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

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Since its discovery in 1983 (Barre-Sinoussi 1985), the retrovirus HIV-1 has infected an estimated 40 million people world-wide (UNAIDS report 2001). Without treatment, the mean incubation period between initial infection with HIV and development of AIDS defining events is approximately 10 years (Munoz 1997).

Two major classes of antiretroviral treatments have been developed to combat HIV infection: the reverse transcriptase inhibitors and the protease inhibitors. Reverse transcriptase inhibitors act on the HIV reverse transcriptase enzyme, by either incorporation into the nascent HIV DNA, terminating the growing chain of HIV DNA (nucleoside analogues, Sluis-Cremer 2000) or by binding to part of the HIV-1 reverse transcriptase enzyme, thereby inhibiting its function (non-nucleosides, Spence 1995, Maga 2000). Protease inhibitors act on the HIV protease enzyme, inhibiting the cleavage of Gag and Gag-Pol precursor polyproteins into functional subunits (Eberle 1995). Other drug classes are currently in development, in particular immunotherapies such as interleukin-2, and fusion inhibitors such as enfuvirtide.

Early in the course of the epidemic, experimental antiretroviral treatments were introduced and their effects on progression to AIDS and death were assessed in clinical trials and cohort studies. The first treatment for HIV infection, AZT, was approved for usage in 1987, based on its effects on improving survival in a placebo-controlled trial (Richman 1988). Similar improvements in survival were detected in routine follow up of clinic cohorts (Moore 1991).

After the approval of AZT, other antiretrovirals – d4C and ddi - were shown to lower rates of clinical disease progression (Kahn 1992, Delta Co-ordinating Committee 1996). This clinical benefit was later shown for treatment with AZT/3TC in a meta-analysis of controlled trials (Chapter 2) and in the CAESAR trial, a large randomised clinical endpoint trial.

While clinical endpoint trials were being conducted to prove clinical efficacy of treatments in the mid-1990’s, early research on surrogate markers was being used to select drug dosages to take further into Phase 3 trials. There was a wide variety of surrogate markers of HIV progression in use in the early 1990’s, including T lymphocyte markers and several measures of viral load.

The primary cell type infected by HIV-1 is the CD4 positive T lymphocyte (Embreton 1993). Reductions in CD4 count have been observed during the course of HIV infection, with lower counts leading to an increased risk of progression to AIDS and death (Phillips 1991). However several factors other than HIV infection can affect the CD4 count (Stein 1992) and so the CD4 count used in isolation cannot fully characterise the degree of immunodeficiency of an individual. Individuals without HIV infection show particular ranges of CD4 count and these may have contributed to the risk of HIV disease progression (Chapter 3). As well as the CD4 marker, other T cell markers have been shown to predict HIV disease progression, such as higher numbers of CD8+,CD38+ positive T lymphocytes (Giorgi 1993). Treatment with highly active antiretroviral therapy (HAART) was found to lead to alterations in the proportion of “naïve” versus “memory” T lymphocytes in peripheral blood (Pakker 1998). In addition, early studies examined the prognostic value of the immunological markers beta-2-microglobulin and neopterin, but with mixed results (Moss 1988)

HIV is a retrovirus with viral RNA encapsulated in a protein core and envelope. HIV RNA copy number per unit volume of peripheral blood is a measure of the number of viruses present in the body of an infected individual. HIV RNA levels have been shown to be higher at late stages of HIV
disease, and to have additional power in prediction of progression to AIDS and death over CD4 count (Mellors 1996). Higher levels of other markers of HIV viral load have also been correlated with a greater risk of HIV disease progression, such as HIV DNA (Panther 1998), p24 antigen (Moss 1998), and immune complex dissociated (ICD) p24 antigen (Morand-Joubert 1994). Other experimental assays measured the viral tropism and the ability of virus to form syncytia of infected cells. One study showed a higher rate of HIV disease progression for patients with predominantly syncytium inducing virus (Tersmette 1992).

After early work on the evaluation of potential surrogate markers, candidate markers were evaluated during Phase 2-3 trials of new antiretrovirals. Treatment with 3TC was found to reduce levels of HIV viral load and increase CD4 cell counts, both in monotherapy and in combination with AZT (Chapter 4). In the mid to late 1990's, the regulatory approval of antiretroviral drugs still required proof of clinical benefit until the value of HIV viral load and CD4 counts could be established as reliable surrogate markers of this clinical benefit. Several treatments were approved on the basis of their clinical benefits observed in large clinical endpoint trials, with effects on HIV viral load and CD4 counts used as supplementary information (ddl, ddC, 3TC, d4T, indinavir, saquinavir, nevirapine).

However the difficulties of conducting clinical endpoint trials were growing - these trials were becoming large and costly to perform, and there were ethical issues in randomising patients to a control arm with potentially inferior treatment, as predicted by surrogate markers in earlier trials. High rates of attrition from clinical trials were observed, which lowered the statistical power of these trials to demonstrate the clinical benefits of a new treatment over standard of care or placebo control arms.

Despite the limitations of clinical endpoint trials, there were several uncertainties in the reliability of surrogate markers, which prevented their usage in regulatory approval of new treatments, as a replacement for clinical endpoint trials. It was not known whether the changes in surrogate markers, such as CD4 count and HIV RNA, would explain a high proportion of the benefit of treatment, or whether there could be other unknown mechanisms underlying the clinical benefit of antiretroviral treatment. A surrogate marker effect observed for treatment using one class of antiretroviral treatment (for example an NRTI) might not translate into the same clinical benefit for a different class of antiretroviral treatment (for example a protease inhibitor). Finally the drugs approved on the basis of clinical endpoint trials had all caused serious or life-threatening toxicities. It was not known whether the potential harm caused by new treatments, from drug toxicity, could outweigh their beneficial effects, as observed in the changes in surrogate markers.

Proof of the reliability of HIV viral load and CD4 counts as surrogate markers of the clinical benefit of antiretrovirals required several stages of validation (Hughes 1995):

1. Baseline levels of the markers were correlated with the risk of clinical progression (Chapter 5).
2. Changes in the markers occurring during treatment were predictive of clinical progression.
3. When controlled for baseline levels, the changes in the markers during treatment explained the majority of the clinical benefit observed for a treatment (given that the treatment did show a clinical benefit in a randomised trial) (Chapters 6, 7).
4. Clinical trials with a greater clinical benefit for a treatment also showed a more beneficial effect on HIV viral load and CD4 cell count (Chapter 8), to ensure that the utility of the surrogate markers was consistent across different drugs and drug classes.

Once these stages of surrogate marker validation were considered by regulatory authorities to be complete (Murray 1997), the regulations on approval of HIV treatments were changed. Subsequent treatments were approved based on their effects on HIV RNA and CD4 count alone (nelfinavir,
delavirdine, efavirenz, amprenavir, lopinavir, tenofovir, enfuvirtide) together with a need for long-term evaluation of toxicity.

Given the lack of treatments for HIV that can eradicate the virus from the body, the prospect of lifelong treatment with antiretrovirals is likely. It is still unknown how the long-term benefits of these treatments, as measured by rises in CD4 count and reductions in HIV RNA, will contrast with harm from long-term toxicities of treatment. The clinical effects of some of these long-term toxicities could be predicted with other surrogate markers such as haemoglobin reductions (Walker 1998), elevations in lipids (Periard 1999) and abnormalities in liver enzymes (Gisolf 2000, Sulkowski 2000).

With the increasing usage of HIV RNA as the primary efficacy endpoint in HIV clinical trials, there was a need to standardise the methods used to analyse and report this endpoint. Until 1999, HIV RNA analyses were being presented at conferences and in publications using a variety of Intent to Treat and other analyses, and using various different lower limits of assay quantification to define undetectability of HIV RNA levels. This led to a potentially wide variety of estimates of the proportion of patients who would show reductions in HIV RNA to undetectable levels during a clinical trial, depending on the set of assumptions and methods used. Suggested standards for reporting and presentation of HIV RNA data from clinical trials are discussed in Chapter 9.

A subsequent candidate measure to predict drug efficacy is the ratio of a drug's minimum plasma concentration divided by its inhibitory concentration (Inhibitory Quotient). The hypothesis was that drug treatments with the greatest mean plasma drug concentration, relative to inhibitory drug concentration, would be expected to provide the greatest clinical efficacy. However, as with analyses of HIV RNA levels, there are many different techniques to define this ratio or “Inhibitory Quotient”. Standardised methods of calculating the quotient have not been defined and this quotient is therefore highly variable depending on the set of assumptions used. The problems associated with interpreting this measure are discussed in Chapter 10.

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