

### Second-line treatment failure most often due to poor adherence in low- and middle-income countries

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Poor adherence rather than drug resistance appears more likely to be the cause of virological failure among patients on second-line antiretroviral therapy (ART) in resource-poor settings, according to a systematic review and meta-analysis published in the advance online edition of *AIDS*.

The cumulative pooled proportion of the 2 035 adults comprising the 19 studies from 8 countries in sub-Saharan Africa and Asia failing virologically was 21.8%, 23.1%, 26.7% and 38.0% at 6, 12, 24 and 36 months, respectively.

The authors note that these estimates should be reviewed with caution as there were considerable differences between the studies as well as substantial statistical differences.

While most of the studies did not provide enough information to be able to distinguish conclusively between poor adherence and drug resistance as reasons for virological failure, in those that did poor adherence was the primary cause.

Nonetheless these findings highlight the limited options available after second-line therapy in resource-poor settings, notably where drug resistance is the cause of virological failure.

The researchers also stress the importance of improved access to greater virological monitoring as well as more intensive adherence counselling before resistance mutations develop.

The scale-up of ART in resource-poor settings has had a considerable effect on reducing death and disease. Standardised regimens, notably simple, affordable fixed-dose combination therapies, have facilitated adherence with rates comparable to those in resource-rich settings. However, in

resource-poor settings limited or no access to viral load or genotyping and poor availability of second-line options mean treatment failure often goes undiagnosed until clinical illness emerges.

For those failing second-line therapy the options are severely limited. The World Health Organization (WHO) provides some guidance for treatment, yet states that because of financial difficulties many countries are unable to offer third-line options, the authors note.

So it is important to understand the numbers and reasons for those failing second-line treatment regimens in resource-poor settings to be able to limit this happening and determine what the future need for choices after second-line will be.

Virological failure, the authors note, happens for a number of reasons. These include having baseline drug resistance before starting treatment, the development of drug resistance during treatment, length of time on treatment and poor adherence.

What is important in terms of programme effectiveness is to be able to distinguish between patients who have failed because of drug resistance and those who are non-adherent and have not yet developed resistance. The former will need to switch to a third-line regimen while the latter need adherence support.

With this in mind the authors chose to undertake a systematic review looking at the rates and reasons for second-line treatment failure in resource-poor settings. Nineteen studies were identified for analysis, undertaken in Botswana, South Africa, Malawi, Uganda, Tanzania, Cambodia, Thailand and China between 2007 and 2011. A high proportion of those on second-line therapy were failing virologically. Most happened within the first 6 months of starting ART.

Of the seven studies reporting virological failure at 6 months the proportions ranged from 8.6% (95% confidence interval (CI): 0.36 - 26.01%) to 37.34% (95% CI: 31.30 -



43.59%). Seven reported on failure at 12 months and ranged from 11.35% (95% CI: 4.89 - 29.97%) to 39.89% (95% CI: 30.27 - 49.93%).

At 24 months five studies reported failure in adults and one in children. Proportions ranged from 8.32% (95% CI: 2.93 - 16.12%) to 41.15% (95% CI: 31.54 - 51.10%) among adults and for the children 20.58% (95% CI: 10.72 - 32.64%).

Of the three reporting failure at 36 months the range was 6.4% (95% CI: 3.18 - 10.64%) to 57.32% (95% CI: 42.07 - 71.88%).

While most of the studies (13) defined virological failure as a viral load greater than 400 copies/ml (WHO definition), only half reported two consecutive measures. Additionally different definitions of virological failure were used.

The authors note the limitation of insufficient information to be able to distinguish, from a programme perspective, between failure due to drug resistance and failure due to non-adherence.

However, all studies that measured adherence, they add, showed poor adherence to be a significant risk factor for failure. For example, a study in Malawi where poor adherence was defined as 'ever missing a dose' after adjustment for potential confounders, those poorly adherent were five times less likely to achieve viral suppression (adjusted odds ratio (AOR): 5.70; 95% CI: 1.16 - 27.93%).

The reported overall low level of resistance mutation, in particular to protease inhibitors (PIs), suggests failure for most patients is due primarily to poor levels of adherence rather than the development of resistance, the authors note.

They point out that these failure rates are higher than reported rates of failure to first-line therapy in resource-poor settings and reported rates of second-line failure in resource-rich settings. This may be explained in part because of the cumulative toxicity associated with nucleosides used in first- and second-line therapy making adherence difficult.

A further challenge to adherence is the issue of drug shortages that have been linked to increased treatment interruption and death. Limitations include: a small sample size; other factors may explain failure including

drug-drug interaction, in particular with tuberculosis drugs; and observational studies present potential biases.

The authors suggest that future studies could provide a better understanding of the role played in second-line failure by non-adherence if they follow WHO recommendations for management of second-line virological failure. After the first viral load result indicating viral rebound, the patient should receive an adherence support intervention, followed by a second viral load test.

Results could be assessed to determine both the effectiveness of adherence interventions and the proportion of failure due to poor adherence.

The need for third-line treatment options in resource-poor settings remains critical for

those failing second-line treatment where adherence is not the issue.

While the cost-effectiveness of viral load monitoring remains in question the authors note that 'recent costings have concluded that when the benefits of guided regimen switches are considered, viral load monitoring is cost-effective and life saving. Improving the feasibility and reducing the cost of viral load [testing] are important policy objectives.'

Ajose O, et al. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *Advance online edition AIDS* 26, doi:10.1097/QAD.0b013e328351f5b2, 2012.

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