The use of surrogate markers in the antiretroviral treatment of HIV-1 infection
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CHAPTER 8

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Meta-analysis of antiretroviral effects on HIV-1 RNA, CD4 cell count and progression to AIDS or death.

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There is uncertainty as to how the effects of antiretroviral treatments on human immunodeficiency virus type 1 (HIV-1) RNA levels and CD4 cell counts can predict reductions in clinical progression to AIDS or death. A meta-analysis was conducted for 27 pairwise comparisons of antiretroviral treatments in 15 randomised trials of antiretroviral treatments. For each trial, three measures of treatment effect were used: (i) 16 week change from baseline in HIV-1 RNA; (ii) 16 week change from baseline in CD4 cell count; and (iii) rate of clinical progression. Treatments which caused greater increases in CD4 cell count and greater reductions in HIV-1 RNA were more effective at reducing the rate of clinical progression comparisons (P<0.05 for each comparison). However, there was variability in the consistency of this correlation between different trials and treatments. The results support the use of HIV-1 RNA and CD4 count as markers of the efficacy of antiretroviral treatment.

Introduction

Epidemiological studies have shown that both CD4 cell count and human immunodeficiency virus type 1 (HIV-1) RNA levels are significantly associated with the risk of clinical progression, defined as progression to a new AIDS-defining event or death. Clinical trials have shown that patients with greater reductions in HIV-1 RNA levels during treatment, and greater increases in CD4 cell count, show a lower risk of clinical progression than those with smaller responses in these markers.

Although CD4 cell count and HIV-1 RNA level correlate with clinical progression, it is not clear to what extent changes in these markers can explain the effect of treatment on clinical progression. The usual approach to ‘validate’ a marker as a surrogate end point is to quantify the ‘proportion of treatment effect (PTE) explained’ - the extent to which difference in clinical outcome between two treatment arms of a clinical trial is explained by difference in treatment effect on the marker. Several studies have used this approach to evaluate HIV-1 RNA as a surrogate end point. Although the results are promising, confidence intervals on the PTE explained by HIV-1 RNA are generally wide. The possibility that effects on HIV-1 RNA may explain only a small proportion of treatment effect on clinical outcome could not be discounted. Furthermore, this type of analysis can be performed only for the subset of trials showing a strong treatment effect on clinical progression, and therefore does not include information from trials showing no significant clinical benefit to treatment.

An alternative approach to the validation of markers is to evaluate the concordance between treatment effects on a marker and on clinical progression in a meta-analysis involving the results from several clinical trials. This method allows inclusion of data from trials with or without significant treatment effects on either the marker or clinical progression. If a marker is a potential surrogate end point, then a strong association with clinical progression would be expected. This technique has been used to show a correlation between antiretroviral treatments causing greater rises in CD4 count and a greater
clinical benefit. The objective of this analysis was to determine the correlation between the effects of antiretroviral treatment on reductions in HIV-1 RNA and CD4 count, and clinical benefit.

Methods

Selection of trials
A search of public domain publications and conference presentations was conducted to identify all randomised clinical trials of antiretroviral treatments in adults infected with HIV-1, in which at least 10 patients per treatment arm showed clinical progression and for which data were collected on HIV-1 RNA levels and CD4 cell count.

Extraction of summary statistics
The 16-week change from baseline was obtained for log10 HIV-1 RNA and CD4 cell count for each treatment arm using published trial reports. In the absence of 16-week data, these values were estimated from the mean of time points either side of 16 weeks. The 95% confidence intervals of the changes in HIV-1 RNA and CD4 cell count were estimated by assuming a constant standard deviation of the 16 week change (100 cells/ml for CD4 cell count and 0.7 log10 copies/ml for HIV-1 RNA). These standard deviations were found to be robust for analyses of six Glaxo Wellcome trials of zidovudine/lamivudine (data not shown).

The relative hazard of clinical progression to AIDS or death (with associated 95% confidence intervals) was extracted from published data. Where the relative hazard could not be obtained directly, the relative risk of progression (and its associated variance) was calculated from the published number of clinical progressions by treatment group, or estimated directly from a Kaplan-Meier plot. Clinical progression was estimated using all follow-up information available for each trial. Thus, the relative hazard refers to different durations of follow up between trials.

All data on treatment effects were collected independently by authors AH and DD, and any differences in the estimates obtained were resolved by RD. The estimates of treatment effect were then sent to the pharmaceutical companies or government trials organisations which had conducted the trials, for review.

This step was included to ensure that the most appropriate source of published data was used.

Treatment comparisons
For each study, a control arm was identified. Pairwise treatment comparisons were then made by comparing this control arm with all other treatment arms in the study. Treatment effects for log10 HIV-1 RNA and CD4 cell count were calculated as the difference between change in the treatment and control arms. The hazard ratio of progression to AIDS and death was expressed as the relative hazard for each treatment arm relative to the control arms. The three measures of treatment effect were displayed graphically for all pairwise comparisons of treatments. Univariate parametric regression was used to analyse the correlation between treatment effects on HIV-1 RNA, CD4 cell count and clinical progression. These tests were weighted by the reciprocal of the sum of the variances of the treatment effects on HIV-1 RNA, CD4 cell count and clinical progression.

The analysis was repeated using the 24-week measures of change in CD4 count and HIV-1 RNA. Twenty-four week data were not available for as many trials as 16-week data and were therefore not chosen for the primary analysis. However the results from the analysis of 24-week data were very similar to those presented below for the 16-week summary statistics. For time points after week 24, summary statistic data on CD4 count and HIV-1 RNA was not available for a sufficient number of trials to allow a meaningful analysis.
Table 1. Trials included in meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Prior treatment</th>
<th>CD4 inclusion</th>
<th>Median FU</th>
<th>Drug classes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DELTA 1</td>
<td>2214</td>
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<td>&lt;350</td>
<td>30</td>
<td>NRTI</td>
<td>[11,12]</td>
</tr>
<tr>
<td>DELTA 2</td>
<td>1083</td>
<td>Pre-treated</td>
<td>&lt;350</td>
<td>30</td>
<td>NRTI</td>
<td>[11,12]</td>
</tr>
<tr>
<td>ACTG 175N</td>
<td>1067</td>
<td>Naive</td>
<td>200-500</td>
<td>31</td>
<td>NRTI</td>
<td>[4,13]</td>
</tr>
<tr>
<td>ACTG 175E</td>
<td>1400</td>
<td>Pre-treated</td>
<td>200-500</td>
<td>34</td>
<td>NRTI</td>
<td>[4,13]</td>
</tr>
<tr>
<td>ACTG 116a</td>
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<td>Naive</td>
<td>&lt;300</td>
<td>12</td>
<td>NRTI</td>
<td>[6,14]</td>
</tr>
<tr>
<td>ACTG 116b/117</td>
<td>913</td>
<td>Pre-treated</td>
<td>&lt;300</td>
<td>20</td>
<td>NRTI</td>
<td>[5,15]</td>
</tr>
<tr>
<td>VA 298</td>
<td>338</td>
<td>Naive</td>
<td>200-500</td>
<td>44</td>
<td>NRTI</td>
<td>[3,16]</td>
</tr>
<tr>
<td>BW34,225-02</td>
<td>180</td>
<td>Naive</td>
<td>&lt;300</td>
<td>22</td>
<td>NRTI</td>
<td>[17]</td>
</tr>
<tr>
<td>ACTG 320</td>
<td>1156</td>
<td>Pre-treated</td>
<td>&lt;200</td>
<td>9</td>
<td>NRTI/PI</td>
<td>[18]</td>
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<tr>
<td>ABT247</td>
<td>1090</td>
<td>Pre-treated</td>
<td>&lt;100</td>
<td>6</td>
<td>NRTI/PI</td>
<td>[19]</td>
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<tr>
<td>MX-028</td>
<td>996</td>
<td>Naive</td>
<td>50-250</td>
<td>13</td>
<td>NRTI/PI</td>
<td>[20,21]</td>
</tr>
<tr>
<td>NV14256</td>
<td>940</td>
<td>Pre-treated</td>
<td>50-300</td>
<td>13</td>
<td>NRTI/PI</td>
<td>[21]</td>
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<tr>
<td>CAESAR</td>
<td>1840</td>
<td>Naive/Pre-treated</td>
<td>25-250</td>
<td>12</td>
<td>NRTI/NNRTI</td>
<td>[9,23]</td>
</tr>
<tr>
<td>DLV 017</td>
<td>896</td>
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<td>0-300</td>
<td>17</td>
<td>NRTI/NNRTI</td>
<td>[24]</td>
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<td>ACTG 241</td>
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<td>NRTI/NNRTI</td>
<td>[25]</td>
</tr>
</tbody>
</table>

NRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; FU – median duration of follow up (months).

Results

Selection of trials

Table 1 details the 15 trials which met the criteria for selection. These trials involved a total of 15038 patients, of whom 9915 were evaluated for CD4 cell count, 4665 were evaluated for HIV-1 RNA at baseline and after 16 weeks of treatment, and 3532 patients clinically progressed.

Nine of the 11 antiretroviral treatments currently approved for use in Europe and/or North America are represented in these trials. Four are nucleoside analogue reverse transcriptase inhibitors (NRTIs) - zidovudine (ZDV), didanosine (ddI), dideoxycytidine (ddC) and lamivudine (3TC). Three are protease inhibitors (PIs) - ritonavir (RTV), indinavir (IDV) and saquinavir (SQV). Two are non-nucleoside reverse transcriptase inhibitors (NNRTIs) - nevirapine (NVP) and delavirdine (DLV). One unapproved NNRTI - loviride (LOV) - is also represented. Two approved antiretrovirals not included in the meta-analysis are stavudine and nelfinavir, since data from randomised trials of these treatments are not publicly available or do not include HIV-1 RNA measurements.

Two clinical trials, DELTA and ACTG 175, were stratified by prior zidovudine treatment. They are referred to in this analysis as DELTA 1 (no prior zidovudine treatment) and DELTA 2 (>3 months prior zidovudine treatment) and ACTG 175N (>4 weeks prior zidovudine treatment) and ACTG 175E (>4 weeks prior zidovudine treatment). Both trials were randomised and analysed independently for naïve and pretreated patients. Six of the 15 trials were conducted in zidovudine-naïve patients, eight in NRTI-pretreated patients and one in both naïve and pretreated patients. No trial recruited patients who had prior treatment with PIs or NNRTIs.

There were 15 published trials with clinical end points in at least 10 patients per arm but with no HIV RNA data available. Fourteen of these trials had been completed prior to 1995, when HIV RNA testing became widely available: one trial with HIV RNA levels determined in a subset of patients did not have a published source for this data. The relative hazard of progression to AIDS and death for treatment arms versus controls did not differ for these trials relative to those included in the meta-analysis (data not shown): this is evidence against a 'publication bias' effect whereby trials with greater treatment effects would be more likely to be included. Additionally there were two trials (Roche NV14604 and ACTG 193a) whose results had been announced only by press release and which had not been presented publicly or published, these trials were not included in the meta-analysis.
Extraction of summary statistics

CD4 cell count data were obtained from most study participants. Levels of HIV-1 RNA, however, were obtained typically from patient subsets in each trial. The Roche Amplicor assay was used in all trials except DELTA$^{1,12}$, which used the Organon-Teknika NASBA assay, and the delavirdine 017 trial$^{24}$ which used an in-house PCR assay.

The assessment of clinical progression used data from variable follow-up. It was not possible to estimate rates of clinical progression over a predetermined period of time, i.e. 1 year, using published data.

Treatment comparisons

A summary of treatment effects on HIV-1 RNA, CD4 cell count and clinical progression for pairwise comparisons in the individual trials is shown in Table 2. A total of 27 pairwise treatment comparisons were performed.

Figure 1 shows the correlation between treatment effects on HIV-1 RNA and the relative hazard of clinical progression. Relative hazard is on a scale of 1.25 to 0, where 1.25 corresponds to a 25% increase in the rate of progression relative to the control arm, 1 corresponds to no effect of treatment, and 0.5 corresponds to a 50% reduction in the rate of progression. Treatments showing less than a 0.25 log$_{10}$ reduction in HIV-1 RNA compared to the control arm showed little or no clinical benefit.

In ACTG 116a, there was no difference in either HIV-1 RNA or clinical progression between zidovudine and didanosine (at both the 500 mg and 750 mg/day doses). For the delavirdine 017 trial there was a 0.05 log$_{10}$ difference in HIV-1 RNA between didanosine/delavirdine and didanosine alone, with an associated 5% difference in clinical progression. The ACTG 241 trial showed a 0.2 log$_{10}$ benefit of zidovudine/didanosine/nevirapine over zidovudine/didanosine on HIV-1 RNA, but a decrease in clinical benefit (24% higher rate of clinical progression). However, this result was not statistically significant. Conversely, there was a modest 0.15 log$_{10}$ HIV-1 RNA benefit of didanosine (500 mg) over zidovudine, associated with a 28% lower rate of clinical progression, in favour of the didanosine arm of the ACTG 116b/117 study.

The remaining comparisons showed a treatment effect on HIV-1 RNA levels of over 0.25 log$_{10}$. None showed an opposite effect on clinical progression. There was variability between trials in the clinical benefit associated with particular HIV-1 RNA responses. In the ACTG 175E trial, both the zidovudine/didanosine and zidovudine/zalcitabine arms showed a benefit of approximately 1 log$_{10}$ HIV-1 RNA over the zidovudine arm. However, clinical progression was 35% lower for zidovudine/didanosine, whereas clinical progression was only 9% lower for zidovudine/zalcitabine, relative to zidovudine. It should be noted that the zidovudine/didanosine arm showed a more pronounced effect on CD4 cell count than the zidovudine/zalcitabine arm, which may explain the difference in clinical benefit despite the similar effects on HIV-1 RNA. A similar trend was observed for the DELTA 1 and DELTA 2 trials.
Figure 2 shows the correlation between treatment effects on CD4 cell count and clinical benefit. Treatments which cause greater rises in CD4 cell count also show larger reductions in the rate of clinical progression. The correlation with clinical benefit appeared to be greater for treatment effects on CD4 counts than effects on HIV-1 RNA although this might, in part, reflect the larger number of patients with CD4 counts measured in the trials.

At the origin of Figure 2 there were two treatment comparisons from trial ACTG 116a with no benefit in CD4 count or clinical benefit for zidovudine versus either of two doses of didanosine. There was one treatment comparison in trial ACTG 241 with a CD4 benefit of 17 cells to zidovudine/didanosine/nevirapine over zidovudine/didanosine, but with a higher clinical progression rate for the triple combination arm. However, the clinical comparison was not statistically significant.

Apart from the ACTG 241 trial and the two points at the origin, all treatment comparisons showed a CD4 benefit together with a clinical benefit; the size of the clinical benefit tended to rise with increasing CD4 benefit. The most marked examples were for the Merck trial 028 which showed a CD4 benefit of over 80 cells and a rate of clinical progression at least 61% lower for the indinavir-containing regimens relative to the control arm of zidovudine.

Univariate analysis showed a significant correlation between treatments that cause greater reductions in HIV-1 RNA, greater rises in CD4 cell count and larger reductions in the rate of clinical progression (P<0.05 for each comparison).

Discussion

This meta-analysis shows an overall correlation between treatments that cause greater reductions in HIV-1 RNA, greater rises in CD4 cell count and larger reductions in the rate of clinical progression. However there is variability around this correlation for treatments in different trials.

Sources for the observed variability in the correlation include the measurement of the treatment effect on CD4 cell count, HIV-1 RNA and clinical progression. Also, trials with similar populations and treatments can generate differing estimates of the treatment effect on clinical progression. For instance, zidovudine/zalcitabine reduced clinical progression by 51% compared with zidovudine alone in the ACTG 175N trial, whereas the same treatment showed only a 20% reduction in clinical progression in the DELTA 1 trial.

The variability in the estimates of treatment effect on clinical progression can also be seen from the confidence intervals around the point estimates for each trial. This is illustrated by the comparison of zidovudine/didanosine with zidovudine in the ACTG 175N trial, where the point estimate of relative
hazard was 0.61 (39% reduction in progression) but the 95% confidence intervals were 0.35 (65% reduction) and 0.95 (5% reduction). Therefore, some of the variability seen in the correlation between treatment effects on markers and treatment effects on clinical progression could arise from uncertain estimation of the treatment effect. Such meta-analyses are best performed using data on individual patients. However it was not possible to use the individual patient data from the diverse industry and government sponsors owing to issues of confidentiality.

In some instances, a treatment appeared to be superior to another in reducing HIV-1 RNA but inferior in raising CD4 cell counts. One example is the comparison of saquinavir with zalcitabine in trial NV14256. The zalcitabine arm showed greater reductions in HIV-1 RNA levels, but less CD4 cell count benefit than the saquinavir arm. However the only treatment comparisons showing 25% or greater reduction in clinical progression were those where the treatment showed a benefit over the control in both CD4 cell count (40 cell rise) and HIV-1 RNA (0.5 log reduction). This reinforces the need to use both CD4 cell count and HIV-1 RNA in the evaluation of treatment efficacy.

For trials of more potent triple combinations it is possible that a 'ceiling effect' could have affected the results, whereby the maximum log reduction in HIV-1 RNA would have been limited by the lower limits of detection of the assay. However, with the exception of ACTG 320, all the trials in this meta-analysis involved treatment arms in which HIV-1 RNA remained detectable in the majority of patients for sustained periods, so the maximal reductions in HIV RNA were not achieved.

The 16 week time point was chosen for evaluation of responses in CD4 count and HIV-1 RNA for this analysis since this was available from all the trials. However, a sensitivity analysis of 24 week summary statistic data showed a very similar result; information for longer term changes in CD4 count and HIV-1 RNA was not available for a sufficient number of trials to perform a meaningful analysis.
It is possible that new trials of more powerful treatments, in which the majority of patients show reductions to under 400 (or 50) HIV-1 RNA copies/ml for sustained periods, may show greater clinical benefit than that predicted by the current trials, particularly if concomitant rises in CD4 cell count are also large and sustained.

Most trials in this meta-analysis included protocol-defined treatment for approximately 1 year. Therefore, some caution should be used in extrapolating the association between treatment effects on HIV-1 RNA and CD4 cell count to longer-term clinical benefit. However, the association between marker benefits and clinical benefits was sustained in the DELTA and ACTG 175 trials which had a follow-up of approximately 30 months.

Ideally, estimates of treatment effects on clinical progression, HIV-1 RNA and CD4 cell count would be based on the same subset of patients. However, the individual patient data on CD4 count, HIV-1 RNA and clinical progression from this wide range of trials were unavailable for a pooled analysis. In some studies (e.g. DELTA, CAESAR, ACTG 175) summary analyses in the published reports indicated that the HIV-1 RNA patient subset was representative of the entire study population.

The majority of trials used Roche Amplicor assay for evaluation of HIV-1 RNA. This is a validated assay used in routine clinical practice and it is unlikely that the performance of the assay would have differed significantly between trials. The Organon-Teknika assay was used in the DELTA trial, but estimates of HIV-1 RNA reduction in the subset evaluated were very similar to estimates made using the Roche Amplicor assay in a smaller subset of patients.

A potential source of bias is that retrospective evaluation of HIV-1 RNA may be limited to those trials with a significant treatment effect on clinical progression. However, examination shows that the trials excluded from the meta-analysis were almost all conducted over 4 years ago, prior to the development of the technology for evaluation of HIV-1 RNA by the PCR technique. The majority of the trials completed since 1995 are included in the meta-analysis.

This meta-analysis included trials of adults only. Considering children in isolation, a good correlation has been shown between reductions in HIV-1 RNA and a reduced risk of progression to AIDS in paediatric trials ACTG 152 and ACTG 300 (FDA Antiviral Advisory Committee July 1997).

In summary, this meta-analysis included 15 clinical end point trials completed since 1995. Clinical disease progression, HIV-1 RNA and CD4 cell count data were analysed. We find that there is a concordance between treatment effects on the markers of HIV-1 RNA and CD4 cell count, when used together, are useful markers of treatment benefit.

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