AIDS briefs

Viral load testing the only way to direct treatment switches

KEITH ALCORN

Further evidence has emerged that a substantial proportion of switches to second-line treatment in a resource-limited setting, triggered in the absence of viral load testing, are unnecessary and result in an avoidable inflation in drug costs as people switch to more expensive regimens.

The findings, published in *Clinical Infectious Diseases,* are likely to lend further support to calls for viral load testing to confirm suspected treatment failure to be made more accessible in resource-limited settings.

In well-resourced settings everyone receiving treatment undergoes regular viral load testing in order to detect viral rebound and failure of treatment. Switches to new treatment take place if viral rebound is detected, as the existing regimen becomes ineffective – due to drug resistance – once viral rebound occurs. In resource-limited settings, viral load testing is rarely available owing to cost and lack of well-equipped laboratories. Failure of first-line treatment can be detected only by monitoring the CD4 count for declines or looking for the development of clinical symptoms.

It had been widely assumed that CD4 counting would tend to result in delayed identification of large numbers of cases of viral rebound because of the time lag between viral rebound and subsequent loss of CD4 cells due to uncontrolled viral replication. It was feared that the major consequence would be that large numbers of patients would develop high-level resistance to some second-line drugs.

However, research presented at the Conference on Retroviruses and Opportunistic Infections in February this year showed that treatment switches on the basis of CD4 counts were often unnecessary, because the patients often continued to have undetectable viral load despite a decline in CD4 count. The researchers who conducted the study, in Uganda, suggested that infections such as malaria could be causing temporary dips in CD4 count.

They also estimated that in a cohort of 125 patients who experienced CD4 declines, 107 would have been switched to more expensive second-line treatment, adding $75 000 in drug costs to the treatment programme's budget.

Now, research from western Kenya has confirmed that the Ugandan observation is a common problem.

AMPATH, a service collaboration between Moi University and local clinics in the Eldoret region of western Kenya, carried out viral load tests on all patients receiving ART who had suspected immunological signs of treatment failure (a CD4 cell decrease of at least 25% over the previous 6 months).

The retrospective study identified 149 patients who had suspected treatment failure. Of these, 58% turned out still to have a viral load below 400 copies, and even among the subset of 42 who experienced a CD4 decline of more than 50% during the previous 6 months, 43% (18) still had a viral load below 400 copies, indicating that there was no need to switch treatment in those cases.

Among those with a CD4 cell count above 200 at the time of suspected treatment failure, two-thirds (66%) had a viral load below 400 copies, compared with 41% of those with a CD4 count below 100 cells/mm^3.

When misclassification was analysed according to CD4 cell percentage rather than absolute number it became clear that the highest risk of 'true' treatment failure occurred in those with a CD4 cell percentage below 10 (65% had viral load above 400 copies, compared with only 26% of those with a CD4 percentage between 20 and 29).

Logistic regression analysis showed that misclassification of treatment failure was more likely if the patient had a higher CD4 count, a shorter duration of treatment and a smaller decline in CD4 cell percentage.

'In our study, there was a high likelihood of failure if the patient had a CD4 cell count of <200 cells/µl and was on therapy for >20 months; there was a low likelihood of failure of therapy if the patient had a CD4 count of <300 and >200 cells/µl and was on therapy for <12 months.'

At AMPATH clinics, viral load testing is now mandatory in all cases of suspected treatment failure, but, say the authors: 'We recognize the fact that … selective virological monitoring may not be instantly achievable. These results suggest the need to reconsider recommendations on immunological monitoring in resource-limited settings.'

They suggest that use of CD4 percentages may improve the sensitivity of immunological monitoring for treatment failure, but say that their findings need to be evaluated in other populations before generalised conclusions can be drawn.

They also note that a previous simulation study carried out by Professor Andrew Phillips, which found only modest benefit to viral load and CD4 monitoring when compared with clinical monitoring in resource-limited settings with regard to cost-effectiveness, was based on the assumption that misclassification of treatment failure occurred in no more than 19% of cases.

They note several limitations: the fact that they could not verify viral load and CD4 measures; an average delay of 2 months between CD4 count and viral load test; and a lack of information about seasonal variations in CD4 count or changes in CD4 count due to intercurrent illnesses such as malaria.

In an accompanying editorial, doctors from Kenya and South Africa say: 'In 2008 Smith and Schooley referred to managing ART without viral load as "running with scissors". The emerging data … suggest it is more akin to throwing these programs onto drawn swords.

'The time has come to work towards the progressive introduction of appropriate viral load monitoring technology in these programs with the same sense of urgency and commitment as the world approached ART access. To do less is to abandon the early success of ART to global collapse.'

Kantor R, *et al.* Misclassification of first-line antiretroviral treatment failure based on immunological monitoring of HIV infection in resource-limited settings. *Clin Infect Dis* 2009; 49: 454-462.

Sawe FE, McIntyre JA. Monitoring antiretroviral therapy in resource-limited settings: time to avoid costly outcomes. *Clin Infect Dis* 2009; 49: 463-464.

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AIDS vaccine funding down 10% in 2008

KEITH ALCORN

Funding for AIDS vaccine research fell by 10% in 2008, the first decline in a decade, according to figures recently released by the HIV Vaccine and Microbicide Resource Tracking Working Group. At the same time, funding for both microbicides and pre-exposure prophylaxis (PrEP) increased by 8% and 13%, respectively, in 2008.

'Support and interest in HIV prevention research from public, private and philanthropic funders over the last decade has supported key R&D priorities, moved the field forward and brought us closer to new HIV prevention options,' said Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition (AVAC).

The 2008 decline in vaccine research was not attributable to the global economic downturn, the working group said. Instead it was partly attributable to the end of the Step and Phambili vaccine trials, which were testing a candidate vaccine developed by Merck. The Step trial showed that the product was not effective, and the results led to a retrenchment in vaccine research which has redirected research efforts towards basic laboratory research.

However, major vaccine studies are continuing. The South African AIDS Vaccine Initiative recently announced the start of a trial to study a vaccine candidate developed by local South African scientists. Results are also expected later this year from the largest vaccine trial ever, which successfully enrolled more than 16 000 participants to the study.

A decrease in investment from the US National Institutes of Health contributed to the overall decline of funding for HIV vaccine R&D. The US government investment fell by $39 million, a 6% decrease. Other governments also decreased funding for HIV vaccine research in 2008: European government funding fell by 13% and total funding from other countries (including Brazil, Canada, India, South Africa, and Thailand) fell by 16%.

'We face tremendous challenges – both scientific and economic – over the coming years, but we must not lose the momentum we have gained. The field needs sustained support from a range of funders. The AIDS epidemic shows no signs of slowing, and the desperate need for new HIV prevention options will not change,' said Mitchell Warren.

'The worldwide economic crisis has fuelled debate about the best way to invest in global health, with some arguing that AIDS takes up resources at the expense of efforts to deal with other diseases and to improve health systems in the developing world. But, given that AIDS is the number one killer in sub-Saharan Africa, and number four in the world, it is imperative that we reverse this pandemic, and that can only be done through improved methods of prevention, including a vaccine. If we can conquer AIDS, we will be able to invest resources in other pressing priorities,' said Seth Berkley, President and CEO of the International AIDS Vaccine Initiative.

The report, 'Adapting to realities: Trends in HIV prevention research funding 2000 to 2008', was released at the Fifth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town, South Africa, by the HIV Vaccine and Microbicide Resource Tracking Working Group.

The report identified investments of almost $1.2 billion in HIV prevention research in 2008, of which $868 million supported vaccine R&D, and $244 million supported microbicide R&D, while other HIV prevention R&D received much lower levels of funding. AIDS vaccine research declined for the first time since 2000, falling by 10% from 2007 levels.

The US government was once again the primary funder for HIV prevention research, supporting 71% of HIV vaccine R&D, 63% of microbicide R&D, and providing 46% of funding for PrEP prevention research in 2008.

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BRIDGET FARHAM

Single Suture

The brain sees tools as extensions of a limb

As far as your brain is concerned, your toothbrush is simply another part of your arm. This is the conclusion of a study that showed that perceptions of arm length change after people use a mechanical tool. The underlying mechanism is the map that our brain makes of the body – when we use tools the brain simply incorporates them into the map.

To test this idea, Alessandro Farnè and colleagues of the Université Claude Bernard in Lyon looked at 14 volunteers who used a mechanical grabber to pick up distant objects. Shortly afterwards, the volunteers perceived touches on their elbow and fingertip as further apart than they really were. They also took longer to point to or grasp objects with their hand than they did before they used the tool.

The team suggests that their brains may have adjusted the areas that normally control the arm to account for the tool and may not yet have adjusted back to normal.

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