, and 0.4 log_{10} copies per milliliter with monotherapy. Virological failure, defined as less than 1 log_{10} reduction per milliliter in viremia, was present in 45 (20%) patients undergoing HAART, 180 (38%) undergoing RTI combination therapy, and 47 (82%) undergoing monotherapy. The proportion of patients reaching undetectable viremia was 12% (n = 7) for monotherapy, 41% (n = 197) for RTI combination therapy, and 63% (n = 137) for HAART. Similar gains of CD4 cells were achieved with RTI combination therapy and HAART. Kaplan-Meier estimates of progression rates to a new acquired immunodeficiency syndrome event at 18 months were 13.6% (monotherapy), 4.7% (RTI combination therapy), and 3.9% (HAART).

Conclusions: The rate of virological failure of antiretroviral treatments was high in this population of treatment-naive patients, even among patients receiving combination regimens. Clinical progression rates were, however, low in patients treated with RTI combination therapy and HAART.

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THE QUANTITATIVE reverse transcriptase polymerase chain reaction allows accurate quantification of plasma viral load as the concentration of human immunodeficiency virus (HIV) RNA copies. Numerous studies that demonstrate the prognostic value of viral load measurements for disease progression have been published. Plasma viral load appears to be the best predictor of long-term clinical outcome, whereas CD4 cell counts predict clinical progression and survival in the shorter term. Although many randomized studies addressed the respective roles of viral load and CD4 cell counts, uncertainty still remains about the best use of these 2 markers outside controlled trials. The Swiss HIV Cohort Study (SHCS), set up as a multicenter project in 1988, represents worldwide one of the largest community cohorts of people with HIV. The SHCS is fairly representative for the country, as more than 70% of patients with the acquired immunodeficiency syndrome (AIDS) and an estimated 38% of all people with HIV are included in the study. Highly active antiretroviral therapy (HAART), including protease inhibitors and quantitative viral load measurements by a commercial assay, was introduced in 1995.

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The present study examines the effect of different modes of antiretroviral therapy on viral load, CD4 lymphocyte counts, and rates of progression to new AIDS events among SHCS participants naive to antiretroviral therapy.
SUBJECTS AND METHODS

STUDY POPULATION

From July 1, 1995, to June 30, 1997, 3687 HIV-infected participants, 70.8% male and 29.2% female, had 10,963 visits in one of the 7 SHCS study centers. The SHCS is an open cohort that continuously enrolls new patients. The length of follow-up thus depends on the date of enrollment. Of 2009 participants who were naive to antiretroviral therapy, 755 (71.8% male; median age, 38 years [range, 22-71 years]; 28.2% female; median age, 34 years [range, 20-53 years]) started treatment during the study period and had follow-up visits. The mode of HIV transmission was as follows: homosexual or bisexual contacts, 35.7%; heterosexual contacts, 25.9%; intravenous drug use, 24.1%; intravenous drug use or sexual contacts, 11.2%; and other reasons, 3.1%.

LABORATORY TESTS

Blood samples were collected with blood collection tubes (Vacutainer CPT; Becton Dickinson, Basel, Switzerland). Plasma was separated within 2 hours and either processed immediately or frozen at −80°C until use. Human immunodeficiency virus RNA viremia was measured using commercially available quantitative polymerase chain reaction equipment (Amplicor HIV Monitor; Roche Diagnostics, Basel, Switzerland). The lower limit of detection of this assay is 400 copies per milliliter. CD4 cell counts were measured with flow cytometry.

ANTIRETROVIRAL THERAPY

Since the introduction of antiretroviral combination therapy, various drug combinations have been used in the SHCS. To simplify matters in the context of the present study, we classified participants into 3 groups according to their initial antiretroviral therapy: (1) monotherapy, therapy with 1 reverse transcriptase inhibitor (RTI); (2) RTI combination therapy, combination treatment with at least 2 RTIs; and (3) HAART, triple combination treatment with 2 RTIs and 1 protease inhibitor (ritonavir or indinavir) or 1 RTI and 2 protease inhibitors (ritonavir and/or saquinavir and/or indinavir).

The following RTIs were used: zidovudine, didanosine, zalcitabine, lamivudine, and stavudine.

STUDY END POINTS

Changes in plasma HIV RNA concentration and CD4 lymphocyte count during therapy were analyzed. In accordance with Fatkenheuer et al,16 we defined virological efficacy as a reduction of HIV RNA by at least 1 log10 copy per milliliter. Virological treatment failure was defined as a reduction of viral load of less than 1 log10 copy per milliliter, an increase in viral load above baseline, or a rebound in viremia to baseline after an initial decrease. Overall treatment efficacy was defined as a decrease of viral load of at least 1 log10 copy per milliliter and an increase of the CD4 cell count by at least 50% of the baseline value. AIDS was defined as clinical stage C of the 1993 classification system for HIV infection.17

STATISTICAL ANALYSIS

Plasma HIV RNA levels were log10 transformed, and values below the detection limit were assigned the value of 2.602 on the log10 scale, corresponding to 400 copies per milliliter. t Tests were carried out for analysis of continuous variables. The χ2 test was used to compare different treatment regimens. Progression to new clinical AIDS events was examined using Kaplan-Meier life table methods and multivariate Cox proportional hazards regression model. Time was measured from the date of starting treatment to the date of the last follow-up visit. Patients were kept in the original treatment group even if treatment was changed later (intention-to-treat principle).

RESULTS

BASELINE CHARACTERISTICS

Of 755 patients, 57 (7.6%) underwent monotherapy; 479 (63.3%), RTI combination therapy; and 219 (29.1%), HAART. The percentage of participants with Centers for Disease Control and Prevention stage C AIDS was higher in the groups starting monotherapy (42.3%) and HAART (38.9%) than in the group starting RTI combination therapy (18.8%). The more advanced disease stage of the participants starting monotherapy or HAART was also reflected in baseline viral load and CD4 cell counts (Table 1).

EFFECTS ON VIRAL LOAD AND CD4 CELL COUNT

Viral load and CD4 cell counts were monitored at least every 6 months. A total of 3029 viral load measurements and CD4 cell counts were performed during 898 years of follow-up, corresponding to a mean number of 3.4 measurements per participant and year. The percentage of participants reaching undetectable viremia (<400 HIV RNA copies per milliliter) during the observation period was higher for those undergoing HAART than those undergoing RTI monotherapy or combination therapy. Similarly, the proportion of participants with CD4 cell counts below 0.20 × 10^9/L (200/µL) decreased more for those undergoing HAART (Figure 1).

About 11.4% of the patients treated with monotherapy, 15.7% with RTI combination therapy, and 26.2% with HAART had a viral load reduction below detection limits and a concomitant increase of CD4 cell counts above 0.20 × 10^9/L. The separate percentages for a viral load reduction to undetectable limits and a CD4 cell increase above 0.20 × 10^9/L were 63.2% and 37.9% for HAART, 40.7% and 34.8% for RTI combination therapy, and 11.6% and 22.1% for monotherapy, respectively.

Table 2 shows that treatment was virologically efficacious in most patients undergoing HAART, in more
than half undergoing RTI combination therapy, and in only a few undergoing monotherapy.

Almost 60% of the participants treated with HAART had a CD4 cell count increase of at least 50% of the baseline value, whereas such an increase was only manifest in about a third of the participants treated with RTI combination therapy or monotherapy. Among the participants who did not change the treatment regimen, 416 (63%) could be followed up for 8 months, 176 (26%) for 12 months, and 67 (10%) for up to 21 months. Highly active antiretroviral therapy induced a reduction of viral load during the first 3 months (Figure 2). Viral load reduction while undergoing RTI combination therapy and monotherapy became manifest from the second month onward. The mean viral load reductions achieved were −0.4, −1.2, and −1.8 log10 copies per milliliter for monotherapy, RTI combination therapy, and HAART, respectively (Figure 2). The course of CD4 cell counts was more variable. With combination treatments, CD4 cell counts peaked during the first 6 months and then gradually decreased. In patients undergoing monotherapy, some increase was observed after the first 3 months. These patients could only be observed for 8 months because of subsequent modifications to therapy or discontinuation of therapy.

CHANGE OF ANTIRETROVIRAL THERAPY

The treatment regimen was modified in 100 (13.2%) of the 755 patients (Table 3). In 8 participants (1.1%), further changes of therapy were made later. In 63 participants, RTI combination therapy was replaced by HAART after an average of 191 days. At this time, the initial viral load reduction was log10 −0.51 copies per milliliter, with a CD4 cell count increase of 0.047 × 10^9/L. During the following 180 days of HAART, a further average viral load reduction of log10 −1.17 copies per milliliter and an additional increase of CD4 cells of 0.095 × 10^9/L were achieved. Sixteen (25%) of the 63 participants who switched therapy demonstrated treatment failure as defined by a viral load reduction of less than 1 log10 copy per milliliter. Nineteen participants undergoing monotherapy without viral load reduction during a median treatment period of 154 days changed to HAART and achieved a viral load reduction of log10 −2.37 copies per milliliter. Ten participants undergoing monotherapy with an average viral load reduction of log10 −0.7 copies per milliliter after a treatment period of 124 days changed to RTI combination therapy and subsequently achieved a further viral load reduction of log10 −0.82 copies per milliliter. Five of these 10 participants demonstrated treat-
ment failure. The replacement of RTI combination therapy or HAART by monotherapy resulted in treatment failure in all 8 participants involved.

EFFECTS OF ANTIRETROVIRAL THERAPY
IN RELATION TO BASELINE CD4 CELL COUNTS

The therapy-dependent change of viral load and CD4 cell counts was analyzed separately for participants with either low ($<0.20 \times 10^9/L$), intermediate ($0.20-0.50 \times 10^9/L$), or high ($>0.50 \times 10^9/L$) baseline CD4 cell counts (Table 4). Independent of the baseline CD4 cell count, HAART always evoked a higher viral load reduction and a more pronounced CD4 cell increase than RTI combination therapy or monotherapy. Highly active antiretroviral therapy was especially effective if the baseline CD4 cell count was low.

DEVELOPMENT OF NEW AIDS-DEFINING DISEASES

During 898 person-years of follow-up, 34 patients developed a new AIDS event. The cumulative rate of developing a new clinical event is shown in Figure 3. At 12 months, an estimated 10.3% (monotherapy), 3.2% (RTI combination therapy), and 3.1% (HAART) had developed a new AIDS event. The corresponding figures for 18 months were 13.6%, 4.7%, and 3.9%, respectively. This was confirmed in Cox proportional hazards regression models. Compared with RTI combination therapy, the hazard ratio was 2.68 (95% confidence interval, 1.07-6.70) for monotherapy and 1.07 (95% confidence interval, 0.47-2.44) for HAART. When the same model was adjusted for baseline CD4 cell count, viral load, and history of AIDS, the risk of progression continued to be increased with monotherapy (hazard ratio, 1.52) but was reduced with HAART (hazard ratio, 0.66); however, differences between treatment regimens were no longer statistically significant ($P = .13$ by the test for trend).

COMMENT

Several observational studies in the United States, Canada, and Europe have documented a substantial reduction in the risk of new opportunistic infections and a reduction in mortality following the intro-
duction of antiretroviral combination therapies. We analyzed the database of the SHCS, a prospective study with national coverage, to compare the effects of HAART, RTI combination therapy, and monotherapy on viral load, CD4 lymphocyte counts, and risk of new AIDS events among participants naive to antiretroviral therapy.

It is widely accepted that monotherapy with 1 RTI should no longer be used. In the present study, antiretroviral treatment was initiated with monotherapy in a few patients only and this exclusively occurred in the beginning of the study period, ie, in 1995. Despite the small number of patients involved, the inferiority of monotherapy compared with combination therapies was evident for all 3 end points considered, ie, suppression of viral replication, CD4 lymphocyte reconstitution, and clinical disease progression. The analysis of clinical progression rates was according to the intention-to-treat principle, and patients were thus kept in the original treatment group even if treatment was changed. Treatment was indeed changed in about half of the patients who started monotherapy, but differences in progression rates were nevertheless evident. The consecutive initiation of antiretroviral drugs has been shown to impair virological efficacy, probably due to the selection of drug-resistant virus strains, and this may have contributed to the differences in clinical disease progression observed in our study.

Comparing RTI combination therapy with HAART, the latter produced a greater viral load reduction, which was sustained over time, despite the more advanced disease stage at baseline among patients treated with HAART. In contrast to viral load, differences between HAART and RTI combination therapies were less consistent for CD4 cell count, except for a more rapid initial response with HAART. Our data are broadly consistent with the findings from randomized trials, although HAART tended to produce a more pronounced reduction in viral load in the randomized trials than in our study. This discrepancy demonstrates that the results reported from controlled trials are not always generalizable to the patient population at large. The SHCS's coverage is national, with study centers in all language regions. The cohort includes patients from all transmission groups and many women. Comparisons with the National AIDS Register have shown that the study includes about 70% of all reported AIDS cases. The experience of the patients analyzed herein is, therefore, likely to be representative for the treatment of naive patients seen in routine practice during the period studied. In the routine setting, adher-

### Table 3. Effect of Change of Antiretroviral Therapy on Viral Load and CD4 Cell Counts

<table>
<thead>
<tr>
<th>Therapy Change</th>
<th>No. of Patients</th>
<th>HIV RNA, log10 Copies per Milliliter</th>
<th>CD4 Cell Count, ( \times 10^9/\text{L} )</th>
<th>Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTI combination → HAART</td>
<td>63</td>
<td>-1.17</td>
<td>0.085</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Monotherapy → HAART</td>
<td>19</td>
<td>-2.37</td>
<td>0.063</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Monotherapy → RTI combination</td>
<td>10</td>
<td>-0.82</td>
<td>0.012</td>
<td>5 (50)</td>
</tr>
<tr>
<td>RTI combination or HAART → monotherapy</td>
<td>8</td>
<td>1.16</td>
<td>0.018</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>

* HIV indicates human immunodeficiency virus; RTI, reverse transcriptase inhibitor; and HAART, highly active antiretroviral therapy.
† Data are given as the median decrease or increase of viral load and CD4 cell count after therapy change.
‡ Data are given as the number (percentage) of participants who had a viral load reduction of less than 1.0 log10 copies per milliliter.

### Table 4. Influence of Treatment Regimens on Viral Load and Lymphocyte Counts According to CD4 Baseline Values

<table>
<thead>
<tr>
<th>CD4 Baseline Value, ( \times 10^9/\text{L} )</th>
<th>Variable Measured</th>
<th>Monotherapy†</th>
<th>RTI Combination†</th>
<th>HAART†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.20 (n = 342) HIV RNA, \log_{10} \ copies per milliliter</td>
<td>0.01</td>
<td>-1.10</td>
<td>-2.39</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, ( \times 10^9/\text{L} )</td>
<td>0.010</td>
<td>0.054</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>0.20-0.50 (n = 345) HIV RNA, \log_{10} \ copies per milliliter</td>
<td>-0.11</td>
<td>-1.42</td>
<td>-1.57</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, ( \times 10^9/\text{L} )</td>
<td>0.040</td>
<td>0.047</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>&gt;0.50 (n = 68) HIV RNA, \log_{10} \ copies per milliliter</td>
<td>-0.61</td>
<td>-1.23</td>
<td>-1.33</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, ( \times 10^9/\text{L} )</td>
<td>0.025</td>
<td>0.054</td>
<td>0.051</td>
<td></td>
</tr>
</tbody>
</table>

* RTI indicates reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy; and HIV, human immunodeficiency virus.
† Data are given as the median increase or decrease after therapy.

![Figure 3. Cumulative frequency of developing a new clinical acquired immunodeficiency syndrome (AIDS) event among patients treated with different antiretroviral treatment regimens. See the "Antiretroviral Therapy" subsection of the "Subjects and Methods" section for definitions of monotherapy, reverse transcriptase inhibitor (RTI) combination therapy, and highly active antiretroviral therapy (HAART).](image-url)
ence to drug regimens will be less complete than among patients who participate in controlled trials. Adherence may be a particular problem for certain groups of patients who also tend to be underrepresented in clinical trials (eg, patients with a history of intravenous injection drug use). Many patients in our analysis had been infected via intravenous drug use.

Twenty percent of patients starting HAART developed virological treatment failure, ie, either a viral load decreased by less than 1 log_{10} copy per milliliter or the initial reduction was followed by a viral rebound. Other observational studies\(^{16,28,29}\) of patients undergoing combination therapies using the same protease inhibitors reported virological failure rates of up to 44%. However, in contrast to our study, most patients included in these studies were not naive to antiretroviral therapy. The discrepant rates of virological treatment failure thus provide indirect support for the notion that a previous history of antiretroviral treatment increases the risk of failure.\(^{23,24}\)

CD4 cell responses in number of cells gained, and clinical progression rates, were similar for patients treated with RTI combination therapies and patients treated with HAART, despite the considerably greater reductions in viral load achieved with HAART. An earlier study\(^{30}\) of the experience from one SHCS study center showed an important effect of combination therapies on CD4 cell counts despite incomplete suppression of viremia. Our study confirms the earlier results and shows that a substantial increase in CD4 cells is observed despite the relatively modest reduction in viral load that was achieved with RTI combination therapies. The present analysis extends these findings to clinical end points and indicates that the CD4 cells gained provided protection from new opportunistic disease, in the group treated with HAART and in the group undergoing RTI combination therapy. In these 2 groups, clinical progression was a rare event, with less than 5% developing a new AIDS event by 18 months. When taking into account the baseline differences that existed between groups in multivariable analysis, a statistically nonsignificant trend indicating a lower risk of clinical progression among patients treated with HAART emerged. We plan to update our analysis and hypothesize that this trend will become statistically significant as more follow-up time accumulates. A recent analysis\(^{31}\) of all patients who initiated HAART from 1995 to 1998 showed that patients who never reached undetectable viremia had a higher rate of clinical disease progression during 30 months of follow-up.

Should we “hit” the virus early and hard before immunodeficiency develops, or should we wait until we are confident that the clinical benefits of treatment will outweigh possible toxicities and adverse effects on quality of life? This question, which should ideally be addressed in a pragmatic controlled trial,\(^{22}\) remains unresolved.\(^{22}\) In our study, the virus was hit hard by HAART in many patients; however, it was hit rather late by today's standards.\(^{22}\) Despite this, important clinical benefits were observed even among patients with relatively modest reductions in viral load.

In conclusion, among treatment-naïve patients participating in a large community cohort, we found a higher rate of virological treatment failure for those undergoing antiretroviral combination regimens than has been reported from controlled clinical trials. However, despite this limited virological success, clinical progression rates remained low. Our findings indicate that virological and immunologic responses should be examined before antiretroviral treatment is considered a failure and the regimen is modified. Controlled trials are required to define the optimal time of initiating HAART and the best therapeutic strategies after virological, immunologic, or clinical treatment failure. In the absence of trials assessing clinical end points, observational data are an important source of information relating new treatment regimens to the risk of serious clinical disease.

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