Surrogate markers now provide physicians with the best means to manage antiretroviral therapy: The case for Graeme J Moyle, Brian G Gazzard

Introduction Disillusionment with the current trial methodology used to evaluate antiretroviral agents is growing among both physicians and patients. In the first 10 years of antiretroviral drug development there was a need to test treatment tactics, strategies, and available treatment markers against clinical endpoints. It has now been convincingly demonstrated that antiretroviral combination therapy prolongs life and extends the disease free period\(^\text{11-13}\) and that most benefits of these therapies are predicted by short term changes in two laboratory markers: CD4 cell count and plasma HIV RNA load.\(^\text{5,7}\) Improvements in our understanding of the pathogenesis of HIV disease and viral dynamics\(^\text{8}\) have provided both patients and physicians with a greater understanding of the tools used to monitor HIV and have enabled the establishment of a new path to our therapy goals. To provide maximal improvement in patient outcome (both length and quality of life) we must arrest the disease process, by blocking viral replication, and improve immune function, by enabling re-expansion of lost T lymphocyte populations. The availability of more potent antiretroviral combinations and of routine viral load measurement has enabled the establishment of an “undetectable” viral load as the optimum response to treatment. This response is typically associated with substantial delays in the selection of drug resistant viral mutants and, hence, is associated with more prolonged therapeutic responses than those observed with less complete suppression of viral replication. Measurement of CD4 and HIV RNA provides physicians with the opportunity to optimise the management of antiretroviral therapy.

Activity markers, disease markers, surrogate markers An ideal surrogate marker must be biologically plausible, easily and reproducibly measurable, and changes in that marker both on and before therapy must accurately predict outcome.\(^\text{9,10}\) No single marker of HIV activity represents a perfect surrogate. However, combined use of CD4 and viral load measurement both on and off treatment provides a quality predictive indicator.

Viral load after seroconversion\(^\text{11-13}\) is a powerful predictor of both future disease progression and death\(^\text{11}\) as well as of non-progression.\(^\text{12,13}\) In the circumstances of a CD4 cell count above 500 × 10\(^{9}/\text{L}\), the CD4 cell count appears to provide no additional predictive value. A high viral load, therefore, implies increased risk of disease progression or death and suggests the need for consideration of treatment intervention.

CD4 represents an excellent staging marker for HIV, telling us if a patient is at immediate risk of an event, be it an opportunistic infection (OD)\(^\text{14,15}\) or death.\(^\text{16,17}\) It is therefore of considerable value in decisions to commence prophylaxis for some OIs such as *Pneumocystis carinii* pneumonia (PCP).\(^\text{18}\)

Indeed, the widespread use of prophylaxis for a range of OIs has helped make clinical trials which make use of clinical events (other than death alone) difficult to interpret. The problems with using clinical events as trial endpoints have been elegantly described and require no further comment.\(^\text{9}\) Clinical events, however, remain a good marker of quality of life. Waiting for a patient to deteriorate clinically before starting treatment or changing a failing therapy is out of step with other areas of medical practice. We do not wait for a stroke in a hypertensive patient before intervening to reduce blood pressure. Nor do we wait for respiratory failure to occur in an asthmatic before intervening, but use oxygen and carbon dioxide levels as markers for the need for intervention. Even the most conservative physician would accept that viral load and CD4 can predict risk of clinical events. It is therefore reasonable to intervene before this inevitability.

CD4 has been used for the past 10 years as the guide to commencing antiretroviral therapy; based on the logic that consistent declines in CD4 are associated with disease progression or death; therefore, we should intervene to prevent or delay the onset of disease events. Interpretation of CD4 should now be made in the context of viral load measurement, but remains a valuable tool in guiding the initiation of therapy.

However, as an on-therapy surrogate marker, short term changes in CD4 are, at best, limited as an individual marker, predicting 50% or less of a treatment effect.\(^\text{7,20,21}\) This is not surprising given that antiretroviral therapy may influence both trafficking and function of CD4 and other immunological cells,\(^\text{22,23}\) information not captured by enumeration from a blood sample. Measurement of CD4 alone is, therefore, not adequate for monitoring a therapeutic response.

Plasma viral RNA load represents the best single on therapy marker currently available. This is biologically plausible, given that it is active HIV replication which drives CD4 depletion and ultimately disease progression.
Furthermore, the viral load measured in a plasma sample is largely derived from a lymphoid replication where 99% of daily viral turnover occurs.\textsuperscript{2,3} Although not necessarily correlating with viral load in all body compartments,\textsuperscript{4} an issue which may be critical to failure on initially effective regimens, changes in plasma viral load with therapy correlate well with changes observed from lymph node samples.\textsuperscript{5} As an individual marker a decrease of 75% in plasma viral load predicts 59% of the treatment effect of zidovudine during the first 6 months of therapy.\textsuperscript{6} Responses of 0·25 log or more with didanosine therapy are associated with improved survival relative to non-responders.\textsuperscript{7} A 0·3 log decrease correlates with a 27% reduction in the relative hazard of disease progression,\textsuperscript{8} and a 0·5 log decrease with a 63% reduction.\textsuperscript{9} In the AIDS clinical trials group study number 175 (ACTG 175), which included both patients receiving nucleoside analogue combination and monotherapy, a decrease of 1·0 log at week 8 correlated with a 65% reduction in risk or disease progression and at week 56 with a 90% reduction in risk.\textsuperscript{10} Similarly, during combination therapy with zidovudine and lamivudine, each 1·0 log change in viral load on therapy was associated with a threefold (adjusted) reduction in risk of disease progression to AIDS.\textsuperscript{11} Measurement of plasma viral RNA load can, therefore, be used as a marker of treatment effect and is now universally accepted to be essential in patient monitoring.\textsuperscript{12}

Two disease markers make a complete surrogate marker and optimise management

Plasma viral RNA load can be seen as analogous to the speed of a vehicle moving towards a destination; only when we know the distance from the destination can we estimate the arrival time. The CD4 cell count is the measure of distance. It is not surprising, therefore, that together they represent an excellent surrogate marker and guide to monitoring patients. O'Brien et al found that a 75% decrease in plasma HIV RNA with a 10% increase in CD4 count explained 79% of treatment effect, with no additional benefit from measurement of β-2 microglobulin or treatment assignment.\textsuperscript{13} Similarly, Phillips et al\textsuperscript{14} found a 1·0 log change in viral RNA with a twofold difference in CD4 cell count provided the best on-therapy predictive value for risk of progression to AIDS during zidovudine/lamivudine. This interaction was not reported in ACTG 175.\textsuperscript{15} Both CD4 and plasma HIV RNA load are continuous variables which require interpretation in the clinical context and with appreciation of the limits of both intra- and interpatient variability. Both are affected by OIs and certainly viral load may rise transiently following vaccination.\textsuperscript{16,17} Viral load does not provide full information about viral pathogenicity or resistance to antiretrovirals. Similarly, CD4 cell count does not provide full information regarding immune function. However, together they provide physicians with the best means to manage therapy with the currently available antiretroviral agents. It remains uncertain whether their validity is fully maintained in the presence of immunomodulators such as interleukin 2.

Markers and management

Use of CD4 and viral load enables optimisation of management. A viral disease is ideally managed by control of that virus. An infection which results in destruction of key cells in the immune system requires assessment of the extent of damage. The role of antiretroviral therapy is to prevent clinical disease and death and to maintain quality of life; using clinical disease to monitor patients is shutting the gate after the horse has bolted. With wise use and interpretation of the available markers, CD4 lymphocyte count and plasma HIV RNA load, physicians can now optimise the use of the potent new therapies to achieve lasting improvement for our patients.

3 DELTA Co-ordinating Committee. DELTA: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine or zidovudine alone in HIV infected individuals. Lancet 1996;348:283–91.
5 Katlama C, on behalf of the CAESAR co-ordinating committee. Clinical and survival benefit of 3TC in combination with zidovudine-containing regimens in HIV-1 infection: interim results of the CAESAR study. 3rd International Congress on Drug Therapy in HIV infection. Birmingham, November 1996; abstract SSZ-1.
Viral load—not yet the holy grail

Tim Peto

Introduction
There are now nine effective antiviral drugs generally available and their numbers are rapidly increasing. The number of different drug combinations is rising even more rapidly. For example, with only the nine drugs there are 36 two drug and 84 three drug combinations available. With the possibility of switching from one combination to a second combination, patients face the bewildering possibility of over 10 000 different regimens even before a second switch of combination is considered.

The advantages of viral load testing
This therapeutic uncertainty means that the clinician is turning to the virologist for help and the recent development of quantitative tests for measurement of circulating plasma HIV RNA (qRNA) appears to offer many advantages. The test has been shown to be repeatable within 0·3 log units as long as the blood sample is processed rapidly or stored at −70°C. Retrospective studies have shown that qRNA appears to be a good prognostic marker, especially in patients with high CD4 counts, and also appears to give a good indication for perinatal infectivity. Patients have a large range of results from < 5000 copies to over 1 000 000 copies. Because of the inaccuracies of the technique, it is preferable to refer to log units (for the values above the log unit equivalents are < 3·3 to > 6). The DELTA study, coordinated by the Medical Research Council, is looking at about 13 000 viral load tests and CD4 counts in about 2000 patients and will relate the results to clinical event rates. It is tempting to assume that CD4 counts will be a good marker of the degree of disease progression while the level of qRNA will be associated with the disease activity and therefore future disease progression.

qRNA has also been used to monitor short term changes in viral load following drug treatment. Zidovudine reduces plasma viral load RNA by about 0·3 log units and two drug combinations of reverse transcriptase inhibitors reduce viral load by up to 1·8 log units. However, the largest changes have been seen in triple therapy regimens which include HIV protease inhibitors. These combinations reduce qRNA by about 2·0 log units and in some cases qRNA fails to fall below the "limit of detection" which ranges from 1 000 copies (4·0 log units) to 20 copies (1·3 log units), according to the assay. The present enthusiasm for protease inhibitors depends much on the dramatic effect that these drugs have on the viral load.
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