A comparison of the CD4 response to antiretroviral regimens in patients commencing therapy with low CD4 counts


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Objective: To compare the immunological response to highly active antiretroviral therapy (HAART) in treatment-naive patients with a baseline CD4 count of <200 cells/mm³.

Design and methods: We identified treatment-naive human immunodeficiency virus (HIV-1)-infected individuals who had commenced HAART since 1996 and who had a starting CD4 count of <200 cells/mm³. Immunological success was defined as achieving a CD4 count of >200 cells/mm³ and treatments were compared using univariate and multivariate Cox’s proportional hazards models in order to establish whether protease inhibitor (PI)-based regimens were significantly different to regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs). Both regimens utilize a nucleoside analogue (NA) backbone.

Results: A total of 599 patients were identified. When the variables were entered into a multivariate analysis, no significant differences between HAART regimens were found. We showed that compared with efavirenz regimens a two NA plus one PI regimen was not significantly less likely to achieve immunological success (adjusted HR: 0.65, 95% CI 0.41–1.03, P = 0.07). Two NA and boosted PI (adjusted HR: 1.33, 95% CI 0.81 to 2.16) or two NA and nevirapine (adjusted HR: 0.93, 95% CI 0.67–1.29) regimens were also not significantly different from efavirenz-based regimens, based on the endpoint of immunological success.

Conclusion: PI-, boosted PI- and NNRTI-based HAART regimens are not significantly different in achieving increased CD4 counts in individuals who commence therapy with a low CD4 count.

Keywords: HAART, immune, PI, NNRTI, boosted

Introduction

In those for whom it is available, HAART has decreased the morbidity and mortality associated with HIV infection.1–3 A central debate since the promulgation of the ‘hit hard and early’ hypothesis4 has focused on the appropriate initial choice of therapy as well as its timing.5–7 A variety of consensus guidelines has been written and all recommend starting HAART well before the CD4 count falls below 200 cells/mm³, this being a threshold below which the risk of opportunistic infections (OIs) is reported to increase significantly.4–10

However, approximately one-third of all patients in the developed world commence HAART with a CD4 count of <200 cells/mm³.11–13 It is essential that these individuals achieve virological suppression and immune recovery as quickly as possible in order to minimize the risk of AIDS-defining OIs. A number of studies have shown that a good virological and immunological response to HAART can be achieved regardless of the CD4 count at initiation of therapy14–16 and though some studies have shown a plateau in CD4 response after 2 years of HAART, there are data to suggest that suppression of viraemia and maintenance of CD4 counts continues through year 5 of therapy in patients who achieve ongoing viral suppression.17,18

While studies have compared different HAART regimens in treatment-naive individuals, there are no prospective comparative data regarding the optimal choice in patients starting treatment with a low CD4 count. Using prospectively collected data from a single centre, we have compared the immunological response to different HAART regimens in patients commencing therapy with a CD4 count of <200 cells/mm³.

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Materials and methods

The Chelsea and Westminster Hospital is one of largest treatment centres for HIV in Europe and data are prospectively collected on the patients who attend. This includes immunological parameters, demographics and treatment history.

Using this database we identified all treatment-naive patients commencing HAART, defined according to consensus guidelines as triple therapy consisting of nucleoside analogue backbone and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs).¹⁰⁻¹¹ HAART was commenced routinely at this institution on 1 January 1996 and all patients commencing treatment...
with a CD4 count exceeding 200 cells/mm$^3$ were excluded. Immunological success was defined as achieving a CD4 count of >200 cells/mm$^3$. Data were extracted for this study on 1 August 2003.

Quantitative data were categorized into quartiles and these were stratified by individuals who achieved immunological success during first-line HAART. Event time was defined as time from commencing HAART to either achieving CD4 cell count >200 cells/mm$^3$, switch from first-line therapy or time of death if it occurred while on first-line therapy; data were otherwise censored on the day of extraction. Time to immunological success was estimated using the Kaplan–Meier product limit survival method. Between-group comparisons of different HAART combinations were assessed using log rank $\chi^2$ test. These were further investigated using univariate and multivariate Cox’s proportional hazards regression analysis to identify these and other factors predicting the likelihood of immunological success.

Variables found to be significant ($P < 0.2$) in a univariate analysis were used to build a multivariate model, as described previously. Since antiretroviral prescriptions have changed over time during the HAART era, the final multivariate model was stratified by year of starting therapy and baseline CD4 cell count, respectively, to match and minimize residual bias due to these factors. Baseline CD4 count was also stratified into quartiles according to Cox’s proportional hazards model. The multivariate model was tested for its distributional assumptions using the Cox–Snell residual plot. All $P$ values presented are two-tailed and all data analyses were performed in SAS statistical software, version 8.0.

CD4 subset analysis was performed routinely using whole blood stained with murine anti-human monoclonal antibodies to CD4 (TetraOne, Beckman Coulter, High Wycombe, UK) and were evaluated on an Epics XL-MCL (Beckman Coulter) flow cytometer.

Results

A total of 1747 individuals at this single institution have commenced HAART since 1996. Of these, 599 (34%) met the study criteria. The majority (86.1%) of the cohort was male with a median age of 37.9 years. The median baseline CD4 cell count and HIV-1 viral loads were 89 (interquartile range 36–149) cells/mm$^3$ and 140 338 (46 003–342 498) copies/mL respectively.

Most of the 599 individuals (62.1%) commenced NNRTI-based HAART (34.4% of these on nevirapine, 65.6% on efavirenz), 31.7% started on a single PI-based regimen and 6.2% on a ritonavir-boosted PI; all included a nucleoside analogue backbone. Of the single PI-based regimens, 37% received indinavir, 28% nelfinavir, 26% saquinavir hard gel and 9% saquinavir soft gel.

Table 1 shows the results of a univariate analysis. This demonstrated that age, baseline CD4 and first-line HAART regimen but not baseline viral load were significantly associated with immunological success. Overall, 63.1% of patients starting an efavirenz-based regimen achieved a CD4 count of >200 cells/mm$^3$, and the rates for nevirapine, boosted PI and unboosted PI were 60.6%, 52.2% and 45.9%, respectively. Unboosted PI-based regimens performed significantly worse than efavirenz in the univariate analysis.

The difference between efavirenz and unboosted PI regimens was not, however, significant when adjusted for confounding factors within the multivariate analysis (Table 2). Using efavirenz results as a baseline, a non-significant trend was shown for unboosted PI regimens to be less likely to achieve immunological success (adjusted hazard ratio 0.65, 95% CI 0.41–1.03, $P = 0.07$). Nevirapine-based regimens were as likely to succeed defined by our criteria (adjusted hazard ratio 0.93, 95% CI 0.67–1.29) and boosted PIs were not significantly better (adjusted hazard ratio 1.33, 95% CI 0.81–2.16, $P = 0.26$). These data were confirmed by analysing the proportion of patients over time that persisted with a CD4 count of <200 cells/mm$^3$; Figure 1 demonstrates no significant differences between the regimens.

Discussion

The multivariate analysis performed in this study demonstrates that no particular HAART regimen is associated with an improved immunological response, based on ability to increase CD4 counts to >200 cells/mm$^3$, an effect that persists over time.

While limitations to this study included the absence of randomization and the likelihood that patients with a low CD4 count were more frequent attenders, these data suggest that ‘effective HAART’ across its recognized classes, is suitable to increase the CD4 count to >200 cells/mm$^3$, in those individuals who commence HAART with a low CD4 count. Censoring of the database was performed at the first switch of therapy as despite the reason for switching (including compliance issues, toxicity, resistance or lack of potency), a lack of immunological response as manifest by a falling CD4 count would have been observed until appropriate re-institution of an alternative therapy.

Comparative studies have suggested previously that there may be superior efficacy of ritonavir-boosted PI-based regimens when compared with unboosted PIs. Inferiority of unboosted PI-based regimens compared with efavirenz is

<table>
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<th>Variable</th>
<th>CD4 &gt; 200</th>
<th>Hazard ratio$^4$</th>
<th>95% CI</th>
<th>$P$-value</th>
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<td>(0.67–1.29)</td>
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<td>EFV</td>
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$^4$Adjusted for age, sex, ethnicity, hepatitis C (HCV) status and NA backbone, and stratified by year of start of therapy and baseline viral load. NVP, nevirapine; EFV, efavirenz. HAART defined as 2NA + 1NNRTI, 2NA + 1PI (including boosted PI).
consistent with the results of other studies though these have generally studied patients with higher starting CD4 counts. Our results would suggest that the same is true in a more severely immunosuppressed population. Study 006 showed significantly better viral suppression at 48 weeks for efavirenz compared with indinavir (both with zidovudine/lamivudine) and similar CD4 cell rises (mean CD4 at entry was 350 cells/mm$^3$)\(^{14}\). In ACTG384, efavirenz was virologically superior to nelfinavir when combined with a zidovudine/lamivudine backbone with similar CD4 changes.\(^{28}\) Efa VIP-2 compared efavirenz with unboosted PI-based regimens (mostly indinavir and nelfinavir) in patients with CD4 counts of <100 cells/mm\(^3\) (median 37).\(^{37}\)

Efa VIP-2 also showed significantly greater discontinuations in patients receiving PI-based as opposed to efavirenz-based HAART for both adverse events and virological failure, though the discontinuation rate in the PI group may, at least partly, have been influenced by the greater proportion in that group receiving a didanosine/stavudine backbone. CD4 cell count increases were also greater in individuals on efavirenz-based regimens with significantly greater CD4 cell count at 24 months with a significantly higher rate of achievement of a CD4 cell count rise of >100 and >200 cells/mm\(^3\)).\(^{39}\)

Our present study also suggests that nevirapine performs no better with respect to immunological parameters as compared with unboosted PIs. The Atlantic study compared nevirapine, indinavir or lamivudine with a stavudine/didanosine backbone in patients with a CD4 count of >200 cells/mm\(^3\) who have received a PI-, an NNRTI- (efavirenz or nevirapine) or boosted PI-based regimen.

Efficacy and tolerability in treatment naive patients. The median CD4 count in these 23 trials was 375 cells/mm\(^3\) (range 185–473), i.e. higher than in our cohort; a comparison within this study between two nucleoside analogues (NA) and PI/NNRTI/3rd NA revealed similar viral suppression and CD4 increases in the three groups at 48 weeks. Neither baseline CD4 nor viral load were significant predictors of viral suppression and once again, while sub-group analysis suggested a better response to efavirenz compared with nevirapine, this was not statistically significant. Our results show similar immunological outcomes for efavirenz and nevirapine.

Prior to the landmark 2NN trial, which compared first-line therapy containing either nevirapine, efavirenz or both in addition to stavudine and lamivudine,\(^{35}\) efavirenz had consistently outperformed nevirapine in a number of cohort studies.\(^{34–39}\) However, the 2NN trial showed no significant difference between efavirenz and nevirapine with respect to virological suppression at 48 weeks, even in patients with a low CD4 cell count at initiation of therapy. It has been argued that the study was underpowered and therefore failed to rule out the inferiority of nevirapine rather than showing the two drugs to be equivalent. A recent sub-group analysis within the 2NN randomized cohort of individuals commencing therapy at CD4 cell counts of <200 cells/mm\(^3\) showed that efavirenz performed significantly better virologically at CD4 counts of <25 cells/mm\(^3\) but that there was no significant difference between the efavirenz- and nevirapine-based regimens in the CD4 cell count range 25–200 cells/mm\(^3\) with respect to viral suppression. Efavirenz and nevirapine have been shown previously to be equally effective but the numbers in this study were small (<30 patients in each arm).\(^{50}\)

Efavirenz has been shown to be highly efficacious regardless of initial CD4 count\(^{43,42}\) and these data support this. While we have not compared the response rates to nevirapine for different starting CD4 counts, our data do reveal similar success rates for both the NNRTIs, suggesting a good response to nevirapine at low CD4 counts.

We were unable to demonstrate a significant difference between HAART regimens in this group of patients, using a prospective database. There was a trend towards poorer CD4 response to unboosted PI-based regimens but these no longer constitute a reasonable choice for first-line therapy. The trend for a superior response to boosted PI- as opposed to NNRTI-based regimens may warrant further studies comparing ritonavir-boosted PIs with NNRTIs in individuals with low CD4 cell counts.

References

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