The use of surrogate markers in the antiretroviral treatment of HIV-1 infection
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CHAPTER 11

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Clinical Endpoint Trials

It was feasible to conduct clinical endpoint trials such as the Concorde, Delta, and CAESAR in the late 1980’s and early 1990’s because of two main factors, both of which no longer apply.

First, since surrogate markers of HIV disease progression had not been validated, it was still considered ethical to randomise patients to a control arm with an inferior effect on CD4 count and HIV RNA and follow patients up to detect long term effects on clinical endpoints. Now that these surrogate markers have been validated, this type of design would no longer be considered ethical for evaluation of antiretrovirals, since the control group would then suffer an unacceptably high risk of clinical progression. Already in the late 1980’s the power of clinical endpoint trials was being eroded by patients attempting to unblind themselves to treatment and to switch onto the treatment with greatest effects on surrogate markers. The power calculations for the CAESAR trial were made by computer simulation, assuming that 15% of patients would switch from control arm onto active treatment during the course of the trial – this led to a large sample size – 1900 patients overall – to provide adequate power to detect a difference in clinical progression rates of 50% between the treatment arms. Other design features were included in the CAESAR trial, such as unequal randomisation (only 25% of patients did not receive 3TC), a fixed period of 1 year of randomised treatment followed by open label access to 3TC for all patients, and use of an experimental NNRTI, loviride, in 25% of patients (CAESAR 1996).

Second, the treatments under evaluation until the mid-1990’s showed relatively poor efficacy; incomplete and transient suppression of HIV RNA levels was observed for NRTI monotherapy or dual NRTI therapy, with relatively small rises in CD4 counts (Staszewski 1996). The rates of clinical progression to AIDS and AIDS related deaths during treatment with these regimens still exceeded background rates of non-HIV-related morbidity and mortality. For example in the CAESAR trial the rate of progression to AIDS and death during 10 months was 20% in the control arm and 10% in the 3TC arm. However, with modern HAART regimens where the majority of patients show reductions in HIV-1 RNA to undetectable levels and concomitant rises in CD4 count, differences in rates of clinical HIV disease progression between treatment arms would likely be much smaller (especially when comparing HAART regimens with similar effects on HIV RNA and CD4 counts), requiring far larger sample sizes and longer follow up times. For example in the ACTG 320 trial of AZT/3TC/indinavir the one year rate of progression to AIDS and death was 5% (Hammer 1998).

In the current climate, it would be necessary to evaluate head-to-head two treatments with similar effects on HIV RNA and CD4 counts, both of which may be unlikely to lead to significant rates of HIV-related clinical events. The contribution of non-HIV treatment related endpoints such as liver failure from Hepatitis B or C co-infection, cardiovascular events, or other non-HIV related deaths may now tend to make treatment arms more similar – this is also called the “equivalence by default” situation, where two treatment arms are considered to be equally efficacious simply because of a high rate of non-treatment related endpoints occurring in both treatment groups. One potential application of a clinical endpoint analysis would be during the introduction of a new treatment class to salvage patients in controlled trials. For example the fusion inhibitor T-20 is being evaluated versus no fusion inhibitor in randomised trials of triple class experienced patients. There is the potential to collect and analyse rates of clinical progression for those receiving and not receiving T-20 in these protocols.

One technique used to increase power to detect treatment effects for rare endpoints is meta-analysis. Pooled analysis of the effects of 3TC treatment on clinical progression was conducted for four surrogate marker trials of 3TC treatment (Staszewski 1997), for trials of early versus deferred zidovudine (HIV Trialists Collaborative Group 2000), and for trials of dual nucleoside treatment versus nucleoside monotherapy (HIV Trialists Collaborative Group 2000). Such meta-analyses
provide more precise estimates of treatment effects than individual trials, and also prevent misinterpretation of isolated results from individual clinical trials. For example the large size of the initial survival benefit of zidovudine monotherapy versus placebo in the BW002 trial, and the apparent effect of early zidovudine usage on higher mortality in the Concorde trial – were both shown to be outliers when results from all trials were combined in meta-analysis (HIV Trialists Collaborative Group 2000).

Clinical endpoint trials may still be of use for new HIV treatments whose efficacy has not been validated with the conventional surrogate markers, or for evaluation of the long-term toxicity of antiretroviral treatment. For example interleukin-2 (IL-2) causes stimulation of the immune system with rises in CD4 count, but no effects on HIV RNA levels (Emery 2000). It is not clear whether this rise in CD4 count has the same protective effect on HIV disease progression as rises seen during antiretroviral treatment – the ESPRIT trial, currently enrolling, is examining the effects of IL-2 versus control treatment on rates of clinical disease progression. Secondly, the effects of antiretrovirals on CD4 counts or HIV RNA are unlikely to explain treatment effects on serious toxicities, such as hypersensitivity, lactic acidosis and pancreatitis. Clinical endpoint trials of long-term treatment are required to determine whether the benefit of treatment in reducing progression to AIDS and death continues to outweigh the potential risk of treatment in causing serious life-threatening toxicities. The recently initiated SMART trial is evaluating this cost-benefit issue, randomising patients to early versus delayed initiation of HAART with a planned 6 year follow up.

Use of surrogate markers in dosage selection
In 1991-2, when the dose ranging trials of 3TC were conducted, it was not clear which markers were most closely linked with treatment effects on clinical progression. Therefore a variety of markers was analysed, including CD4 count, beta-2-microglobulin, neopterin, anti-CD3 antibodies, p24 antigen, ICD p24 antigen, HIV RNA and cellular viraemia.

In typical Phase I/II development of an antiviral drug, a range of dosages are evaluated for antiviral potency and safety, and the dosage with maximal efficacy but below the threshold level correlated with toxicity is chosen for future development. This dosage is referred to as the “maximum tolerated dosage”. This is in contrast to the “minimal effective dose” which may provide equivalent efficacy to the maximum tolerated dosage but with a lesser potential to produce long-term toxicity.

For correlations to be established between levels of any surrogate marker and the dosage of a treatment in Phase I/II trials, two issues are critical: (i) the range of dosages used in the trials need to cover the limits of the drug’s therapeutic window, and (ii) the patients treated with different drug dosages need to be well balanced for baseline characteristics. For the development of 3TC, a drug with a wide therapeutic window, a range of dosages was investigated but the second condition was not met, making selection of a dosage for future development problematic.

The two Phase I/II dose ranging trials were non-randomised - patients were enrolled into dosage cohorts at successively higher dosages with the aim of identifying a minimally effective and a maximally tolerated dosage (Van Leeuwen 1995, Pluda 1995).

Analysis of both trials showed few consistent correlations between the dosage of 3TC received and changes in surrogate markers, including the rate of development of the M184V mutation (Schuurman 1995). Analysis of virological markers showed a significantly greater reduction in cellular viraemia for those treated with higher dosages of 3TC (Ingrand 1996), but these trends were observed only for subsets of patients in the trial, and were not consistent for analysis of p24 antigen across all patients in the two dose ranging trials. Baseline characteristics of the successive dosage cohorts differed and it was difficult to determine whether differences in response between the dosage cohorts were caused by differences in baseline characteristics, the efficacy of the drug at new dosages or differences in the emergence of resistance. For example, it is known that baseline levels of HIV RNA are predictive of
the likelihood of sustained HIV RNA suppression during NRTI treatment (Opravil 1997), yet there was a range of the baseline levels of viral load between the dosage cohorts in the two 3TC trials.

When three randomised trials of 3TC were conducted to compare the efficacy and safety of 3TC 300 mg twice daily versus 150 mg twice daily, comparable efficacy (measured by clinical endpoints and surrogate markers) was observed at the two dosage levels, suggesting that a plateau of efficacy had already been achieved and that the minimally effective dosage may be lower (Staszewski 1996, Staszewski 1997, Eron 1995, Bartlett 1996). New dose ranging trials of 3TC may find that dosages lower than the 150 mg twice daily may provide equivalent efficacy. Such dose reductions would lower costs of treatment in resource poor countries (Hill 2001). Analysis of the concentration of 3TC triphosphate – the active metabolite of 3TC – showed a significant correlation with efficacy for patients treated at 150mg bid (Fletcher 2000), however this analysis was restricted to only 7 patients, and it is not clear whether adherence to treatment or between patient variability in drug metabolism explained part of this correlation. A comparison of the intracellular pharmacokinetics of 3TC dosed at 150mg BID and 300mg BID also showed high interpatient variability, and showed no significant difference in triphosphate concentrations between the two dosages (Moore 1999).

Difficulties in dosage selection have also been found for other antiretrovirals, with a similar plateau effect characterised after initial drug approval. The initially approved dosage of zidovudine – 1200 mg per day (200 mg every four hours) was later reduced to 500-600 mg per day (250-300 mg twice daily) based on a large dose ranging study conducted after drug approval (Nordic MRC 1992), which showed similar efficacy of lower dosages of zidovudine, but with a better toxicity profile. Similarly the two dosages of the new protease inhibitor atazanavir (400 mg once daily and 600 mg once daily) have similar efficacy, but with a trend for greater symptomatic hyperbilirubinaemia at the higher dosage (Cahn P 2001).

Boosting of PI drug levels was initially conducted using a dosage of ritonavir of 400 mg twice daily (Katzenstein 2000); subsequent trials have shown that dosages of 50-100 mg ritonavir once or twice daily is sufficient for this boosting effect (Veldkamp 2001, Kurowski 2001). Lower ritonavir dosages have the advantage of lower toxicity as well as lower costs (Buss 2001).

Randomised trials comparing different dosages of an antiretroviral are likely to provide a more accurate determination of dosage than the non-randomised dose escalation design used for 3TC and other nucleosides, because it is more likely that baseline characteristics of patients receiving different drug dosages will be more balanced. Randomised dose ranging trials have been conducted for the new protease inhibitors atazanavir (Cahn 2000) and lopinavir/r (Murphy 2001).

Validation of surrogate markers

Of the range of surrogate markers used in the early 1990’s, only two have passed the various tests of surrogacy required to be used in regulatory approval of new treatments as a substitute for clinical endpoint trials. Five key stages of analysis were required in order to prove this surrogacy:

1. Baseline levels of the surrogate markers predict progression to AIDS/death in natural history studies.

This criterion was passed for many potential surrogate markers, in the late 1980’s and 1990’s. High rates of progression to AIDS and death were associated with abnormal levels of neopterin, beta-2-microglobulin, p24 antigenaemia, HIV RNA, SI phenotype, low CD4 count, higher age and clinical symptoms such as oral candidiasis and oral hairy leucoplaikia (Lange 1989, Moss 1988, Spijkerman 1998). Multivariate analyses of these databases provided various combinations of markers most closely associated with progression. The choice of a more restricted set of markers to use in subsequent trials was guided by two factors: (i) the ease of measurement and standardisation in interpretation of the markers, and (ii) robustness of the correlation between markers and progression across cohort studies. By the mid 1990’s, a variety of cohorts and clinical trials had shown consistent correlations between low CD4 count, high HIV RNA levels and progression to AIDS or death (de

2. Changes in the marker during treatment predict progression to AIDS/death.
There are certain markers that HIV treatment may not affect and therefore which could not qualify as surrogate markers of treatment effect, despite being strong markers of HIV disease progression. For example, not all HIV treatments affect SI phenotype or haemoglobin levels; clearly none could affect age or HLA haplotype, all of which had been established as prognostic markers.

Studies of HIV clinical trials established that patients with the greatest rises in CD4 count and reductions in HIV RNA during treatment had the greatest reduction in the subsequent risk of progression to AIDS or death (Fiscus 1998, Staszewski 1998).

3. Surrogate markers need to be measured in clinical trials of a treatment that has a significant effect on progression to AIDS or death.
This is a necessary pre-condition for the validation of surrogate markers in any disease. In order to characterise the predictive value of a surrogate, a clinical trial needs to have shown a significant reduction in clinical disease progression, which can then be correlated to changes in the surrogate markers to evaluate their predictive power (Hughes 1995). The treatment effects in early clinical trials of antiretrovirals had been relatively small, making analysis by the Prentice Criteria difficult.

4. The “Prentice criterion”
This was a condition claimed to be critical to establish the surrogacy of a candidate marker. This condition states that, when adjusted for pre-treatment levels, the changes in the markers during treatment are able reliably to predict the actual clinical benefits of the treatment (Fleming 1994).

The Veteran Affairs study showed a clinical benefit to early versus deferred zidovudine monotherapy (Hartigan 1992). By application of the Prentice criteria to this trial, it was determined that a high percentage of this benefit could be “explained” by rises in CD4 count and reductions in HIV RNA during the early phase of the trial (O’Brien 1996). This analysis has since been criticised by others both in terms of methodology and application of the same methods to other trials. In terms of methodology, the Prentice criteria calculation has the potential to produce a percentage of treatment effect explained (PTE) of over 100%, or a negative number, both of which are counterintuitive. Also the confidence intervals on the PTE can range from zero to over 100%, so in cases such as the Veteran Affairs trial, it is not possible to exclude the possibility that the surrogates explain none of the clinical benefits of treatment (Hughes 1995).

When the Prentice Criteria were applied to the CAESAR trial, the PTE was also high (Montaner 1998). A similar analysis was applied to clinical data from two North American trials of ZDV/3TC treatment, with similar results (Phillips 1997). However given that the median follow up time these trials was short, it is not clear the extent to which the surrogate marker changes are explaining a concurrent clinical benefit, versus predicting a clinical benefit occurring subsequent to the marker changes.

The Prentice Criteria were also applied to the MRC/INSERM Delta trial, which compared the clinical efficacy of treatment with ZDV/ddI, ZDV/ddC and ZDV monotherapy – in this case, the clinical benefits predicted from early changes in the HIV RNA and CD4 counts were divergent from the actual clinical benefits observed (Delta Co-ordinating Committee and Virology Group 1999).

An additional problem with the Prentice Criterion was the selection of a subset of clinical trials with significant effects of treatment on clinical progression for validation of surrogate markers. It was claimed that analysis of the entire set of clinical trials of a treatment, including those without such clinical benefits, would provide a more representative conclusion over surrogacy (Hughes 1995).
5. The “Hughes criterion”.
Given the potential methodological limitations of the Prentice Criterion above, an additional test of surrogacy was devised by Michael Hughes at the Harvard School of Public Health. This criterion was that, across a range of treatments, there is a correlation between surrogate marker benefits and clinical benefits of treatment – i.e. those treatments with the greatest improvement in surrogate markers also show the greatest reductions in progression to AIDS/death.

This technique was applied to clinical trials using summary measures of surrogate marker and clinical effects (Hill 1998) and later using raw data, albeit on a more limited set of clinical trials (HIV Surrogate Marker Collaborative Group 2000). Both analyses showed a correspondence between the effects of treatment on CD4 and HIV RNA and their effects on clinical progression, but the results did not reach statistical significance in all analyses.

Overall the analysis of CD4 count and HIV RNA has not completely passed all the criteria for validation of surrogate markers. However the correlations observed between surrogate marker and clinical effects have been sufficiently strong, and the difficulties of running clinical endpoint trials sufficiently great, for a pragmatic decision from regulatory authorities to adopt these markers as the basis for full approval of new antiretrovirals.

It is possible for a treatment to lower rates of progression to AIDS but also to cause significant mortality through drug toxicity – in such cases the surrogate markers may again be incomplete in their prediction of overall clinical benefits (Machado 1990). Ongoing surveillance is required to determine whether long-term toxicities of HIV treatment which may to some extent counterbalance the early clinical benefits predicted from rises in CD4 count and reductions in HIV RNA levels.

The future – the need for standardisation in analysis of HIV surrogate markers.
Now that HIV RNA and CD4 count are accepted as the primary markers of antiretroviral treatment effect, there is a need for standardised techniques of analysis and interpretation of clinical trials data involving the two markers. After calls for such standardisation in the late 1990’s, HIV RNA data from clinical trials is now typically presented with an Intent to Treat analysis, with a description of how missing data is classified (AVANTI Steering Committee 1999). However there are still differences in how data are presented. In particular the two key areas with greatest differences between trial presentations are:

1. **Inclusion of randomised patients who never received trial medication.**
The validity of statistical tests for differences in treatment arms relies on the assumption that the patients were allocated into the treatment groups in a truly random fashion – any bias in this allocation – either from clinicians or patients, who may favour one treatment over another – can invalidate the assumptions of these tests.

In clinical trials, there can be patients who are allocated a particular treatment at randomisation and then decide not to receive this treatment at the baseline visit. If these patients were less likely to respond to this treatment, then this may lead to a “selection bias” effect and the random allocation of patients is no longer maintained. There are two approaches to assessing these patients in ITT analyses:

- **“ITT all” analysis** – all randomised patients are included, whether or not they received a single dose of randomised treatment. Patients who were randomised but did not receive randomised treatment are automatically classified as treatment failures in the analysis. The advantage of this analysis is that it does not violate the rule of random allocation of patients to treatment groups. However the disadvantage is that, with patients who never received treatment being classified as treatment failures, conservative estimates of treatment efficacy can be obtained.

- **“ITT exposed” analysis** – only those patients who were randomised and received at least one dose of trial medication are included. Patients who were randomised but did not receive trial
medication are excluded from the ITT analysis. This analysis may allow the entry of selection bias to the trial, if either the clinician or patient is aware of the treatment they had been randomised to prior to treatment initiation. However, in some cases, patients are lost to follow up after randomisation with no knowledge of their treatment allocation. The advantage of this analysis is the benefit of assessing efficacy and safety of a treatment for patients who had all received this treatment.

The choice of “ITT all” versus “ITT exposed” analysis makes little difference to the conclusions made from a clinical trial if the number of patients randomised but never treated is small and evenly balanced between treatment arms.

However, recently two clinical trials of were conducted where patients were randomised to either continued protease inhibitor treatment or a switch to efavirenz. In these trials, more patients randomised to the PI arm than the efavirenz arm never initiated treatment (Katlama 2001). All patients who never initiated treatment were excluded from the final ITT analysis, since inclusion of the never treated patients would have potentially biased the trial against the continued PI arm. In the MaxCmin 1 trial there were 10/158 patients in the saquinavir arm and 1/159 patients in the indinavir arm who were randomised but never treated (Dragsted 2001). The ITT analysis was conducted using both the “ITT all” and “ITT exposed” approaches. In this trial, four of the ten patients randomised but never treated with saquinavir had been unaware of the treatment arm allocated when lost to follow up.

2. **Inclusion of patients who switch from their randomised medication to a salvage treatment.**

There are two schools of thought in the interpretation of Intent to Treat analysis for patients discontinuing randomised treatment:

- **regulatory (“switch equals failure”) approach** – for regulatory authorities granting marketing approvals to new treatments based on clinical trials data, the key issue is the intrinsic potency and tolerability of this particular treatment in the trial. Those who discontinue their randomised treatment for any reason (virological failure, toxicity, non-adherence) the product labels for the treatments have typically classified these patients as treatment failures, regardless of the outcome of subsequent second-line or salvage treatments. Classifying discontinuations as treatment failures has also been termed “switch equals failure”, “ITTd” or “non-completer equals failure” analysis.

- **treatment strategy (“switch included”) approach** – for clinical trials where patients are randomised to an initial treatment but with pre-defined second-line treatments available, the measure of interest may be the success of the overall sequence of treatments received, rather than the success of the initial randomised treatment considered in isolation. For example in the MRC/INSERM Initio trial, patients are randomised to one of three sequences of 2 treatments and a pre-defined salvage option – the primary protocol endpoint is the virological suppression achieved by following each of the different sequences of treatment. Analyses which examine the overall outcome of a sequence of treatments are often termed “Intent to Treat – switch included”.

Since the two analytical approaches are attempting to answer different questions, both have validity in different situations.

One issue with the “switch equals failure” approach is that it may not well characterise the potency of a treatment, because many of the treatment failure endpoints could be the result of loss to follow up or withdrawal owing to toxicity, with relatively few true virological endpoints. This was observed in the CNA3005 trial of ZDV/3TC/Abacavir versus ZDV/3TC/indinavir, which had a high rate of withdrawal from randomised medication in both treatment arms (Staszewski 2001). In the Intent to Treat analysis with “switch equals failure, the two treatment arms were found to be equivalent. However in As Treated analysis including only virological failure, the indinavir arm was associated with a higher proportion of patients achieving HIV RNA undetectability (Staszewski 2001). Therefore
an As Treated analysis is necessary to provide supplementary information on potency, to combine with the ITT results which combine potency and tolerability of a treatment.

Conclusions from clinical trials analysed using the “switch included” approach need to be described carefully in terms of the salvage options included in the trial design. Two treatments may appear equivalent in this type of analysis even when one strategy has led to a higher rate of usage of salvage treatments. This was found in the BEST trial, where the proportion of patients with HIV RNA < 400 copies/ml at 48 weeks was similar between the two arms in the ITT-switch included analysis (87% for indinavir 800 mg TID versus 85% for indinavir/r 800/100 mg BID) even though significantly more patients discontinued the initial randomised treatment in one arm – the success of these patients on subsequent salvage treatments led to the two arms giving similar results in the ITT switch included analysis. The result from the ITT non-completer equals failure analysis showed a significant benefit of indinavir 800 mg TID versus indinavir/r 800/100 mg bid (74 versus 57%, p=0.001) (Gerstoft 2001).

Other potential surrogate markers
It may be that other markers of treatment effect are incorporated into routine clinical practice in the future. Two new markers - the lymphocyte subtype CD8+CD38+, and HIV DNA level - have both been correlated with clinical progression independently from the CD4 count and HIV RNA in cohort studies (Liu 1998, REF). In addition, the presence of active co-infection with the flavivirus GBV-C, as measured by GBV-C RNA – is strongly associated with improved survival and lower rates of progression to AIDS in cohort studies (Tillmann 2001, Xiang 2001). New analyses, involving cohorts where several markers have been measured on the same patients, are required to determine whether the apparently beneficial effect of this co-infection can be explained by effects on CD4 count and HIV RNA.

Other cohort studies have found that haemoglobin is a strong, independent predictor of survival during HAART treatment (Mocroft 1999, Chene 1997). However it is unclear whether this correlation reflects the effects of underlying HIV disease rather than the potential effects of treatment for HIV. If haemoglobin were reliable as a surrogate marker this would suggest that a treatment such as zidovudine, or zidovudine-lamivudine, which cause reductions in haemoglobin levels (Hester 1998, Tseng 1998), would therefore increase mortality, and that a treatment such as erythropoietin could improve survival by increasing haemoglobin levels. These possibilities would need to be investigated using the same techniques used to establish HIV RNA and CD4 count as surrogate markers. This type of analysis would need to be conducted for large clinical trials with long-term follow up, comparing HAART regimens which had different effects on anaemia.

Inhibitory quotient
Intuitively, one would expect that the plasma levels of a drug need to be above those required to inhibit viral replication, and that drugs with plasma levels several multiples higher than inhibitory levels would provide the most reliable long-term viral suppression. However further analysis of this issue revealed large uncertainties in the components of inhibitory quotient. There is a high variability and lack of standardisation for estimates of inhibitory drug concentrations, trough plasma levels, and adjustments of these levels for binding of active drug to plasma proteins or intracellular accumulation (Montaner 2001). So given that the inhibitory quotient is a product of three highly variable parameters, it is unlikely that this measure will reliably predict differences in potency between treatments in the absence of randomised clinical trials. Indeed a prediction was made by Condra and colleagues, from one set of calculated values of inhibitory quotient, that indinavir, boosted by ritonavir, would have superior efficacy to saquinavir boosted by ritonavir (Condra 2000). However the 24-week analysis of a randomised head-to-head clinical trial of indinavir/r versus saquinavir/r in 306 treated patients showed no significant differences in virological failure between the two treatment arms (Dragsted 2001).

Inhibitory quotient is therefore not a reliable surrogate marker, like HIV RNA or CD4, for predicting the relative efficacy of different treatments. There may be a limited benefit of inhibitory quotient for assessing responses to individual treatments, if validated within large clinical trials.
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