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Cheap viral load test is urgently needed for resource-poor settings, say treatment advocates

Need for viral load testing should be revisited

"The question of whether high-quality, effective HIV care can be provided without viral load monitoring needs to be revisited," they say.

Regular viral load monitoring – perhaps no more than twice a year – may even be cost-effective in the long-term. This is not just because drug resistance on a population level will be minimised but because a failure to achieve undetectability can also indicate poor adherence as well as treatment failure. Detecting patients with adherence difficulties at an early stage can mean that interventions to improve adherence can be targeted at these individuals before they develop resistance and before they need to switch to a more expensive second-line regimen.

Calmy and colleagues highlight the success achieved by just such an approach at Khayelitsha in South Africa which, in 2001, became one of the first developing-world locations for an ARV treatment programme. In an update of the Khayelitsha programme presented at the Glasgow conference (Orrell), over 98% of 823 patients remained on a first-line regimen (any two of d4T, ddI, 3TC or AZT plus either nevirapine or efavirenz) after 32 months (patients who switched between first-line drugs due to side-effects were not classified as viral failures in this analysis). Although 20% of patients had at some time during the 32 months had a viral load over 1000 copies/ml, the number with viral loads over that figure at month 32 was exactly zero, though 14% did have a viral load over 50 copies/ml at this point.

This was achieved with intensive adherence support – and with six-monthly viral load testing. Patients were allocated a personal adherence peer counsellor and had to attend three treatment readiness group sessions before starting ARVs. When a patient showed clear virological failure – and 7.2% did at some point – their treatment was temporarily interrupted and they were given more counselling and attended refresher workshops. Fifty-three per cent of those with viral loads over 1000 copies/ml were re-suppressed to below 50 copies/ml, and none of remaining 47% had viral loads over 1000 copies/ml by month 32.

The frequency of viral load testing is crucial here: only 25% of patients who were left for more than six months without a viral load test and proved, upon testing, to have detectable viral load were able to re-suppress their HIV below 50 copies/ml compared with 71% of patients who had a viral load test within four months of their last one.

So, treatment can be done in a way which maximises the time on first-line therapy – but, in this case, by using viral load monitoring, which rather undermines Gilks's point.

Clinical markers show limited ability to replace viral load for treatment monitoring

Could the WHO's recommended algorithm achieve similar results? Not if a retrospective study of the usefulness of such indicators to

predict failure in US patients is anything to go by. Shashwatee Bagchi and colleagues from the University of Birmingham, Alabama in an article in the same issue of *Clinical Infectious Diseases* as Calmy's Viewpoint article describe a retrospective analysis of 466 patients who had visited the university clinic for care between January 1995 and August 2004 (its lead clinician, Michael Saag, was one of the first doctors in the world to prescribe HAART).

They defined virological failure as a viral load over 50 or over 400 (depending on which year the test was done) at 12 months after the initiation of HAART, and they defined immunological failure as a failure to achieve a rise in CD4 count of less than 50 cells by six months after the initiation of HAART. They then took four of the WHO's recommended indicators – lymphocyte count, haemoglobin level, platelet count, and body weight – and asked: is there a significant correlation between these results and virological or immunological failure?

The answer was yes – to a degree – in the case of body weight and viral load. Weight gain of more than 10% during the first year of treatment was the only clinical or immunological factor significantly associated with a viral load below 50 copies/ml at one year ($p=0.031$). However the association between body weight and immunological failure was not significant.

The other tests had no significant predictive value whatsoever, with correlations between test results and virological or immunological failure in the region of zero to nine per cent. Bagchi and colleagues dismiss the relevance of body weight as a useful indicator of therapy failure in itself: "This variable is influenced by many other factors that limit its precision and utility, especially in resource-poor settings," they say, meaning that there may be other reasons people may fail to gain weight, such as a poor harvest or a higher than usual incidence of digestive disease in the population. Equally people may gain weight despite being ARV failures, for instance if a TB treatment programme is initiated at the same time as HAART.

What sort of viral load test is needed?

However we are left with the problem that there is currently no viral load test that is practicable for use out in the field in a resource-poor setting far from laboratory facilities. Current tests require taking a vial of blood from a vein, refrigerated transport to a laboratory, mains electricity to run equipment, an assortment of scientific paraphernalia, instruments that cost in the region of \$30,000-\$60,000, about eight hours to produce a result and a technician with advanced training in molecular biology lab techniques.

In early 2006 MSF organised a consultation among academics and workers in ARV rollout programmes to find a specification for an ideal viral load test for resource-poor settings. They decided that it should require no more than a fingerstick's worth of blood (about a tenth of a millilitre), a single cartridge into which a sample of blood could be inserted and which would give a result, that it should not require refrigeration, be able to be run on batteries, should not cost more than \$1000 per instrument and \$8 per test, should give a result within two hours and would be able to be done by a field health worker with 1-2 days' training.

Such a test does not yet exist, though price reductions have been negotiated for the current systems, and reagents that do not require refrigeration have been developed. Costs can be greatly cut by making the test one which will give a simple either/or result to the question of whether the viral load is above a certain level, rather

than measuring a continuous variable between 50 copies and 1 million copies.

What this level should be is likely to be a matter for debate. Calmy and colleagues point out that evidence from the PLATO Collaboration, an international merging of 13 HIV cohort studies which contributes 2,488 patients experiencing triple-class virologic failure, suggests that, as long as the viral load remains below 10,000 copies, CD4 counts remain stable and the risk of clinical progression is low. So do other cohort studies (see Schechter). "Clearly a qualitative test with a cutoff value of 10,000 copies/mL would be of immediate practical use," they say.

However avoiding AIDS is one thing and avoiding drug resistance and the failure of any subsequent regimen is another, and evidence both from Khayelitsha and from an older analysis of the same PLATO Collaboration (see Ledergerber) shows that if patients are allowed to maintain a viral load over 1,000 for more than four months, only a minority are able to re-suppress HIV on a new regimen.

Researchers at Cambridge University in the UK (see Dineva) are developing a prototype 'dipstick' that would indicate the presence of a significant viral load (over 500 is the lower limit) by the intensity of a single test line. The difference between 1,000 and 10,000 copies may not be all that crucial if the illustration of the dipstick results accompanying Calmy's article are what it will eventually look like: whereas viral loads under 500 produce a faint line and over 10,000 a strong one, viral loads in between produce a line whose fuzziness is a matter of interpretation, so perhaps the indication should be that "any line that isn't faint means you switch". Dineva and colleagues say that the dipstick test can produce a viral load result "with an efficiency similar to that of a complex, expensive, and instrument-dependent method."

What of the WHO and its public health approach? The organisation is wary of any tendency to "make the best be the enemy of the good" and would continue to oppose any demand that ARV programmes not be instituted where viral load testing is unavailable. But the organisation has shifted its position on other guidelines. At Glasgow Gilks said that single-dose nevirapine to prevent mother-to-baby transmission, another strategy supported by WHO in the past, "is now substandard", and the WHO has started to shift its position on d4T, saying that "some governments may want to choose alternative options" due to this drug's side effects.

However some are wishing that the WHO would move faster and would explicitly echo the same sense of urgency, before health systems in the developing world are swamped by tens of thousands of patients with NNRTI and thymidine-analogue resistance mutations. In an editorial in the same issue of *Clinical Infectious Diseases* Robert T Schooley of the University of California, San Diego compares the current situation to the old joke where a man jumps off a 10-floor building and is asked by someone in the fifth floor how he is as he falls past. "Doing fine so far," is the reply. "We must avoid invoking the 'fifth-floor syndrome' by failing to act to prevent what we know will happen if viral load testing is not expanded in concert with the access to antiretroviral drugs," is Schooley's comment.

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