Confirmatory viral load reduces HIV treatment switches fourfold in 6-country African study

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Targeted viral load testing to confirm treatment failure reduced unnecessary treatment regimen switches four-fold compared with clinical-immunological criteria alone (viral load <1 000 copies/ml 12.4% and 46.9%, $p<0.001$, respectively) among 250 patients in six African countries according to Kim CE Sigaloff and colleagues[1] in a cross-sectional analysis of a multicentre prospective observational study published in the advance online edition of the *Journal of Acquired Immune Deficiency Syndromes.*

However, switching on the basis of confirmatory viral load testing did not reduce the risk of drug resistance.

Nucleoside reverse transcriptase inhibitor (NRTI)-associated cross-resistance was seen in close to 50% (87) of the 183 specimens available for genotypic analysis and did not differ by the type of failure identification used (clinical-immunological failure alone or with the addition of targeted viral load testing).

NRTI cross-resistance and the accumulation of thymidine analogue mutations (TAMs) were both associated with length of time on antiretroviral treatment and zidovudine (AZT) use; tenofovir (TDF) use was additionally linked to NRTI cross-resistance.

The presence of at least one clinically significant mutation in 88% after first-line failure suggests late failure detection, the authors noted.

Increased access to first-line antiretroviral treatment in sub-Saharan Africa over the past decade has shown good short-term results. Long-term follow-up remains limited. Treatment failure for some is inevitable, increasing the risk of HIV-related morbidity and mortality.

Recent World Health Organization (WHO) guidance supports the use of viral testing if feasible to improve identification of treatment failure. Financially and logistically this is impossible in most resource-poor settings. So reliance on clinical criteria and CD4 cell counts is the norm for clinicians to determine treatment failure and help guide switches to second-line regimens.

Studies have shown use of clinical and immunological criteria alone in African countries cannot accurately determine virological failure in first-line treatment.

WHO recommends a switch in treatment if the CD4 count falls by more than 50% from its previous peak level, or if the CD4 count falls to its pre-therapy baseline (or below); or if it persistently remains below 100 cells/mm^3.

Immunological criteria for switching have been found to result in unnecessary switches to second-line treatment, however.

For example, a study conducted in Uganda found that only 18 of 125 immunological non-responders receiving antiretroviral treatment had a detectable viral load. The investigators noted that 107 patients would have switched treatment unnecessarily, at an extra cost of $75 000 a year for drugs alone.

Incorrect diagnosis of treatment failure in the absence of a confirmatory viral load test leads to inappropriate switching to more expensive and toxic second-line regimens.

Late failure detection can result in considerable resistance to antiretrovirals, notably cross-resistance within the NRTI drug class. This can then hamper the effectiveness of standard second-line regimens comprised of a dual backbone of NRTIs and ritonavir-based protease inhibitor (PI) prevalent in resource-poor settings. Benefit would derive primarily from the boosted PI so patients would essentially be getting monotherapy, so lowering the barrier of PI resistance.

The objective of the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) multicentre prospective observational study of HIV-infected adults who get antiretroviral treatment at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe is to look at the consequences of the use of clinical immunological criteria to determine treatment failure and guide treatment switching.

The authors undertook a cross-sectional analysis to look at how frequently unnecessary changes to second-line regimens were made, the patterns of resistance that developed in those on failing first-line antiretroviral treatment and the risk factors for the accumulation of NRTI-associated mutations.

Participants were included if switched to second-line antiretrovirals regardless of criteria to determine failure. Comparisons were made according to clinical-immunological failure in the absence of viral load testing (CIF only group) and CIF with local targeted viral load testing (targeted VL group).

Definition of an unnecessary switch to second-line ART used three reference viral load cut-offs: <400 copies/ml; <1 000 copies/ml; and the WHO recommended threshold of <5 000 copies/ml.

NRTI cross-resistance was defined as the presence of ≥ two TAMs, the TDF-associated mutations K65R or K70E, or the Q151M complex.

Of the 250 patients with clinical-immunological failure switched to second-line antiretrovirals between March 2007 and September 2009 targeted viral load testing was used in 75% (186) and 25% (64) with CIF alone.

Median time on antiretroviral treatment was 28.3 months and 25.3 months in the CIF alone and targeted VL groups, respectively.

At a viral load cut-off of <1 000 copies/ml 53 (21.2%) had unnecessary switches, of which 30 (46.9%) were in the CIF alone group and 23 (12.4%) in the targeted VL group. At the more stringent cut-off of <400 copies/ml targeted viral load reduced unnecessary switches six-fold (46% compared with 8.6%, $p<0.001$).

Mutations associated with cross-resistance to NRTIs in 48% of the participants comprised multiple TAMs (37%), K65R (7.1%), K70E (3.3%) or Q151M (3.3%).

One of the major strengths of the study, note the authors, is that it involves a large international sample of patients diagnosed with treatment failure at a diverse range of clinics representative of current clinical practice in a number of African antiretroviral programmes.

Their study 'underscores the importance of targeted viral load testing to maximise the clinical benefits of first-line regimens and prevent unnecessary switches to expensive second-line antiretroviral treatment'. Late detection of treatment failure resulted in extensive cross-resistance to NRTIs, limiting treatment options and impairing the effectiveness of (standard) second-line regimens.

The authors conclude: 'The development of more affordable, point of care viral load assays is a public health priority for resource-limited settings.'

1. Sigaloff KCE et al. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. JAIDS advance online edition, doi: 10.1097/QAI.0b013e318227fc34, 2011.

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