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Additive or Sequential Nucleoside Analogue Therapy Compared with Continued Zidovudine Monotherapy in Human Immunodeficiency Virus–Infected Patients with Advanced Disease Does Not Prolong Survival: An Observational Study

Remko van Leeuwen, Gouke J. Bonsel, Peter Reiss, Sven A. Danner, and Joep M. A. Lange

To study the effect of sequential or additive use of zalcitabine or didanosine on survival in 308 human immunodeficiency virus–infected patients with advanced disease treated with zidovudine, an observational study using time-dependent Cox proportional hazards models was done. Changing to sequential or additive therapy was based on deterioration of a patient’s health status, a significant drop in CD4 cell count, or intolerance for zidovudine. The median CD4 cell count at baseline was $110 \times 10^6/L$; 42% of patients had AIDS. The median count before a change in therapy was $50 \times 10^6/L$. Additive or sequential treatment was associated with an increased risk for death (relative hazard, 1.59; 95% confidence interval [CI], 1.01–2.49; and 1.58; 95% CI, 1.10–2.37, respectively). Adjustment of the models for prognostic factors failed to substantially affect this observation. Possibly the lack of benefit in this study is because patients switched therapy at advanced stages, whereas the switch may be more effective in early disease.

Zidovudine treatment has considerable benefit in patients infected with the human immunodeficiency virus (HIV), yet monotherapy with the drug does not prevent ultimate HIV-related disease progression and death. Additive or sequential use of other antiretroviral agents has increased the options for antiretroviral treatment. Combining drugs may provide the advantage of synergistic activity of drugs, while the emergence of resistant viruses may be delayed (reviewed in [1, 2]) and different cellular reservoirs of the virus may be targeted [3, 4]. A combination of antiretroviral agents may be administered to antiretroviral-naive patients or as additive treatment to patients who were previously treated with zidovudine monotherapy. Sequential therapy, that is, switching to alternative drugs, may also provide advantages over monotherapy, while toxicities may be reduced compared with that seen in combination treatment.

Recently, two large prospective studies that addressed the impact of combination and additive treatment on the clinical outcome of HIV infection were completed. Although these studies were consistent with respect to the effect of combination therapy in previously untreated patients, showing a marked benefit for patients receiving either a combination of zidovudine and zalcitabine or zidovudine and didanosine over zidovudine monotherapy, there was a difference in the overall study outcome and interpretation of the results in patients who had received prior antiretroviral treatment [5, 6]. While AIDS Clinical Trials Group (ACTG) protocol 175 showed a clinical benefit for patients receiving zidovudine-didanosine treatment and significant improvements in CD4 cell parameters for patients in all combination arms, the European-Australian Delta-2 study showed a less-pronounced benefit of combination therapy in patients previously treated with zidovudine. The most obvious difference between the studies is the difference in the baseline CD4 cell count, which was just above $300 \times 10^6/L$ in ACTG 175 and just below $200 \times 10^6/L$ in Delta-2 [5, 6].

While there have been many reports of positive effects on immunologic and virologic parameters following first-line combination, additive, or sequential therapy with various antiretroviral agents [7–11], only few of them have addressed whether such treatment ultimately results in a more durable clinical benefit as judged by parameters such as disease progression and survival.

As no other prospective studies are expected to generate estimates of the clinical benefits of combination and additive therapy, there is a clear need for additional data on the optimal timing of these strategies. We analyzed data from an observational database of patients attending a large referral hospital in Amsterdam, many of whom had severe symptomatic disease and changed therapy because it was believed that they were refractory or intolerant to monotherapy with zidovudine. In this population with advanced disease, we determined the effects on survival of adding didanosine or zalcitabine to therapy with zidovudine or switching to monotherapy with these drugs as alternative treatment strategies to continuing zidovudine monotherapy. Since this is not a randomized study, we applied specific survival techniques analyses that allow for adjustment for potential biases.
Methods

Patients. We included all HIV-1–infected patients attending the outpatient clinic of the Academic Medical Centre in Amsterdam, who started treatment with zidovudine monotherapy between 1 January 1990 and 31 August 1994. Homosexual contacts were the predominant risk factor for HIV infection in this group. The hospital policy for prescribing antiretroviral treatment was based on the consensus guidelines of the Dutch AIDS treatment specialists (reviewed in [12]).

Zidovudine was started in asymptomatic patients with CD4 cell counts <300 × 10^9/L or in patients with CD4 cell counts <400 × 10^9/L and additional laboratory indicators of a poor prognosis or symptoms of HIV disease. Patients could either start with zidovudine monotherapy or participate in one of the clinical trials in which they might receive double-blinded or open-label experimental antiretroviral agents. The latter group of patients, who did not start with zidovudine monotherapy, was excluded from the analysis. However, patients who initially started zidovudine monotherapy and were subsequently included in one of these studies were not excluded from the analysis to avoid selection bias for evaluating the effect of subsequent treatment. The 1987 AIDS case definition for adults of the Centers for Disease Control and Prevention (CDC) [13] was used. As this definition requires patients to be at least 13 years of age, younger patients were excluded.

Changes in antiretroviral treatment were usually based on a deterioration of a patient’s health status, a significant drop in CD4 cell count, or intolerance for zidovudine. Zidovudine was either continued with the addition of didanosine or zalcitabine (additive treatment) or discontinued and followed by the subsequent administration of didanosine or zalcitabine only (sequential therapy). For the purpose of the analysis, treatment groups were defined as follows: patients who started additive therapy, patients who started sequential therapy, and patients who continued zidovudine monotherapy.

The use of acyclovir was limited to short-term treatments for herpes simplex virus infections only. Prophylaxis for Pneumocystis carinii pneumonia (PCP) was strongly encouraged in all patients with CD4 cell counts <200 × 10^9/L. Preferably, a once-daily dose of cotrimoxazole was used, while monthly pentamidine inhalations were available for those patients who were cotrimoxazole-intolerant. A previous study has shown that in the Netherlands, compliance with this regimen is very good [14].

The usual starting dosage of zidovudine during the study period was 200 mg three times daily or 250 mg twice daily. Didanosine became available in August 1990: at first within a double-blinded randomized study comparing two different dosages of the drug (750 vs. 200 mg/day; didanosine-ALPHA study), from October 1991 onwards in a parallel-track program (dosages dependent on body weight, 375–750 mg/day), and from 1993 as a registered drug (standard dosage, 200 mg twice daily). Within the didanosine-ALPHA study, patients were required to be zidovudine-intolerant; within the other programs, the drug could also be administered to patients whose condition was deteriorating during zidovudine monotherapy. Zalcitabine became available in the fall of 1991, initially for a short period through a community-based HIV treatment organization and later within an official parallel-track program as monotherapy or in combination with zidovudine in patients in whom zidovudine treatment was not effective (doses up to 2.25 mg/day).

Laboratory methods. Blood was usually sampled in the morning for the determination of the CD4 cell counts, which were measured by use of peripheral blood mononuclear cells isolated from heparinized venous blood by flow cytometry. This was quality controlled and performed according to standard methods. The usual interval for measuring CD4 cells was every 3 months; other laboratory measures were usually sampled on each visit.

Data collection. The observational database that was used for this study was derived by combining several computer files with laboratory and clinical information on these patients. The data have been computerized both for purposes of patient care (in particular laboratory data) as well as for several research and surveillance purposes (in particular such data as antiretroviral treatment and time of death). The final database included all routine laboratory markers from these patients, as well as all AIDS-related illnesses and the date of death or last follow-up. Most data were collected prospectively. However, as hospital patients are often referred from other health care settings, chart abstraction to define the patients’ baseline status was allowed.

Statistical analysis. Homogeneity of baseline characteristics was established using the χ² test for categorical variables and the Wilcoxon rank sum test or the Kruskal-Wallis test for continuous variables.

Cox proportional hazards models were fitted using the PROC PHREG program of SAS software (release 6.03 for DOS; SAS Institute, Cary, NC). The primary outcome analyzed was survival, defined as time from the start of zidovudine therapy (baseline) until death. Subjects were censored at the date of their last follow-up if alive at the end of the follow-up period, which was 31 December 1994. The significance of parameter estimates derived from the proportional hazards models were tested with the Wald statistic [15].

Once patients switched to either additive or sequential therapy, continued use of the same treatment was presumed until death or censoring. This method has been applied in other proportional hazards modeling in HIV studies over the past few years [16–18], because of its advantage of ignoring changes in therapy that occur after the initiation of a therapy, which could bias estimates of effectiveness. The disadvantage of using this method is that potential benefits can be masked or, alternatively, over-estimated if a therapy change occurs more frequently in one of the study arms. Therefore, the number of patients who discontinued the antiretroviral treatment within each study arm was tabulated and tested. No evidence was found for a selective discontinuation in one of the study arms.

The use of Cox proportional hazards models with updated measurements of the covariates provides a means to update the prognosis of a patient on the basis of each new observation. Thus, the timing of sequential or additive treatments is taken into account, which controls for survival bias: For example, a patient who survives for a longer period may be more likely to receive (new) treatment compared with the likelihood for a patient who has a shorter survival (reviewed in [19]). Also, the inclusion of CD4 cell counts and other factors as time-dependent variables adjusts for these prognostic factors at each time the treatment groups are compared. The method of complete time-dependent adjustment...
might, however, mask potential benefits of a switch in therapy, in case this benefit could be explained by changes induced by treatment in the variables that are used for adjustment of the models. Therefore, additional models were constructed that adjusted until the change in therapy but were unadjusted thereafter.

The following covariates with updated measurements were included in the models at monthly intervals from (and including) the time of the first use of zidovudine: the presence of Kaposi’s sarcoma without other AIDS-defining conditions (dichotomous: yes or no), presence of all other AIDS-defining conditions (i.e., including Kaposi’s sarcoma simultaneously presenting with other AIDS-defining events, dichotomous: yes or no). The treatment variables were examined in two ways: One model included the use of zalcitabine either as sequential or additive therapy (dichotomous: yes or no) and the use of didanosine also as additive or sequential therapy (dichotomous: yes or no). Another model examined the use of additive therapy of zidovudine with either didanosine or zalcitabine (dichotomous: yes or no) or the use of sequential therapy with either didanosine or zalcitabine following zidovudine therapy (dichotomous: yes or no). To adjust for potential use of other antiretroviral medication, the use of other experimental or blinded antiretroviral drugs was examined (dichotomous: yes or no).

Since the indication for PCP prophylaxis was having a CD4 cell count <200 × 10⁹/L, by including the CD4 cell count as time-dependent variable, we have controlled for the use of PCP prophylaxis. We did not control the models for CDC class B symptoms, as a vast majority of patients were symptomatic at baseline.

Given the average frequency at which CD4 cell counts were sampled in these patients, laboratory values were included in the model at 3-monthly intervals. If more than one value was available within this period, the first known value was included in the model. The variables were coded as follows: hemoglobin level (continuous: per mmol/L increment), leukocyte count (continuous: per 10⁹/L increment), platelet count (continuous: per 10⁹/L increment), CD4 cell count (continuous: per 100 × 10⁹/L increment). The age of the patient at baseline (continuous: per 10 years increment) and the timing of the start of zidovudine monotherapy (dichotomous: before 1992 [about halfway through the study period] or from 1992 onwards) were examined as time-fixed covariables, given the deterministic nature of their changes over time (reviewed in [20]). To investigate the influence of the duration of the preceding period of zidovudine use for the outcome with sequential or additive therapy, three time-dependent dummy variables were fitted representing categories of time since starting zidovudine (<12 months, 12–24 months, and ≥24 months).

To exclude the possibility of introducing a bias by a difference between the study arms in number of patients who permanently discontinued their antiretroviral treatment at a considerable time before death, we tabulated the number of patients with such a premature discontinuation. No difference was found in the number of patients (χ², P = .66) that discontinued therapy prematurely or in the average time of discontinuation prior to death (Wilcoxon rank sum test, P = .39).

A stepwise procedure was performed to determine the relative importance of the laboratory and clinical covariates. The first step in the development of a final model was to identify the most important prognostic variables. Those variables that were determined significant (P < .15) were retained in the model and were subsequently used to adjust the models that included the treatment variables. The relatively high P value for inclusion of variables in the intermediate models was chosen so as not to miss potentially important parameters that might be less significant because of the power of the study. Since the CD4 cell count has been well-established as a predictive marker, we decided to include this variable in all multivariate models. Departures from the proportionality assumption of the models were examined by multiplying the covariates with the log-transformed follow-up time (the log scale was used because of the skewed distribution of the follow-up time) and testing whether these interaction variables had a significant contribution to the models.

Results

Three hundred eight patients started zidovudine treatment between 1 January 1990 and 31 August 1994. At baseline (the initiation of zidovudine therapy), CD4 cell counts, hematologic parameters, and the number of patients with AIDS did not significantly differ between the groups (table 1). Patients receiving sequential therapy (n = 66) had received zidovudine monotherapy for a shorter period than had the patients receiving additive therapy (n = 43) (P = .01, log rank test). The patients receiving additive therapy had a slightly higher median CD4 cell count prior to the change in therapy: 70 × 10⁹/L (90% reference range, 10–480) versus 40 × 10⁹/L (90% reference range, 0–360) for those receiving sequential therapy (P = .36, Wilcoxon rank sum test). The number of deaths within the study was 174 (table 1).

The effects of potential prognostic laboratory parameters were first estimated in unadjusted time-fixed (data not shown) and time-dependent univariate models (table 2), which showed that the probability of survival was predicted by the CD4 cell count, hemoglobin levels, the leukocyte count, and the platelet count. We examined the hematologic parameters separately in a time-dependent multivariate model to investigate their mutual predictive independence, which showed that the hemoglobin level was the primary predictive parameter for survival.

The clinical parameters were also first fitted in unadjusted time-fixed and time-dependent models. The diagnosis of AIDS and the age of the patient were both predictive for survival, while the year of inclusion in the study was not (table 2). Since it is known that survival is influenced by the initial AIDS-defining event [21–23], we analyzed in a bivariate model the patients who were diagnosed with Kaposi’s sarcoma separately from those who presented with other AIDS-defining events. In this time-dependent model, a diagnosis of Kaposi’s sarcoma was only marginally significantly predictive for survival, while the predictive value of a diagnosis of any other AIDS-defining event was improved. When we adjusted this bivariate model for the CD4 cell count, a diagnosis of Kaposi’s sarcoma was no longer found predictive for survival (relative hazard, 1.37; 95% confidence interval [CI], 0.78–2.40; P = .26).
A stepwise procedure to define statistically significant predictors for survival resulted in a time-dependent model that included the following variables: CD4 cell count, the hemoglobin level, a diagnosis of AIDS (excluding those patients who presented with Kaposi’s sarcoma only), and the age of the patient (table 3). The same variables were found when we constructed a time-fixed model in a stepwise procedure. The predictive value of the parameters in the final model was stable when individual variables were deleted from the model.

The therapeutic variables were examined without and with adjustments of the models. First, we compared the effect of the use of either additive or sequential therapies versus zidovudine alone (table 4) in unadjusted time-dependent models. The use of both treatments was associated with increased probability of death. The other model included the use of didanosine or zalcitabine compared with the continued use of zidovudine monotherapy. Again, these changes in therapy were also associated with an increased probability of death.

To assess whether this poor prognosis of a change in therapy may have been confounded by other factors, we examined different models that controlled for several prognostic variables. We first considered the adjustment for CD4 cell counts in time-dependent models. Both in the model that examined the use of either zalcitabine or didanosine and in the model that assessed the use of either additive or sequential therapy, the inclusion of the CD4 cell count decreased the relative hazard.
ard for death compared with that in the unadjusted models. Subsequent adjustment in time-dependent models for hemoglobin levels, age, and the presence of AIDS-defining conditions yielded models with similar relative hazards.

Although the adjustment for several prognostic variables is necessary to deal with survivor bias, it might mask potential benefits of a switch in therapy, if this benefit could be explained by increases in, for example, the CD4 cell count. To study this in more detail, we considered time-dependent models that were adjusted for the same set of prognostic variables until the change in therapy and were unadjusted thereafter (table 4, right-hand column). By use of this method, we were not able to demonstrate any additional benefit of the therapy changes.

Finally, we assessed whether the effect of alternative regimens would depend on the length of the preceding period of zidovudine monotherapy. This time-dependent model did not reveal any consistent or significant trend for an effect of the duration of zidovudine treatment (data not shown). Similarly, when we assessed whether other (potential) HIV treatments might have biased our findings, we did not find that the use of these alternative treatments was predictive for survival (relative hazard, 1.07; 95% CI, 0.50–2.31; P = .85).

**Discussion**

The main conclusion of the study is that within this patient population, no survival benefit of additive therapy with didanosine or zalcitabine or for switching to monotherapy with these drugs could be demonstrated in patients who had initially been treated with zidovudine monotherapy. In fact, unadjusted and partially adjusted models showed a small increased risk for death after switching therapy. Since an increased drop in CD4 cell counts was observed immediately before the switch in therapy, this increased risk is likely to reflect that changes in therapy were often based on deterioration of a patient’s clinical status or laboratory indicators, which are associated with a poor survival. Adjustment of the models for the CD4 cell count resulted in lower estimates of the risk for death after switching therapy compared with the estimates from the unadjusted models, but no survival differences were detected between the study groups. Nevertheless, a potential benefit of a switch in therapy may have been overshadowed by a deterioration of HIV disease in our patients, while additive and sequential treatment strategies might well be effective in other populations. Alternatively, increased toxicity of the combination of drugs in late-stage patients may also have contributed to our findings. The absence of therapeutic benefit in late-stage patients is in accordance with the recent demonstrations of the highly dynamic nature of HIV replication [24–26], resulting in increasing amounts of viremia during subsequent stages of the infection [27, 28]. There are studies that provide support for these hypotheses.

A study reported by Graham et al. [18], who analyzed data for subjects within the Multicenter AIDS Cohort Study (MACS), showed that by use of time-dependent proportional hazards models adjusted for CD4 cell counts, platelet counts, hemoglobin levels, HIV symptoms, PCP prophylaxis, and acyclovir use, a small decrease in the probability of death could be detected in patients who had changed zidovudine monotherapy to sequential or additive therapy with either zalcitabine or didanosine. While this finding was statistically significant, the absolute magnitude of this benefit was only estimated at a maximum of 3–6 months over continued zidovudine monotherapy.

A possible explanation for the seemingly different results in our study and the MACS analysis is the difference in baseline disease stage and the level of CD4 cell depletion at the start of zidovudine monotherapy. The median CD4 cell count for the different treatment groups in the MACS analysis at baseline ranged from 284 to 342 × 10^6/L, and all subjects were selected before the development of an AIDS-defining event. Although

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### Table 4. Multivariate time-dependent hazards models for survival for treatment parameters, adjusted for laboratory and clinical parameters.

<table>
<thead>
<tr>
<th>Treatment Parameters</th>
<th>Unadjusted models</th>
<th>Adjusted for CD4 cell count, hemoglobin, age,* and AIDS' for complete study period</th>
<th>Adjusted for CD4 cell count, hemoglobin, age,* and AIDS' until therapy switch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH (95% CI)</td>
<td>P</td>
<td>RH (95% CI)</td>
</tr>
<tr>
<td>Additive therapy</td>
<td>1.59 (1.01–2.49)</td>
<td>.04</td>
<td>1.53 (0.97–2.40)</td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>1.58 (1.00–2.37)</td>
<td>.01</td>
<td>1.36 (0.94–1.97)</td>
</tr>
<tr>
<td>ddI (additive/sequential)</td>
<td>1.39 (0.93–2.10)</td>
<td>.11</td>
<td>1.27 (0.84–1.92)</td>
</tr>
<tr>
<td>ddC (additive/sequential)</td>
<td>1.80 (1.22–2.65)</td>
<td>.003</td>
<td>1.58 (1.07–2.32)</td>
</tr>
</tbody>
</table>

**NOTE.** All patients with CD4 cell counts ≤200 × 10^6/L were offered *Pneumocystis carinii* pneumonia prophylaxis; acyclovir was used intermittently for herpes simplex virus infections only. These two factors were therefore not used to adjust models. RH, relative hazard for death; CI, confidence interval.

* Excluding AIDS diagnoses based on Kaposi’s sarcoma only.
our hospital protocol allowed patients to start antiretroviral therapy at CD4 cell counts below 300–400 × 10^6/L, the median CD4 cell count prior to the start of zidovudine therapy was only 110 × 10^6/L, while 128 (42%) of the patients were diagnosed with AIDS before the start of zidovudine therapy. This difference between the hospital guidelines for starting treatment and the actual CD4 cell counts of patients at entry into the study reflects a referral bias: A hospital population selects for patients with later stages of HIV infection. Also, many patients with higher CD4 cell counts did not start zidovudine monotherapy but were included in antiretroviral drug studies. Other differences between both studies, such as the length of the study period, the frequency of follow-up visits within the study, the number of study sites, differences with respect to the clinical care of HIV-infected patients (e.g., the type of PCP prophylaxis used in the study period), and regional differences in CD4 cell measurements [29], may all have contributed to the different clinical and statistical findings of both studies.

It should be appreciated that the character of both studies was observational. The estimates that are provided by this study may be biased; therefore, the interpretation of our findings should be conservative. Yet, our study, as well as the analyses of the MACS cohort, is of key importance for the interpretation of the different outcomes of two recently completed studies of combination treatment (ACTG 175 and Delta) [5, 6], as no other prospective studies are expected to further address the clinical outcome of combination therapy. The ACTG 175 study showed a statistically significant clinical benefit for zidovudine/didanosine treatment in patients who had received prior antiretroviral treatment but not for zidovudine/zalcitabine treatment, although it might be argued that the point estimates of the relative risks for both combination arms suggest a benefit over zidovudine monotherapy and that their confidence intervals are largely overlapping. The European-Australian Delta study, on the other hand, demonstrated only a modest benefit for either of the combination arms [5, 6].

The most obvious difference between both studies is the baseline CD4 cell count at the start of additive therapy. The average CD4 cell count in the ACTG 175 study was 338 × 10^6/L, whereas in the Delta study it was just below 200 × 10^6/L. Another indication that patients with less advanced disease may benefit more from combination treatment comes from ACTG 155, which compared a combination of zidovudine and zalcitabine with either drug alone. This study did not demonstrate overall differences in progression rates. Nevertheless, a subgroup analysis within this study suggested a clinical benefit in patients with CD4 cell counts >150 × 10^6/L [8].

The above explanation for the differing outcome of antiretroviral treatment depending on the level of immunodeficiency is supported by other prospective studies. Study ACTG 116B/117 showed a clinical benefit of sequential monotherapy with didanosine over continued monotherapy with zidovudine, but there was no difference detected between treatment groups for subjects who entered the study with a prior diagnosis of AIDS [30]. Similarly, a smaller study comparing sequential therapy with didanosine to continued zidovudine in patients who had used zidovudine monotherapy for at least 6 months showed a clinical benefit on progression to new AIDS-defining events or death for patients switching to didanosine; this benefit was most apparent among patients with CD4 cell counts at entry of 100 × 10^6/L [31]. Finally, the long-term follow-up of study ACTG 019 on the effects of zidovudine monotherapy in asymptomatic patients suggested a more durable response in patients with CD4 cell counts >300 × 10^6/L [32].

These studies provide cumulative evidence that successful treatment of HIV infection may depend not only on the number of drugs that are used but also on the level of immunodeficiency at which such treatment is initiated. Recent data on the changes in HIV RNA load during monotherapy with different nucleoside analogues (including zidovudine) show that substantial inhibition of the virus is seen only within a narrow treatment window following the start of treatment [33–35]. Therefore, a direct combination of drugs might be more effective than additive or sequential strategies, as is also suggested by studies that show that a combination of zidovudine and lamivudine in naive patients [36, 37] confers superior benefits on CD4 cell parameters compared with the addition of lamivudine in zidovudine-experienced patients [38, 39]. Preliminary findings from these studies have also suggested that initial suppression of viral replication by use of the specific combination of zidovudine and lamivudine is more potent than the effects caused by the combinations used in our analysis [39].

There may have been differential biases that could not be successfully modeled either in this study or in the MACS study [18]. These could be responsible for the different findings of both studies. Another possible explanation for the lack of benefit in our study is that patients in this study switched therapy at advanced stages, whereas this switch may be more effective in early disease. This explanation will have important clinical implications, as successful improvement of the effects of antiretroviral therapy, especially in, but probably not restricted to, advanced HIV disease, will depend on a powerful combination of drugs [40, 41]. Preliminary results from studies with triple-combination therapy including protease inhibitors have shown that even in late-stage and pretreated patients, successful antiretroviral treatment has become possible [42] (reviewed in [43]). Long-term efficacy studies on these regimens will be observational studies; for ethical reasons a randomized control arm can no longer be included. The methodology that is used within our study may therefore be an important tool for the analyses of these and future studies.

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