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For debate

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,^{1,2} 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,³ 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 falls to below the "limit of detection", which ranges from 10 000 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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Problems with the interpretation of viral load

How then, should we interpret these changes? Unfortunately, we have little data to help us. Retrospective surveys show that qRNA is a good prognostic marker. However, any drug or treatment induced changes in prognostic markers should *not* be used to infer that these changes will be translated into clinical efficacy. The experience from other medical conditions (for instance, cardiac disease, cancer, osteoporosis) has shown that the use of surrogate markers can often give misleading and even frankly wrong conclusions. Our experience from HIV to date is no better. It appears from preliminary virological results from the DELTA and Concorde trials that, like CD4 count changes, small reductions (about 0.3 log units) in qRNA are not translated into clinical benefit while somewhat larger but transient falls (1.8 log units peaking at 8 weeks and falling back to baseline within 96 weeks) are related to clinical benefit lasting for more than 2 to 3 years. The larger falls in viral load seen with the protease inhibitors are related to larger rises (about $100 \times 10^6/l$) in CD4 counts and anecdotal accounts of patient reported increases in "wellbeing". However, the duration of these benefits is not yet known nor has the effect on survival been shown to be appreciably better than that caused by the combination of zidovudine and didanosine.

The case for qRNA as a prognostic marker is therefore essentially based on its advantages as a prognostic marker, its pathophysiological attractiveness, and on the large changes in plasma viral load produced by the protease inhibitors which appear to be associated with large increases in CD4 counts. However, there are some major gaps in our knowledge which need to be filled before measurement of plasma viral load can be used reliably by clinicians. Some unanswered questions about the interpretation of viral load are discussed below.

ARE ALL HIV STRAINS DETECTED IN THE ASSAY?
Some viral types commonly found outside North America may not be reliably detected.⁴ It is also possible that one effect of treatment is to distort the assay either by creating avirulent virions which are still detected by the assay or virulent virions which escape detection.

IS CIRCULATING VIRAL LOAD IDENTICAL WITH DISEASE ACTIVITY?

The pathophysiological basis for "disease activity" is still unknown. Although there is evidence that circulating viral load is correlated with disease activity, it is equally possible that viruses replicating in fixed tissues is the key driving force of the disease and can only be assayed by relevant tissues biopsies.⁵

CAN WE INTERPRET STEADY STATE VIRAL LOAD LEVELS FOR INDIVIDUALS?

Most of the data available are correlating groups of viral load results with outcomes.^{1,2,6} Much more detailed cohort data are required from randomised clinical trials before reliable guidelines on "safe" or "dangerous" levels of

viral load can be established. It is unclear how many patients tolerate prolonged high viral loads well or how many progress early in spite of low viral loads. The interpretation of viral loads in conjunction with serial CD4 counts has not yet been fully evaluated.

WHAT IS THE RELATION BETWEEN VIRAL LOAD CHANGES AND CLINICAL BENEFIT?

Existing knowledge is based on the pooled data from clinical trials. The DELTA trial virology substudy suggests that the effect of only a transient fall in viral load can produce a much more lasting clinical benefit. However, before individual viral load changes can be reliably interpreted, much more information is needed from the serial viral load estimations of many thousands of patients over many years. It is possible that patients who fail to have a fall in viral load may still obtain a clinical benefit from the drug.

CAN WE MEASURE DRUG RESISTANCE?

At present there is no reliable assay for detecting clinical viral resistance. It is unclear whether a rising viral load (or falling CD4 count) in the face of continuing treatment represents true viral resistance to the drug or simply a drug induced change in the distribution of virions (or CD4 cells) within the patient.

Clinical role of viral load testing

Individual patient monitoring of viral load appears to be scientifically rational and is clinically attractive because it provides the clinician with an early indication of disease progression, drug response, and drug failure and therefore provides some form of order in an environment of therapeutic confusion. The effect of using viral load, rather than depending simply on clinical signs and CD4 counts, is to encourage clinicians to start antiviral treatment earlier and to switch combinations earlier. It is possible that some patients will run out of effective drug combinations before they develop symptomatic disease.

Unfortunately there is no evidence that the use of viral load testing improves clinical outcome. Although a reduction in viral load is associated with increased survival over several months, most patients starting on drug treatment expect to survive for much more than a few months. There is clinical uncertainty as to whether the early or late treatment of high viral load produces greater clinical benefit and survival over a period of at least 3 to 5 years. It would be an immense tragedy if the use of oversensitive viral load testing lured clinicians into squandering valuable anti-HIV drugs on otherwise clinically stable patients allowing them to develop drug resistance or alternatively switching patients away from clinically effective drug combinations simply because of a rising viral load.

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