

When to switch for antiretroviral treatment failure in resource-limited settings?

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Thanks to the leadership of the World Health Organisation (WHO) [1], and massive financial support from programmes such as the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR), the number of HIV-infected individuals accessing antiretroviral therapy (ART) in resource-limited settings has tripled from 2001 to 2005. An estimated 1.3 million HIV-infected individuals were on ART in 2005, representing 20% of those in need of treatment [2].

Contrary to initial fears, numerous reports have now been published describing successful early outcomes in many ART patient populations [3]. This is as a result of a number of factors including the fact that the majority of patients are treatment naive, that a low prevalence of primary drug resistance still prevails, and that adherence is better than expected, particularly in patients receiving treatment free of charge [4,5].

Nonetheless, even in the most successful programmes, a significant proportion of patients are failing their first-line ART. The lack of virological monitoring means that the vast majority of these patients are being switched at the point of immunological or clinical treatment failure [6].

The article in this issue of *AIDS* by Seyler *et al.* [7] looks at the impact of viral failure and the presence of resistance mutations on the CD4 lymphocyte count gain and clinical outcome in a cohort of patients in Abidjan, Côte d'Ivoire. At study entry, patients had been on treatment for a median of 37 months. After a median of 18 months, no difference in mortality and morbidity was seen between patients with viral failure (median <10 000 copies/ml) and major

mutations at inclusion and patients with undetectable viral loads. CD4 cell counts also remained stable for the majority of patients with virological failure at baseline (with or without major resistance mutations).

Although the data might sound reassuring in a context of limited access to ART, we should interpret these results with caution. The Abidjan cohort constitutes a selected group of patients that has survived the first 3 years of therapy. In addition, the situation in Côte d'Ivoire does not reflect the situation in most resource-limited settings. Whereas in most places the standard first-line therapy is a fixed-dose combination of non-nucleoside reverse transcriptase inhibitors (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTI), more than half the patients in this cohort received a protease inhibitor regimen as first-line ART. Also, importantly, 10 of 23 patients (43%) with major resistance mutations at baseline were actually switched to another regimen.

The Abidjan study is, however, important as it encourages the discussion regarding what time would be best to switch ART in resource-limited settings and how viral load results should be used if available [8].

According to the new WHO guidelines, viral load measurements are still not recommended for the monitoring of ART in resource-limited settings [9]. For those resource-limited settings in which viral load testing is available, the WHO does not recommend switching patients for virological failure alone, unless the viral load is greater than 10 000 copies/ml. It is important to note, however, that these pragmatic WHO recommendations

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were extrapolated from western data. These data, which suggest that patients may remain immunologically and clinically stable if their viral load remains below 10 000 copies, are from highly treatment-experienced patients. Such patients may be very different to patients in resource-limited settings failing their first-line regimen as a result of variations in viral fitness [10].

We are concerned about the medium and long-term implications of switching patients after a prolonged period of virological failure as such a delayed switching will lead to the accumulation of resistance mutations.

First, for individual patients, the acquisition of drug resistance mutations may limit the efficacy of the available second-line regimens in resource-limited settings. Most first-line ART regimens in resource-limited settings are NNRTI-based regimens with a lamivudine and thymidine analogue backbone. The likely accumulation of thymidine analogue mutations may well impact on the efficacy of all other available NRTI, which might have been used subsequently with a boosted protease inhibitor (e.g. lopinavir/ritonavir). This may well limit the effectiveness of second-line ART regimens, thus shortening (not increasing) the overall 'clinical durability' of available ART for patients in resource-limited settings [11].

The second major concern if patients are allowed to fail and accumulate resistance on a large scale is that drug-resistant viruses will be transmitted to sexual partners. This will eventually increase the prevalence of primary resistance in these populations, which will jeopardize the prevention of mother-to-child transmission interventions and limit the efficacy of simple and affordable ART treatment for future generations [12]. Preventive interventions should target patients virologically failing in order to limit the spread of drug resistance into the community.

Whereas the WHO aims for universal access by 2010 [13], we need to understand quickly how to interpret and manage virological failure in resource-limited settings in order to maximize the clinical effectiveness of limited ART resources. This may involve using the currently available ART regimens in a different way to limit cross-resistance between regimens. Possibilities include changing the thymidine analogues of the first line for tenofovir to preserve zidovudine for second line [14], testing induction-maintenance strategies and using an NRTI-only regimen such as zidovudine/lamivudine/tenofovir that is used in the Development of Antiretroviral Therapy in Africa (DART) trial to spare NNRTI [15]. Virological monitoring should be made more available and less expensive to resource-limited settings, so that providers can make more informed decisions about when to switch

patients to second-line ART [16]. Research into alternative methods is currently half hearted and needs to be accelerated [17].

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