Predictors of CD4⁺ T-Cell Counts of HIV Type 1–Infected Persons After Virologic Failure of All 3 Original Antiretroviral Drug Classes

The Pursuing Later Treatment Option II (PLATO II) Project Team of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE)†

**Background.** Low CD4⁺ T-cell counts are the main factor leading to clinical progression in human immuno-deficiency virus type 1 (HIV-1) infection. We aimed to investigate factors affecting CD4⁺ T-cell counts after triple-class virological failure.

**Methods.** We included individuals from the COHERE database who started antiretroviral therapy from 1998 onward and who experienced triple-class virological failure. CD4⁺ T-cell counts obtained after triple-class virological failure were analyzed using generalized estimating equations.

**Results.** The analyses included 2424 individuals with a total of 23,922 CD4⁺ T-cell count measurements. In adjusted models (excluding current viral load and year), CD4⁺ T-cell counts were higher with regimens that included boosted protease inhibitors (increase, 22 cells/µL [95% confidence interval (CI), 3.9–41]; \( P = .017 \)) or drugs from the new classes (increase, 39 cells/µL [95% CI, 15–62]; \( P = .001 \)), compared with nonnucleoside reverse-transcriptase inhibitor–based regimens. These associations disappeared when current viral load and/or calendar year were included. Compared with viral levels of <2.5 \( \log_{10} \) copies/mL, levels of 2.5–3.5, 3.5–4.5, 4.5–5.5, and >5.5 \( \log_{10} \) copies/mL were associated with CD4⁺ T-cell count decreases of 51, 84, 137, and 186 cells/µL, respectively (\( P < .001 \)).

**Conclusions.** The approximately linear inverse relationship between \( \log_{10} \) viral load and CD4⁺ T-cell count indicates that there are likely immunologic benefits from lowering viral load even by modest amounts that do not lead to undetectable viral loads. This is important for patients with low CD4⁺ T-cell counts and few drug options.

**Keywords.** HIV-1; antiretroviral agents; triple-class virologic failure; CD4 lymphocyte count; HIV cohort study.
Continued viral replication and the resulting decrease in CD4+ T-cell count are the main factors leading to clinical AIDS-defining diseases and mortality. We have shown in the Pursuing Later Treatment Options (PLATO) collaboration that increases in CD4+ T-cell count can be achieved even when virus is not completely suppressed [9]. However, many of the participants in that study started antiretroviral therapy (ART) with a suboptimal monotherapy or dual therapy regimen and virtually had sequential monotherapies for several years, so the relevance for the current ART era is uncertain. The incidence of triple-class virologic failure has been declining, mainly because more people currently receiving treatment started ART as combination therapy (cART) including 2 NRTIs with a NNRTI or a ritonavir-boosted protease inhibitor (PI/r) but also because new and potentially better tolerated drugs have become available [3]. In another study of the PLATO II project, we showed that the probability of achieving viral levels below the limit of detection after triple-class virologic failure increased, from 19.5% in 2000 to 57.9% in 2009 [10]. Nevertheless, because of improved survival, the prevalence of persons with triple-class virologic failure has remained stable [3, 11] or is even increasing [2, 12]. The aim of this study was to investigate which factors affect CD4+ T-cell counts after triple-class virologic failure in the current ART era, in which cART is used from the time of initiation of therapy.

METHODS

Patients

COHERE is a collaboration of most HIV observational cohorts in Europe [13]. The 24 cohorts participating in the PLATO II project submitted data in a standardized format [14] (updated versions are available at: http://www.hicdep.org/) to one of two regional coordinating centers, where error checks were performed prior to merging the cohort data to form the COHERE database. Individuals appearing in >1 cohort were identified, and duplicate records were removed. This analysis on data merged in 2010 was restricted to ART-naive persons aged ≥16 years who started ART from 1998 onward and who experienced triple-class virological failure. Individuals were followed from the start of ART to their last viral load measurement. Virological failure of a drug was defined as 1 viral load of >500 copies/mL after at least 4 months of continuous use. Triple-class virologic failure was defined as virologic failure of 2 NRTIs, 1 NNRTI, and 1 PI/r. To be eligible for the analyses presented here, concurrent CD4+ T-cell counts and viral loads had to be available at the time of and at least 1 time after detection of triple-class virologic failure.

Statistical Analysis

We analyzed absolute CD4+ T-cell counts measured from the time of triple-class virologic failure onward. Counts were analyzed by marginal linear regression, using generalized estimating equations with exchangeable correlation structure and robust standard errors taking into account repeated measures per individual. This approach differs slightly from our previous analysis [9], in which we studied ongoing changes in CD4+ T-cell counts. In addition to the linear term, we added a quadratic term for the CD4+ T-cell count obtained at detection of triple-class virologic failure, to account for the fact that increases will not be linear across all CD4+ T-cell counts but will likely be reduced at higher CD4+ T-cell counts (i.e., a ceiling effect). In addition to CD4+ T-cell count, sex and HIV acquisition through contaminated needles (i.e., injection drug use [IDU]) were used as fixed (baseline) covariables. Age, viral load, type of ART, and calendar year were introduced as time-updated covariables. Continuous variables were checked for linearity of associations. We grouped antiretroviral treatment into the following regimen types: NNRTI plus 2 NRTIs, PI/r plus 2 NRTIs, PI (unboosted) plus 2 NRTIs, ≥1 NNRTI plus ≥1 PI plus ≥1 NRTI, regimens containing a new class, other regimens, and no receipt of treatment. Fusion inhibitors, integrase inhibitors, and CCR5 coreceptor antagonists were considered new classes. We lagged treatment information by 1 month to reduce the risk of reverse causality effects. Results of the multivariable model were then used to predict CD4+ T-cell count changes from a fixed baseline value (e.g., 300 cells/µL at triple-class virologic failure) at a specific time point after triple-class virologic failure (e.g., 2 years), for different current viral levels and for the different regimen types. In sensitivity analyses, we used random-effects models instead of generalized estimating equations, and we also evaluated estimates without including the quadratic CD4+ T-cell count term.

We used Stata software, version 12.1/SE (StataCorp, College Station, TX), and SAS software, version 9.1, for statistical analyses.

RESULTS

There were 91 764 eligible persons from 24 cohorts who initiated ART, of whom 2722 experienced triple-class virologic failure. CD4+ T-cell count and viral load at the time of triple-class virologic failure and at ≥1 subsequent time point were available for 2424 individuals (89%). The characteristics of the selected persons are shown in Table 1. Compared with the 2424 analyzed people, the 298 excluded individuals had experienced triple-class virologic failure in more recent years (2007 vs 2005; \(P < .001\)), had received ART for a longer period at the time of triple-class virologic failure (5.1 vs 4.3 years; \(P < .001\)), and were more likely to be receiving regimens with an NNRTI (13% vs 11%) or a boosted PI (59% vs 52%; \(P = .022\)). The other characteristics did not differ significantly. The 2424 persons contributed 23 922 CD4+ T-cell count measurements over a total of 7117 person-years of follow-up after triple-class
virologic failure. The proportion of follow-up time spent with CD4+ T-cell counts of <50, <200, <350, and <500 cells/µL was 7.1%, 28%, 54%, and 75%, respectively. Before 2004, the proportion of follow-up time spent with a CD4+ T-cell count of <200 cells/µL was 36%; from 2004–2007, 32%; and after 2007, 24%. For the time spent with viral loads <50 and <500 copies/mL, the proportions were 40% and 59%, respectively. The median number of CD4+ T-cell count measurements per person was 9 (interquartile range [IQR], 5–15), corresponding to a median frequency of 3.9 measurements/patient-year (IQR, 3.0–5.2). The median CD4+ T-cell count at the time of triple-class virologic failure was 270 cells/µL, with a significant increase over calendar time, from 226 cells/µL for those developing triple-class virologic failure in 2000 to 319 cells/µL for those developing triple-class virologic failure in 2009 (P < 0.001, by the nonparametric test for trend). The courses of CD4+ T-cell counts before and after triple-class virologic failure, according to the calendar period in which triple-class virologic failure occurred, are shown in Figure 1. From 2 years prior to triple-class virologic failure until 2 years after triple-class virologic failure, there was a continuous increase in median CD4+ T-cell count for all periods, but the wide IQRs revealed substantial heterogeneity in CD4+ T-cell counts in the population. As these findings may have been affected by survivor bias (ie, people with very low CD4+ T-cell counts were more likely to die), we repeated the analysis with CD4+ T-cell counts set to 0 after death of the 182 persons who died. The resulting curves were virtually unchanged (data not shown).

Associations between CD4+ T-cell counts after triple-class virologic failure with various covariables are shown in Table 2. Univariable models (data not shown) yielded results very similar to those of bivariable models that adjusted for the linear and quadratic terms of CD4+ T-cell counts at triple-class virologic failure. Bivariable models showed a strong inverse linear association between CD4+ T-cell counts and viral load, resulting in a CD4+ T-cell count decrease of 48 cells/µL (95% CI, 45–51) per log10 increase in HIV-1 RNA copies. In addition, older age and later calendar time were positively associated with higher CD4+ T-cell counts. Furthermore, compared with NNRTI-based regimens, treatments with a boosted PI or treatments including new drug classes were positively associated with CD4+ T-cell count. No receipt of treatment, however, was associated with a markedly lower CD4+ T-cell count (~64 cells/µL; 95% CI, −90 to −39). Of persons who received drugs from new classes during follow-up, 174 (7%) received a fusion inhibitor, 208 (9%) received an integrase inhibitor, and 26 (1%) received a CCR5 coreceptor antagonist. Associations with different regimens were only slightly affected when the model was adjusted for demographic variables and whether viral load had ever been suppressed.
Table 2. Predictors of CD4+ T-Cell Counts Among Human Immunodeficiency Virus Type 1 (HIV-1)–Infected Subjects After Triple-class Virological Failure (VF)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bivariable Models</th>
<th>P</th>
<th>Multivariable Model 1</th>
<th>P</th>
<th>Multivariable Model 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>−5.0 (−17 to 6.6)</td>
<td>.40</td>
<td>36 (21–52)</td>
<td>&lt;.001</td>
<td>24 (12–37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (per 10 y increase)⁵</td>
<td>109 (90–127)</td>
<td>&lt;.001</td>
<td>98 (81–116)</td>
<td>&lt;.001</td>
<td>59 (45–72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV-1 RNA load never &lt;500 copies/mL prior to triple-class VF</td>
<td>−12 (−29 to 5.3)</td>
<td>.18</td>
<td>−6.3 (−28 to 15)</td>
<td>.57</td>
<td>21 (2.7–38)</td>
<td>.024</td>
</tr>
<tr>
<td>HIV-1 acquisition via IDU</td>
<td>−1.4 (−18 to 18)</td>
<td>.87</td>
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<tr>
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<td>197 (−218 to −175)</td>
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<td>PI/r + 2 NRTI</td>
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<td>Old 3 classes⁴</td>
<td>61 (37–86)</td>
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Results are based on 2424 individuals with 23,922 CD4+ T-cell count measurements. Results from additional models also adjusted for calendar year are available in the Supplementary Materials.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; IDU, injection drug use; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor.

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Prior to triple-class virologic failure (Table 2). However, adjustment for the most recently measured viral load eliminated or even reversed the associations between regimen types and CD4+ T-cell count, suggesting that the differential effect of regimen types is primarily mediated through most recently measured viral load (Table 2). The increase of CD4+ T-cell count with calendar time was 21 cells/µL per year (95% CI, 18–24) in the bivariable model. This association was only marginally affected in adjusted analysis without current viral load (19 cells/µL per year [95% CI, 16–21]) and with current viral load (14 cells/µL per year [95% CI, 11–16]; Supplementary Table). Of note, all models had a significant negative quadratic term for CD4+ T-cell count at triple-class virologic failure, indicating a ceiling for CD4+ T-cell counts after triple-class virologic failure of 480–650 cells/µL. Figure 2 shows predicted CD4+ T-cell counts at 2 years after triple-class virologic failure for assumed starting values of 300 cells/µL at the time of triple-class virologic failure. There was very little difference between the regimens once viral load was taken into account.

Without differentiating by regimen, the predicted CD4+ T-cell counts attained at viral levels of 2, 3, 4, 5, and 6 log₁₀ copies/mL were 386 (95% CI, 379–392), 342 (95% CI, 337–348), 299 (95% CI, 294–305), 256 (95% CI, 249–263), and 213 (95% CI, 204–222) cells/µL, respectively. Overall, decreasing CD4+ T-cell counts were seen at viral levels of >4.12 log₁₀ copies/mL (ie, 13 000 copies/mL), for which the predicted CD4+ T-cell count was 294 cells/µL (95% CI, 289–299; note that the upper boundary of the 95% CI did not include the starting value of 300 cells/µL).

The estimates remained virtually unchanged in sensitivity analyses with random-effects models instead of generalized estimating equations and in models that omitted the quadratic term for the CD4+ T-cell count.
DISCUSSION

We have shown that the current virus concentration in plasma is the single most important predictor of the current CD4+ T-cell count in 2424 people who started ART during or after 1998 and then experienced triple-class virologic failure. There is close to a inverse linear relationship between log_{10} viral load and CD4+ T-cell count. These results confirm and extend the findings from our previous study of individuals with triple-class virologic failure, of whom most had started antiretroviral treatment with monotherapy or dual therapy, a situation less relevant to current practice than our analysis reported here [9]. The group with triple-class virologic failure we are studying here is likely to be heterogeneous and also includes people who have previous or ongoing issues involving treatment adherence. Of note, 12% of people in our study had not attained undetectable viral levels prior to the time of triple-class virologic failure. If adherence problems can be overcome before resistance has developed, the drugs should remain active, and options have not been lost. However, it is often not easy to know in practice whether resistance in such cases is really absent, because minority variants harboring drug resistance may have emerged but are missed with routine genotypic assays [15]. Some individuals may also have been infected with HIV strains resistant to certain components of the initial regimen before baseline resistance tests were introduced and thus potentially may have received suboptimal treatments [16]. Unfortunately, we did not have information on adherence, drug concentrations, or resistance to antiretroviral drugs available for our analyses.

Although it is clear that complete viral suppression with a new fully active regimen is the optimal approach, the approximately linear inverse relationship between log_{10} viral load and CD4+ T-cell count indicates that there are likely CD4+ T-cell count benefits of lowering viral load even by modest amounts that do not lead to undetectable viral levels. This may be important for patients with low CD4+ T-cell counts and few drug options. The superior effect of boosted PIs over unboosted PIs and NNRTIs, which we found in univariable and bivariable models, is consistent with results from our initial study [9] and from a large subsequent study from the EuroSIDA Study Group [17]. This effect was removed when current viral loads, which directly reflect the desired treatment effects, were included in the model. However, although the difference in CD4+ T-cell counts between regimens seemed to disappear after adjustment for viral load, the heterogeneity within the regimen categories may have concealed differences in immunologic response despite similar viral suppression of some of these regimens, as observed in clinical trials with treatment-naive individuals [18, 19]. We used incremental models to demonstrate the effect of including new variables that are correlated with existing variables on the parameter estimates. For example, calendar time is correlated with the introduction of new drugs over time, and estimates of the latter are substantially altered when both variables are analyzed together.

The positive association of CD4+ T-cell count with age may be explained by better adherence among older people [13], but it also may be due to the correlation of time-updated age with calendar time and, thus, the increased availability of better drugs over time. In fact, the association with age disappeared in models that were also adjusted for calendar time.

It may be confusing that never having achieved an undetectable viral load prior to the triple-class virologic failure is positively associated with CD4+ T-cell counts in models including current viral load. A possible explanation could be that, once we condition on a given low current viral load, people who have not previously experienced viral suppression might tend to enjoy a higher CD4+ T-cell count increase, as is observed in the first few weeks of treatment. In other words, if a low viral load can be attained in persons who have not...
previously suppressed the viral load, they will experience greater CD4+ T-cell count benefits, as CD4+ T-cell count increases are greater in those who have recently started ART.

Descriptive analyses showed that, on average, people have experienced triple-class virologic failure at higher average CD4+ T-cell counts in recent years, which can be explained by a trend toward earlier initiation of ART. Furthermore, the observation that CD4+ T-cell counts continue to increase after triple-class virologic failure may be related to the fact that new drugs, including those with novel targets, decrease viral load even in patients with several previous virological failures.

We used the definition of triple-class virologic failure that has been used in previous studies of our group [10, 11, 20]. As described by Lodwick et al [11], results were robust with regard to modifications of the definition.

Our study has several potential limitations. It could be challenged that we assumed a strong effect of viral load on CD4+ T-cell count, rather than a strong effect of CD4+ T-cell count on viral load. We acknowledge that there could be some confounding, such that the observed relationship is not entirely due to the causal effect of viral load on CD4+ T-cell count, but we think there is good reason to consider that the observation is mainly driven by this effect rather than by a causal effect of CD4+ T-cell count on viral load. This is supported, for example, by the observation that, in untreated patients, the viral load remains relatively stable over many years across a wide range of CD4+ T-cell counts [21]. Treatment strategies, availability of antiretroviral drugs, and methods of laboratory assessments may have differed somewhat between the collaborating cohorts. The cohorts in this collaboration cover most countries across Western Europe. Cohorts from France, the Netherlands and Switzerland include a majority of individuals on ART (>70%), the UK study includes close to 50% from the country. People from these countries represent 66% of patients enrolled in the present study. However, we cannot rule out the possibility that clinics participating in cohorts have a higher standard of care and a higher level of viral suppression than clinics that are not participating. In contrast to first-line treatments, ART regimens administered to individuals after they experience triple-class virologic failure are very heterogeneous. It was therefore not possible to include specific drugs or regimens in our analyses. In addition, we had to combine drugs from novel classes, which have quite different antiviral potencies, into a single group because small numbers of individuals were receiving these agents. Furthermore, we did not have information on co-infection with hepatitis C virus, which has been described by some studies [22] but not others [23] as potentially influencing recovery of the CD4+ T-cell count during ART.

In conclusion, we have identified a strong inverse linear relationship between log_{10} viral load and CD4+ T-cell count in people with virologic failure of the original 3 drugs in the modern ART era. Thus, any degree of viral suppression is likely to bring benefits in terms of CD4+ T-cell count and, hence, risk of clinical disease. In contrast, not receiving ART is clearly associated with lower CD4+ T-cell counts, although there may be some confounding in play, along with the causal effect of stopping, such as poor adherence, illicit drug use, alcohol abuse, or psychiatric problems. There are implications for patients with an unsuppressed viral load and a low CD4+ T-cell count. Although for individuals with a high CD4+ T-cell count it may be possible to wait until new active drugs are available, for those with a low CD4+ T-cell count it is important to use the regimen most likely to achieve maximal achievable viral suppression. We found that the current viral load is closely linked to the CD4+ T-cell count, suggesting a rapid benefit of viral load suppression. Therefore, for an individual who is not fully adherent, any increase in adherence is likely to provide immediate benefits in terms of reduced risk of clinical disease, unless the individual’s virus is fully resistant to the actual regimen, which is unusual. In addition, we identified associations between use of drugs from specific classes and improved CD4+ T-cell counts, which were mediated by the differential effects of these regimens on viral load.

**ANALYSIS AND WRITING COMMITTEE (PLATO II PROJECT TEAM)**

All members of the PLATO II analysis and writing committee participated in discussions on the design of the study, the choice of statistical analyses and interpretation of the findings, and critically reviewed the manuscript. Dominique Costagliola, Bruno Ledergerber, Carlo Torti, Ard van Sighem, Daniel Podzamczzer, Amanda Mocroft, Maria Dorroci, Bernard Masquelier, Andrea de Luca, Klaus Jansen, Stephane De Wit, Niels Obel, Gerd Fätkenheuer, Giota Touloumi, Cristiana Mussini, Antonella Castagna, Cristoph Stephan, Federico Garcia, Robert Zangerle, Xavier Duval, Santiago Perez-Hoyos, Laurence Meyer, Jade Ghosn, Céline Fabre-Colin, Jesper Kjaer, and Genevieve Chene contributed to data acquisition and management. Céline Fabre-Colin, Jesper Kjaer, and Jesper Grarup provided administrative, technical, and material support. Bruno Ledergerber, Andrew Phillips, Dominique Costagliola, and Rebecca Lodwick were responsible for the study concept and design, have full access to the data set, performed all analyses, interpreted the data, and drafted the report.

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**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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Potential conflict of interest. All authors: No reported conflicts.

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