Pretreatment HIV-1 drug resistance is strongly associated with virologic failure in HIV-infected patients receiving partly active antiretroviral regimens

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Evaluation of: Hamers RL, Schuurman R, Sigaloff KCE *et al.* Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicenter cohort study. *Lancet Infect. Dis.* 12, 307–317 (2012). The scale-up of antiretroviral therapy in sub-Saharan Africa has significantly reduced mortality from AIDS. Hamers *et al.* explores the impact of pretreatment HIV-1 drug resistance on virologic failure, immunologic response, and acquisition of drug resistance after 1 year of first-line antiretroviral therapy by longitudinally evaluating 2579 participants with pretreatment drug resistance results from the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) cohort. Participants with pretreatment drug resistance who were given a treatment regimen with reduced activity to at least one prescribed drug had a significantly greater risk of virologic failure and acquired drug resistance compared with both participants without pretreatment drug resistance, and participants with pretreatment drug resistance who were prescribed fully active regimens. This paper by Hamers *et al.* validates the need for at least three fully active antiretroviral drugs to prevent the acquisition of drug resistance and to optimize treatment success in resource limited settings.

Summary of methods & results

The scale-up of antiretroviral therapy in sub-Saharan Africa using standardized regimens and national treatment guidelines has dramatically reduced mortality from AIDS, saving an estimated 740,000 lives between 2004 and 2008 [1]. Hamers *et al.* used the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) cohort [2] to evaluate the effect of pretreatment drug resistance on the success of subsequent empirically prescribed first-line antiretroviral (ARV) therapy (ART) [3]. Encompassing 13 clinics in six sub-Saharan African countries, the PASER-M cohort is comprised of HIV-positive adults eligible for ART through local criteria, consisting generally of CD4⁺ T-cell counts less than 200 cells/ μ l and/or WHO clinical stage 3 or 4. The study design excluded individuals whose regimen did not contain two nucleoside reverse transcriptase inhibitors (NRTIs) with an non-nucleoside reverse transcriptase inhibitor (NNRTI), or who had received a first-line regimen in the previous 30 days, but did allow enrollment of individuals who had used ART more than 30 days previously. This prior use could include but was not limited to full ART;

dual therapy or monotherapy for treatment of HIV; single-dose nevirapine or combination regimens for prevention of mother-to-child transmission; or postexposure prophylaxis.

A total of 2733 participants started first-line ART, of whom 145 (5%) had previous ARV exposure. Drug resistance, as defined by the presence of at least one major amino acid substitution from the International Antiviral Society (IAS)-USA mutation tables [3], was detected in 7% of participants with a pretreatment drug resistance test result (175 out of 2579). Virologic failure was defined as HIV RNA ≥ 400 copies/ml after 12 months of ART. There were several key findings from this dataset. First, participants with pretreatment drug resistance to at least one prescribed drug had increased risk of virologic failure compared with those without pretreatment drug resistance and those with pretreatment drug resistance who were prescribed fully active ART. In addition, the recovery of CD4⁺ T cells was significantly higher over time in participants without pretreatment drug resistance, compared with those with pretreatment drug resistance, regardless of whether the ART

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prescribed was fully or partially active. Other significant factors associated with virologic failure were previous ART exposure and adherence <80% as measured by a 30-day visual analog scale of pill counts.

184 participants had post-treatment drug resistance; of the 156 successfully genotyped, 113 (72%) had one or more major drug resistance mutation. Most commonly seen were NNRTI resistance mutations (98; 63%), followed by NRTI (94; 60%). Protease inhibitor mutations were rare (two; 1%). Half of the participants had dual-class resistance (80; 51%). Only 20 (18%) participants had pretreatment drug resistance while 87 (77%) did not; the status of six (5%) was unknown. Amongst those with pretreatment drug resistance, the risk of virologic failure and acquired drug resistance was significantly lower ($p < 0.05$) in those prescribed fully active ART compared with those with reduced susceptibility to at least one prescribed drug.

Discussion

Treatment scale-up in sub-Saharan Africa began with the '3 by 5' initiative launched in 2003 to provide 3 million individuals access to ART by 2005. An even more ambitious target was set in 2005 for universal access to HIV prevention and treatment by 2010 [4,5]. This rapid increase in ARV use has made a significant impact on the epidemic; however, a consequence has been a rise in HIV drug resistance, not just in those with treatment failure, but also in those newly infected.

In a recent survey, the prevalence of transmitted drug resistance in treatment-naïve individuals ranged from 1.1% in Pretoria, South Africa to 12.3% in Kampala, Uganda [6]. Although the WHO threshold surveillance method had previously classified countries in sub-Saharan Africa to have rates of transmitted resistance as <5%, these rates have been increasing in countries with greater access to ART such as South Africa [7,8]. When transmitted resistance reached 8% in the USA in 2003, genotyping and/or phenotyping was recommended before an initial ART regimen was selected for treatment-naïve HIV-infected patients [9].

Despite the rising prevalence of resistance in treatment-naïve individuals in sub-Saharan Africa, similar to that seen in the USA in 2003, routine laboratory monitoring including plasma HIV RNA and standard genotyping remains uncommon in resource-limited settings. Through partnerships with the Linking African and Asian Societies for an Enhanced Response

to HIV/AIDS (LAASER) program and the PharmAccess Foundation, Hamers *et al.* were able to obtain genotyping results both pretreatment and after one year of follow-up to evaluate the effect of pretreatment drug resistance on plasma HIV-1 RNA, CD4⁺ T-cell counts, and acquisition of drug resistance in a cohort of individuals starting first-line therapy. Hamers *et al.* found that virologic failure and acquisition of drug resistance occurred in those receiving partially active regimens. Those with pretreatment drug resistance receiving fully active regimens still had the full benefit of all ARVs in the regimen despite having virus with drug resistance mutations. These findings are not surprising given that similar results were obtained over a decade ago in resourced countries. A standardized analysis of multiple cohorts showed that the number of active drugs in a regimen was predictive of virologic outcome [10].

One critique of this study is that enrollment into the PASER-M cohort was not restricted to patients without prior ARV exposure or suspected transmitted resistance. This aspect limits the ability to differentiate among the possible causes of pretreatment drug resistance, such as transmitted or acquired from single-dose nevirapine, dual therapy or pre-exposure prophylaxis. In a subsequent sensitivity analysis, the authors noted that exclusion of participants with prior ARV drug exposure did not change the results. Additionally, the following adjustments also showed the same results as the main analysis: changing the definition of virologic failure to ≥ 50 copies/ml; classifying all missing data as failures; exclusion of participants with the M184V mutation; and exclusion of participants with HIV RNA >1000 copies/ml without major IAS-USA drug-resistance mutations after 12 months of ART to account for possible infection with low-frequency resistant mutants.

Future perspective

The use of partially active regimens before the advent of combination ART in the USA and Europe has resulted in high rates of both acquired and transmitted resistance and the recommendation that baseline resistance testing be performed on all HIV-infected patients before initiating or switching ART [11]. Laboratory monitoring in sub-Saharan Africa is still very limited. In a modeling study, Kimmel *et al.* showed that HIV RNA-based monitoring to guide initiation of second-line ART increased life expectancy by 61%, with the increase being 46% with CD4-based monitoring, and only

24% with clinical-based monitoring, compared with continuing first-line ART [12]. With CD4 as current standard of care in many settings, cost and infrastructure barriers have been major obstacles to having HIV RNA or resistance test-guided therapy, which is the standard of care in developed countries. Without such monitoring in resource-limited settings, the rising prevalence of drug resistance is likely to compromise the effectiveness of standardized first-line regimens over time. The clear impact of pretreatment resistance on ART success highlights the need for improved laboratory infrastructure and the development of simple, low-cost assays that can be used to assess plasma HIV RNA and drug resistance before starting first-line therapy and for guiding treatment switches. Routine resistance surveillance is also needed in areas of treatment scale-up to accurately track the levels of both acquired and transmitted resistance that would influence the selection of optimal regimens for first-line ART.

Not mentioned in the article is the possibility of increasing transmitted resistance from continuation of ARVs in individuals who already have resistance to them. The selection of additional mutations is likely to occur with long-term suboptimal drug exposure, resulting in

more efficient viral replication and transmission. Progression to AIDS may also be associated with evolution of compensatory mutations [13].

With the expectation that pretreatment drug resistance will increase in the coming years, Hamers *et al.* emphasize several implications for public health policy. Expansion of drug resistance testing and quality control as initiated by the WHO [14] is needed at a population level in areas of treatment scale-up. Better alternative regimens that are not cross-resistant to NRTIs and NNRTIs are also urgently needed. Finally, optimal strategies to maintain patients in care, improve adherence and control the spread of drug resistance are essential to ensure the long-term success of ART in reducing the human toll of HIV/AIDS.

Financial & competing interests disclosure

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Executive summary

Background & scope

- Scale-up of combination antiretroviral therapy (ART) has been conducted using standardized drug regimens and limited laboratory monitoring.
- Subsequently, there has been an increase in both transmitted and acquired HIV drug resistance.
- This study evaluates the impact of pretreatment drug resistance on virologic and immunologic responses, and acquisition of drug resistance.

Methods

- A cohort of participants starting first-line therapy were evaluated for pretreatment drug resistance, were followed for 1 year and were re-evaluated for drug resistance if HIV RNA was >1000 copies/ml.
- Differences in outcome in those with and without pretreatment drug resistance were compared statistically.

Results

- Factors associated with virologic failure or acquired drug resistance included:
 - Pretreatment drug resistance and partially active ART
 - High pretreatment plasma HIV RNA
 - Younger age at ART initiation (women only)
 - Previous ART or prevention of mother-to-child transmission exposure
 - No CD4 count increase 6 months after initiation
 - Adherence <80%

Conclusion

- At least three fully active antiretroviral drugs are needed to ensure an optimum response to first-line non-nucleoside reverse transcriptase inhibitor-based ART regimens and to prevent the acquisition of drug resistance.
- Extended genotypic drug resistance testing as part of population-based surveillance is needed in regions where ART is scaled up.
- Improved access to drugs without cross-resistance to nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors are needed to ensure the continued effectiveness of ART rollout.

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