The use of surrogate markers in the antiretroviral treatment of HIV-1 infection
Hill, A.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 12

Summary
CHAPTER 12

Summary

This thesis is on the usage of surrogate markers in the development of treatments for HIV. Following an introduction to this area of research in Chapter 1 the thesis is divided into four sections:

1. Studies of the clinical benefits of antiretroviral treatment

Chapter 2 describes a meta-analysis of clinical endpoints observed in four randomised clinical trials of treatment with zidovudine-3TC combination treatment versus controlled treatment. These four clinical trials, in a total of 972 patients, were designed to detect differences in CD4 counts between treatment arms, but clinical endpoints (AIDS related complex and AIDS and death) were also collected as adverse events. The justification for combining the trials in the meta-analysis was that the trials were conducted in parallel using very similar trial protocols, the same dosages of zidovudine and 3TC, and collecting clinical endpoints using identical case report forms, which were entered and validated under blinded conditions. A total of 118 patients progressed to a first new CDC B or C (ARC or AIDS) event during the four trials, with 28 progressing to a first new AIDS event. Meta-analysis of the trials showed a 49% reduction in progression to ARC or AIDS across the four trials, and a 66% reduction in progression to AIDS, for patients receiving zidovudine-3TC treatment relative to control treatment (zidovudine or zidovudine-zalcitabine). Breslow-Day tests showed no evidence of heterogeneity of this treatment effect across the four clinical trials. Results were similar for treatment naïve and nucleoside analogue experienced patients.

Chapter 3 acts as an additional part of this section, showing evidence of one factor which could predispose patients to different responses to antiretroviral treatment and different rates of progression to AIDS/death. Analysis of seven laboratory workers showed that individuals without HIV tend to track their own individual level of CD4 counts within a restricted part of the normal range of values. The hypothesis was made that people with lower individual CD4 counts prior to infection with HIV might then show faster rates of progression to AIDS, post-infection since they would have a smaller reserve of CD4 cells to be destroyed during HIV infection. This hypothesis was then tested using data from a cohort of haemophiliacs at the Royal Free Hospital in London. In this cohort, those with lower [extrapolated] pre-infection CD4 counts did have faster rates of progression to AIDS or death.

2. The effects of antiretroviral treatment on surrogate markers

In this section, the effects of treatment with 3TC on surrogate markers are examined.

Chapter 4 is an analysis of clinical trials of the combination of 3TC and zidovudine. The aim was to find factors predicting the likelihood of achieving HIV RNA levels under 400 copies/ml during treatment. The trials used for the analysis were 1083 patients from the six double-blind placebo controlled trials of 3TC and zidovudine. Only on treatment data were included in the analysis.

The analysis showed that NRTI pre-treated patients were less likely to show reductions to under 400 copies/ml during treatment with 3TC-zidovudine. Multivariate analyses showed no significant effect of age, gender, race, baseline CD4 count or CDC disease stage on the probability of sustained HIV RNA suppression under 400 copies/ml. However the baseline HIV RNA level was highly predictive of long-term HIV RNA suppression. Treatment naïve patients with under 5000 HIV RNA copies/ml at baseline had a 71% probability of sustained HIV RNA suppression with 3TC-zidovudine treatment, while those with baseline HIV RNA levels between 50,000 and 200,000 copies/ml had only a 14% probability.
3. Correlation between surrogate markers and clinical benefits of antiretroviral treatment

Chapters 5 to 8 describe levels of evidence which were needed in order to "validate" CD4 count and HIV RNA as surrogate markers of the clinical benefit of antiretrovirals, to the extent that these markers were then adopted by regulatory authorities as a replacement for clinical endpoints in new HIV drug approvals.

In Chapter 5, different surrogate markers were correlated with the progression to AIDS and death for the 104 patients taking part in a dose ranging trial of 3TC. Of these 104 patients, 85 had complete data for CD4 counts and HIV RNA levels. After a median follow up time of 713 days, 16 of the 85 patients progressed to AIDS. The patients who progressed to AIDS were characterised by a combination of a CD4 count under 200 copies/ml and a high level of HIV RNA. This HIV RNA was measured by an in-house HIV RNA PCR assay at the University College London Medical School and should not be compared directly with assays currently available. The data suggested that the combination of CD4 counts and HIV RNA provided a more reliable prediction of progression to AIDS and death than either of the markers used in isolation.

In Chapter 6, data were combined from six randomised clinical trials of 3TC-zidovudine (1488 patients) to determine the levels of CD4 count and HIV RNA at which progression to AIDS and death was most likely. The trials included patients with CD4 counts from 25 to 500 CD4 cells/ml at entry. The likelihood of progression to AIDS or death was correlated with the CD4 counts observed after 8 to 52 weeks of treatment with either 3TC-zidovudine or NRTI based control treatments. During a median follow up of 1 year, progression to AIDS was largely restricted to those patients with both CD4 counts under 200 cells/mm$^3$ and HIV RNA levels above 5000 copies/ml. The progression rate in this group was 26%. Those with one of these abnormalities showed lower rates of progression (3.5-5.1%), and rates were lowest (0.6%) for patients maintaining CD4 counts above 200 cells/mm$^3$ and HIV RNA levels below 5000 copies/ml. The AIDS defining events occurring for those with HIV RNA levels below 5000 copies/ml were generally atypical (for example immunoblastic lymphoma, Mycobacterium tuberculosis).

Chapter 7 was a further attempt to calculate the proportion of the clinical benefits of treatment which could be explained by changes in CD4 count and HIV RNA. In this paper, patients in the CAESAR trial were retrospectively analysed for HIV RNA levels. The retrospective analysis included 487 patients with data on CD4 cell count and HIV RNA after 12-20 weeks of treatment with either 3TC-zidovudine or control treatment. The correlation between baseline levels of CD4 count, HIV RNA and clinical progression in the control arm of the trial was used to predict the clinical benefit in the 3TC arm, given the effect of the 3TC arm on CD4 count and HIV RNA. The clinical benefit of treatment predicted was a 59% reduction in progression to AIDS or death, which was close to the actual benefit observed of a 57% reduction in clinical progression.

In Chapter 8 the correspondence between treatment related effects on CD4 counts, HIV RNA levels and clinical progression was assessed with a meta-analysis of data from all publicly available randomised clinical trials where all three measures had been taken. Randomised trials included those evaluating NRTI treatment, NNRTI treatment and protease inhibitor treatment. Within each clinical trial, the metric used was the difference between treatment arms in 16 week change in CD4 count and log reduction in HIV RNA, which was correlated with the corresponding difference in progression to AIDS or death between the arms. The results showed that, overall, treatments causing greater rises in CD4 counts and larger reductions in HIV RNA levels tended to provide greater clinical benefits. However there was substantial variability in the consistency of this correlation between different trials and treatments.

4. The need for standardisation in the reporting of measures of antiretroviral efficacy.

Chapter 9 covers the issue of different techniques for analysing HIV RNA reductions in HIV clinical trials. The percentage of patients achieving HIV RNA undetectability has become the primary
method of evaluating treatment efficacy. Given the large number of potential combinations of the available drugs used for HIV treatment, it would be impossible to compare all potential HAART regimens in randomised clinical trials, and so cross-study comparisons of antiviral efficacy are inevitable, despite their inherent shortcomings. Using data from clinical trials AVANTI 2 and AVANTI 3, the analysis showed that it is possible to produce a wide variety of estimates of percent undetectable, depending on the set of assumptions used in the analysis. In particular the choice of assay cut-off for undetectability (400 versus 50 HIV RNA copies/ml), the method for classifying missing data and the choice of Intent to Treat versus As Treated analysis can raise or lower the estimates of percent undetectable. The paper concludes that those presenting clinical trials data on HIV RNA should always include an Intent to Treat analysis of their results, and should state clearly the assumptions made in the choice of assay cut-off used as well as the handling of missing data, from either loss to follow up, withdrawal for toxicity or switches to other treatments.

Chapter 10 covers a similar issue for another emerging measure of treatment efficacy – the “Inhibitory Quotient”. This is the ratio of plasma drug concentration, divided by the drug concentration required to inhibit viral replication. As with HIV RNA analyses, there are many potential techniques for the definition of Inhibitory Quotient, none of which has emerged as necessarily the most appropriate to use across all antiretrovirals. The plasma drug concentration can be defined as either the minimum concentration, Area under the Curve or maximum concentration, and may be based on measures in plasma or within cells. Adjustments for protein binding can be calculated in different ways and inhibitory concentrations measured using a variety of cell types and definitions of response. As with HIV RNA undetectability, it is shown that a variety of estimates of the Inhibitory Quotient can be made for different treatments depending on the assumptions made, and therefore that randomised clinical trials are required to definitively determine the relative antiviral efficacy of HAART regimens.

There is a discussion of the overall results and their implications in Chapter 11.