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

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CHAPTER 7

The effects of lamivudine treatment on HIV-1 disease progression are highly correlated with plasma HIV-1 RNA and CD4 cell count

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The effects of lamivudine treatment on HIV-1 disease progression are highly correlated with plasma HIV-1 RNA and CD4 cell count

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Objective
To determine the value of plasma HIV-1 RNA and CD4 cell count as predictors of the clinical benefit of antiretroviral treatment.

Design and setting
The CAESAR (Canada, Australia, Europe, South Africa) trial randomised 1840 patients (inclusion CD4 cell count, 25-250 × 10^6/1) to add either placebo, lamivudine (3TC) or 3TC plus loviride in a double-blinded fashion to baseline treatments (zidovudine, zidovudine-didanosine or zidovudine-zalcitabine) for 1 year.

Patients
This analysis included 487 patients with data on CD4 cell count and HIV-1 RNA after 12-20 weeks of treatment and subsequent follow-up for clinical progression.

Main outcome measures
The correlation between 12-20-week change in CD4 cell count, HIV-1 RNA and progression to AIDS or death in the placebo group was used to predict the clinical benefit of the 3TC-containing arms of the trial, given their effects on CD4 cell count and HIV-1 RNA.

Results
After 12-20 weeks of treatment, HIV-1 RNA fell by 0.37 log_{10} copies/ml in the 3TC arms versus a rise of 0.05 log_{10} copies/ml in the placebo arm. The 12-20 week CD4 cell count rose by 35 × 10^6/1 in the 3TC arm versus a fall of 8 × 10^6/1 in the placebo arm. After 12-20 weeks of treatment, a reduction in HIV-1 RNA of 1 log_{10} at 12-20 weeks predicted a 49% reduction in progression [hazard ratio (HR), 0.51; 95% confidence interval (CI), 0.30-0.87] and a rise in CD4 cell count of 50 × 10^6/1 predicted a 51% reduction in progression (HR, 0.49; 95% CI, 0.33-0.73). Using the model from the placebo arm, the rises in CD4 cell count and reductions in HIV-1 RNA during 3TC treatment predicted a 59% reduction in progression to AIDS or death. The observed clinical benefit was a 57% reduction in progression for the 3TC arms versus placebo (HR, 0.43; 95% CI, 0.26-0.71).

Conclusions
Rises in CD4 cell count and reductions in HIV-1 RNA were reliable in predicting the clinical benefit of 3TC in the CAESAR trial. ©1998 Rapid Science Ltd

Introduction
There is strong evidence to suggest that higher baseline levels of plasma HIV-1 RNA and lower CD4+ lymphocyte counts are associated with higher rates of progression to AIDS and death in untreated HIV-1 infection. Rises in CD4 cell count and reductions in HIV-1 RNA have been associated with improved clinical outcome within trials of nucleoside analogues, protease inhibitors and non-nucleosides.
However, the degree to which treatment-related rises in CD4 cell count and reductions in plasma HIV-1 RNA can predict the clinical benefit of treatment has not been fully characterised. If such changes in CD4 cell count and plasma viral load were shown to be highly predictive of the clinical benefit, this would strongly support the use of CD4 cell count and HIV-1 RNA instead of clinical endpoints in clinical practice, clinical trials and drug development.

Two methods have been used to investigate the reliability of CD4 cell count and HIV-1 RNA as surrogate markers for individual trials. First, the 'proportion of treatment effect explained', using the method of Prentice, has been used for several studies; however, this method can only be used for trials with a strong effect of treatment on clinical progression, and confidence intervals on the estimates usually overlap 1 and 0 so it is difficult to make an accurate estimate of the reliability of a marker. The second method, which is employed in this analysis, uses the correlation between markers and clinical benefit in the control arm and the difference in marker profiles between the control and treatment arms to predict what the clinical benefit of the treatment arm should be. This predicted benefit is then compared with the actual clinical benefit seen for the treatment relative to the control.

A close correlation between the predicted and observed clinical benefit of treatment is taken as evidence that the markers can reliably predict the clinical benefits of treatment.

**Methods**

The methods for the CAESAR trial have been described in detail elsewhere. Briefly the CAESAR trial randomly assigned 1840 patients with inclusion CD4 cell counts of 25-250 x 10^6/l to receive 1 year of treatment with either placebo, lamivudine (3TC), or 3TC plus loviride in a double-blind fashion in addition to zidovudine (ZDV)-containing regimens (ZDV monotherapy, ZDV-zalcitabine or ZDV-didanosine). The randomisation was conducted with a 1:2:1 ratio for placebo: 3TC: 3TC-loviride. All AIDS and death endpoints were collected prospectively and independently reviewed under blinded conditions. The trial was terminated after a significant reduction in progression, CD4 cell count or HIV-1 RNA, and therefore the two treatment arms were combined for the purposes of this analysis and compared with the placebo arm.

During the trial, 179 patients from investigational centres in France and Belgium were evaluated prospectively for CD4 cell count and plasma HIV-1 RNA at central laboratory. After termination of the trial, data on CD4 cell count and plasma HIV-1 RNA were obtained from two additional groups: (i) patients with under 4 weeks of prior nucleoside analogue treatment (n = 259), and (ii) patients who progressed to AIDS or death during the trial (n = 180) and a random sample of the patients who did not progress (n = 188).

Plasma HIV-1 RNA was determined using the Amplicor assay (Roche, Nutley, New Jersey, USA) [lower limit of quantification, 400 (2.6 log_{10}) copies/ml] using prospectively collected samples which were assayed at a single laboratory. CD4 cell counts were obtained from the clinical laboratories of investigational centres for naive patients and from the sample of progressors and non-progressors. Of the 806 patients with HIV-1 RNA data available, 487 patients had data on both CD4 cell count and HIV-1 RNA at baseline and after 12-20 weeks of treatment, and had been followed up for clinical progression beyond week 20: patients progressing to AIDS or death prior to week 20 were excluded from the analysis.

**Statistical analysis**

All analyses were conducted on an intent-to-treat basis with no data exclusions. The predicted clinical benefit was then calculated and compared to the observed clinical benefit as outlined below.

First, a Cox proportional hazard model was applied to the placebo arm to estimate the correlation between the 12-20-week change in CD4 cell count and plasma HIV-1 RNA and subsequent progression to AIDS and death, adjusting for baseline CD4 cell count and plasma HIV-1 RNA.
Second, the mean change in CD4 cell count and plasma HIV-1 RNA after 12-20 weeks of treatment was calculated for the placebo arm and the 3TC arm. HIV-1 RNA values were log_{10}-transformed, and values under the lower limit of quantification were assigned a value of 400 (2.6 log_{10}) copies/ml. The predicted risk of progression in the 3TC arm was estimated using the difference between the treatment arms in CD4 cell count and HIV-1 RNA level after 12-20 weeks and the correlation between these marker responses and clinical progression from the Cox model in the placebo arm.

Third, the observed hazard ratio of progression-free survival was generated for the comparison of 3TC and placebo and was compared with the predicted hazard ratio. The test of surrogacy for this model was as follows: if the observed and predicted hazard ratios of progression were identical, then the CD4 cell count and HIV-1 RNA level fully predicted the clinical benefit of the 3TC arm in the CAESAR trial.

The summary of statistics of the 12-20 week change was chosen after discussions with the US Food and Drug Administration over appropriate measures of response. In sensitivity analyses, other summary statistics of change in CD4 cell count and HIV-1 RNA level were investigated (peak change, 8-28-week change, duration of change), producing nearly identical results. Analyses were conducted using SAS software (SAS Institute, Cary, North Carolina, USA) and the observed versus predicted analyses were conducted using SUDAAN Version 7.0 software (Research Triangle Institute, Research Triangle Park, North Carolina, USA). In addition, the analyses were repeated excluding all data from the 3TC-loviride arm of CAESAR: the results from these analyses were very similar to those including the data from the 3TC-loviride arm.

**Results**

Table 1 shows the baseline characteristics of the 487 patients included in the analysis. The median baseline CD4 cell count was 126 x 10^6/l with a median HIV-1 RNA level of 4.9 log_{10} copies/ml; 27% of patients had a prior diagnosis of AIDS. Of the patients, 87% had received under 4 weeks of treatment, and of those previously treated the median duration of prior treatment was 27 months. The treatments received during the trial were ZDV monotherapy (n = 263), ZDV-zalcitabine (n = 137) or ZDV-didanosine (n = 87). In addition to the baseline treatment, patients were randomised to receive either placebo (n = 125) or 3TC-containing treatments (n = 362).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lamivudine arm (n = 362)</th>
<th>Placebo arm (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) CD4 cell count (x10^6/l)</td>
<td>129 (26-286)</td>
<td>121 (26-250)</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} copies/ml)</td>
<td>4.9 (2.6 - 6.5)</td>
<td>5.1 (2.6 - 6.4)</td>
</tr>
<tr>
<td>Patients with AIDS* (%)</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Prior treatment (%)</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Baseline treatment (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>ZDV + zalcitabine</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>ZDV + didanosine</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Mean (range) age (years)</td>
<td>36 (20-67)</td>
<td>38 (24-57)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>93</td>
<td>94</td>
</tr>
</tbody>
</table>

*According to the Centers for Disease Control and Prevention criteria.
ZDV, Zidovudine

Table 2 shows the results of multivariate analysis of the hazard of progression to AIDS and death based on results from the placebo, 3TC and combined arms. In the placebo arm, both the baseline levels and 12-20-week changes from baseline in CD4 cell count and HIV-1 RNA level were correlated with progression. For each increase in baseline CD4 cell count of 50 x 10^6/l there was a 29% lower risk of progression, and for each incremental rise of 50 x 10^6/l in CD4 cell count at weeks 12-20, there was a 54% reduction in risk of progression. Similarly, for each decrease in the baseline HIV-1 RNA level of 1 log_{10}, there was a 59% lower risk of progression, and there was a 42%
reduction in the risk of progression for each incremental log_{10} reduction in "HIV-1 RNA level during the first 12-20 weeks of treatment.

**Table 2. Multivariate analysis of progression to AIDS and death.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RH (95% CI) Placebo arm</th>
<th>3TC arms</th>
<th>Combined arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 cell count*</td>
<td>0.72 (0.48-1.07)</td>
<td>0.65 (0.46-0.94)</td>
<td>0.69 (0.54-0.90)</td>
</tr>
<tr>
<td>12-20 week change in CD4 cell count*</td>
<td>0.46 (0.21-1.00)</td>
<td>0.53 (0.32-0.87)</td>
<td>0.49 (0.33-0.73)</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA†</td>
<td>0.31 (0.15-0.65)</td>
<td>0.39 (0.21-0.70)</td>
<td>0.35 (0.22-0.55)</td>
</tr>
<tr>
<td>12-20-week change in HIV-1 RNA†</td>
<td>0.59 (0.22-1.58)</td>
<td>0.49 (0.26-0.94)</td>
<td>0.51 (0.30-0.87)</td>
</tr>
</tbody>
</table>

*Per 50 x 10^6/ml increase. †Per 1 log_{10} copies/ml decrease. RH, Relative hazard; CI, confidence interval.

Figure 1 shows the median change in CD4 cell count and HIV-1 RNA level for the 3TC arms versus the placebo arm. The 3TC arms showed a mean rise of 44 x 10^6/ml at 8 weeks, which was sustained 33 x 10^6/ml above baseline at week 20. The corresponding changes in the placebo arm were +4 x 10^6/ml and −9 x 10^6/ml. There was a mean 0.52 log_{10} copies/ml reduction in HIV-1 RNA level in the 3TC arm at week 8, which was sustained 0.3510 log_{10} copies/ml below baseline at week 20. By contrast, the placebo arm showed no significant reduction in HIV-1 RNA level throughout the trial.

For individual patients, there was a significant correlation between the extent of the HIV-1 RNA reduction and the corresponding rise in CD4 cell count after 12-20 weeks of treatment (r = -0.40, p < 0.001). However, there was a high degree of scatter around the line of correlation: for a given reduction in HIV-1 RNA a wide variety of changes in CD4 cell count was observed. There were some patients with rises in both CD4 cell count and HIV-1 RNA level, or reductions in both markers.
Using the multivariate model (Table 2) and the difference in CD4 cell count and HIV-1 RNA level between the 3TC and the placebo arms, the expected effect of 3TC on clinical progression was calculated as follows:

\[
\text{RH (3TC/placebo)} = \exp [(\text{CD4 cell benefit} \times \text{CD4 cell lnRH}) + (\text{HIV-1 RNA benefit} \times \text{HIV-1 RNA lnRH})] = \exp [0.86 \times -0.77] + (0.42 \times -0.53) = 0.41
\]

This relative hazard (RH) of 0.41 corresponded to a 59% reduction in progression for the 3TC arm relative to the placebo arm.

Figure 2a shows the Kaplan-Meier estimates of progression for 3TC and placebo arms, unadjusted for CD4 - cell count and HIV-1 RNA. There were 92 progressions to AIDS events or death between weeks 20 and 52 of the CAESAR trial. The progression rate was 14% (52 out of 362) in the 3TC-containing arms versus 32% (40 out of 125) in the placebo arm (RH, 0.43; 95% confidence interval, 0.26-0.71; p = 0.0009). Therefore, the clinical benefit of 3TC predicted from the multivariate model (59% reduction) was close to the 57% reduction in progression observed in the trial. Figure 2b shows the Kaplan-Meier estimates of progression after adjustment for the effect of 3TC on CD4 cell count and HIV-1 RNA level in the multivariate model. After this adjustment there was no longer a difference in CD4 cell count and HIV-1 RNA level placebo arms.

![Fig. 2. Kaplan-Meier curves of rates of progression to AIDS and death after week 20, (a) unadjusted and (b) adjusted for effects of lamivudine (3TC) on CD4 cell count and HIV-1 RNA level at weeks 12-20.](image)

**Discussion**

The combination of treatment-induced changes in plasma HIV-1 RNA and CD4 cell count between 12 and 20 weeks post-randomisation provided an accurate estimate of the clinical benefit of the addition of 3TC to ZDV-containing regimens in this large double-blinded trial.

Several other trials have shown a correspondence between treatment effects on HIV-1 RNA level, CD4 cell count and clinical benefit\(^5,8,9\), and a meta-analysis of several trials of nucleoside analogue treatments has shown that treatments causing larger rises in CD4 cell count also cause greater reductions in progression to AIDS and death.\(^11\)

A similar analysis of the UK Medical Research Council/INSERM Delta trial showed that the clinical benefit from treatment with ZDV-didanosine and ZDV-zalcitabine was substantially less than the benefit predicted from the changes in CD4 cell count and HIV-1 RNA level.\(^4\) However, the analysis of the Delta trial correlated responses at 16 weeks with clinical progression occurring up to 3 years later, when patients were often no longer on their original randomised treatment, and many had received alternative treatments. This is in contrast to the CAESAR trial, where responses in CD4 cell count and HIV-1 RNA up to 20 weeks post-randomisation were correlated with clinical progression occurring up to 1 year post-randomisation, and compliance with randomised treatment was good.\(^10\) It is also possible that other methodological differences between the Delta and CAESAR trials, such as
the patient population recruited or the methodology of HIV-1 RNA evaluation used, could explain the
difference in the results obtained.

There have been treatments that have had a favourable effect on HIV-1 RNA but with opposite effects
on clinical progression relative to the control regimen.12 Such mismatches between effects on markers
and clinical outcome might be explained by drug toxicity or non-adherence to the regimen, which
cannot necessarily be captured by treatment effects on CD4 cell count or HIV-1 RNA; therefore, it
cannot be assumed that two treatments with equivalent effects on CD4 cell count and HIV-1 RNA
will have identical effects on clinical progression. These analyses therefore need to be repeated for
trials of other antiretroviral agents.

The CAESAR trial showed a clinical benefit of treatment in the context of a partially suppressive
therapeutic strategy. Such partial reductions in HIV-1 RNA may be the only response achievable for a
proportion of patients even when given potent triple combinations.13,14 The clinical benefit associated
with sustained viral load undetectability is currently unknown given that clinical follow-up in
aggressively treated patients is limited.13,14 However, reductions in HIV-1 RNA to under the limit of
qualification are the only durable mechanism to avoid resistance15 and have become the aim of
antiretroviral therapy.16

There is an increasing switch towards the use of HIV-1 RNA and CD4 cell count rather than clinical
endpoints as the primary measures of efficacy of antiretroviral treatment, both for monitoring
treatments in the clinic and in the approval of new antiretrovirals. It is important to show that this
switch is justified. There was close concordance between the clinical benefit of 3TC predicted from
the effects on HIV-1 RNA and CD4 cell count, and the actual clinical benefit observed in the
CAESAR trial. Results from other trials will be required to ensure that this correlation between effects
on HIV-1 RNA, CD4 cell count and clinical benefit remains consistent for long-term treatment and
for other classes of antiretrovirals.

Acknowledgements
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