

EDITORIAL

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The impact of adherence to HIV/AIDS antiretroviral therapy on the development of drug resistance



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“It is very clear that there is a distinct relationship between the degree of adherence to the antiretroviral medications and the virologic suppression.”

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During the last decades, since 1996, there has been a strong commitment to reach both therapeutic efficacy and avoidance of drug resistance in case of virologic failure. The development of modern drug classes has facilitated the life of those involved in HIV/AIDS treatment, particularly HIV-infected subjects. There is still a gap between the perfect efficacy and the maximal adherence and tolerability, and of course all three aspects are interconnected.

It is very clear that there is a distinct relationship between the degree of adherence to the antiretroviral (ARV) medications and the virologic suppression. This was initially demonstrated by the ARV regimen during the first highly active ARV therapy (HAART) era and has been confirmed more recently with combination drugs, including non-nucleoside reverse-transcriptase inhibitors (NNRTI). The optimal cut-off is, again, the 95% adherence [1]. In both developing and developed countries there have been many demonstrations on how adherence affects clinical outcomes. Such an example comes from the the AIDS support organization initiative in Uganda: data show that,

even within the first year and a half of ARV therapy, there is a significant difference, of approximately 40%, in survival between adherent and nonadherent subjects [2]. In the MACS cohort [3], $\geq 80\%$ suppression was observed with 80–84% adherence and the odds ratio for suppression versus $\geq 95\%$ adherence was 1.43 (0.61,3.33). In the ALIVE study [4], where $< 35\%$ were on newer drugs, only 71.4% were suppressed among those who reported $\geq 95\%$ adherence. This suggests concerns related to nonadherence may be less of a barrier to the initiation of modern HAART regimens [5]. In the ICONA cohort, nonadherence was responsible for only 2% of treatment discontinuation in HIV-1 infected individuals starting their first-line ARV regimen after 2008 in Italy [6].

Nonadherence rates improve over time with the extension of follow-up visits, as shown by the CAPRISA initiative in South Africa. The nonadherence rate was $> 40\%$ at the initial visit and decreased to roughly 15% at visit 17 [7]. HAART adherence levels for individuals who started therapy in British Columbia increased over

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“There is a tight interplay between adherence and virological suppression, and drug resistance..”

time during 1996–2012. While only 37% of individuals had adherence levels $\geq 95\%$ in 1996, this increased to 71% for individuals ($p = 0.0032$) by 2012 [8]. There is a tight interplay between adherence and virological suppression, and drug resistance, as shown by the work of Nachega *et al.* Lower pill burden was significantly associated with both better adherence and virological suppression in 19 studies including 6312 adult patients [9]. Likely due to safer and more effective drugs and an improvement in patient’s adherence, recent data dealing with the epidemiology of resistance to ARVs showed a declining prevalence of HIV-1 drug resistance in experienced individuals in Western Europe (SEHERE collaboration) with the exception of NNRTI [10]. The proportion with extensive three-class resistance over calendar years by the last and the cumulative genotype decreased between 2005 and 2008 and the proportion of cases with an exhaustion of drug options by the last and the cumulative genotype was $<5\%$ in 2008 [10].

When we think about drug resistance, the paradigmatic view ranges from an easy probability of developing drug resistance, detected via minority variants methods, *id est*, resistance toward NNRTI and the extent of cross-resistance to newer compounds. An example of the first dynamic is the low frequency of NNRTI mutations K103N, Y181C and NRTI mutations M184V, K65R, and the risk of NNRTI-based ARV treatment failure. Minority drug-resistant variants were found in 14% of samples in this systematic review [11]. The second example is illustrated by the resistance to the newest ARV class, which is well established in the clinical arena: the integrase inhibitors (INI). A recent report from the USA underlines that one out of five patients tested during the first 3 years of the availability of a genotypic resistance test for INI harbored at least one major integrase-resistance mutation [12]. The positive aspect of the resistance to INI is that cross-resistance between raltegravir, or elvitegravir,

and dolutegravir is very contained in raltegravir-naive patients. In raltegravir-pretreated patients, 50 (41.7%) of the integrase sequences obtained at failure of raltegravir therapy did not contain any mutation at codons 143, 148 and 155 [13].

A totally different story may be told in the upcoming scenario of long-acting (LA) compounds, that is, cabotegravir and rilpivirine that can be administered via a subcutaneous or intramuscular injection. These compounds possess a very long half-life, thus can resolve most of the problems connected with adherence. But there are still missing spots: we have no data regarding the virologic protection after the final injection of these compounds. If a patient withdraws from a trial, will the pharmacological ‘tail’ still be protective or pose a serious threat for the development of drug resistance? A single case of an emergent NNRTI-resistant virus has been reported in a subject from a rilpivirine LA 300 mg Phase I tissue pharmacokinetic study [14]. The LA pharmacokinetics may not be sufficient in non-adherent patients and consequences of this insufficient drug exposure could appear later on, without being adjustable thus jeopardizing patient’s therapeutics [15].

Thus, there is still an ongoing debate on situations when the maximal virologic efficacy is essential and maximizing drug adherence is a priority. In the near future, more friendly drug regimens/administration devices will help in maintaining optimal therapeutic results and keeping regimen forgiveness at the highest level.

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