Disregarding drug resistance mutations without peril

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Data from sequencing proviral DNA provide the opportunity to review the evolution and history of HIV throughout its replication in an infected individual, while the sequencing of plasma RNA only permits interrogating what is happening on the day of collection. These RNA sequences reflect the recent selective pressures (drug treatment, humoral and cellular immunity) determining today's most fit virus. DNA sequencing permits obtaining information about, for example, antiretroviral drug resistance that could compromise future treatments when plasma RNA cannot be sequenced from an individual who is well suppressed on a current ART regimen. Li *et al.* [1] show that the detection of certain drug resistance mutations in cellular DNA may disproportionately reflect proviruses that are replication incompetent. More specifically, Li *et al.* [1] describe the enrichment in hypermutated proviruses of certain mutations, most importantly M184I, which confers high level resistance to lamivudine (3TC) and emtricitabine (FTC).

The mutations they identify as over-represented in replication incompetent proviruses are generated by host cell ABOBEC3 enzymes which also generate numerous other mutations in the same provirus, thus rendering these hypermutated proviruses replication incompetent [2,3]. The APOBEC family of genes code enzymes with cytosine deaminase activity, which changes cytosine (C) bases in DNA to uridine (U) after reverse transcription, resulting in guanosine (G) to adenosine (A) mutations in HIV DNA. These host enzymes mediate, for example, DNA editing for antibody maturation and antiviral restriction to help protect cells from a number of viruses [3]. The HIV *vif* gene largely, but not completely, mediates the ubiquitination and degradation of certain APOBEC3 enzymes via the proteasomal pathway. Unsuccessful elimination of an APOBEC3 enzyme results in the production of virions producing reverse transcripts with numerous G to A mutations rendering the provirus in the newly infected cell replication incompetent, but also increasing the proportion in the archived HIV DNA of those drug resistance mutations that can result from a G to A mutation, such as M184I. The wild-type methionine coded by ATG is mutated after an APOBEC3G to A mutation to ATA, which codes for isoleucine.

Li *et al.* [1] show that certain other drug resistance mutations are found more frequently in hypermutated proviruses. These include the subset of mutations that result from a G to A replacement. Most notable is the rilpivirine resistance mutation E138K, but not E138A which does not result from the G to A replacement. Other mutations seen more frequently in hypermutated viruses include the NNRTI resistance mutations, M230I and G190E, and the protease inhibitor mutations D30N and M46I.

Does this information about enrichment of certain drug resistance mutations in replication incompetent proviruses aid in guiding patient management? There are a number of limitations about the potential impact of the results that the investigators acknowledge. Only 25 individuals were studied, although that number is clearly sufficient to identify enrichment of certain resistance mutations in hypermutated sequences. The samples were obtained from individuals during 2000–2010. As a result, all of the antiretroviral therapy (ART) regimens used in these subjects are no longer recommended. The integrase

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inhibitors, dolutegravir or bictegravir, and the boosted protease inhibitor, darunavir, which are the currently recommended regimens without caveats [4], would not be compromised by the mutations described by Li *et al.* [1]. The presence of an M184V or I mutation has been shown not to compromise regimens of these drugs in combination with a tenofovir prodrug as well as lamivudine or emtricitabine [5,6]. Two regimens that might be compromised by the mutations described by Li *et al.* [1] are the two drug regimens of dolutegravir/lamivudine and long-acting rilpivirine/cabotegravir. These regimens have proven noninferior to three drug regimens in individuals with no prior ART treatment histories and absence of resistance in pretreatment plasma samples. Preexisting mutations compromising rilpivirine have been associated with rilpivirine/cabotegravir failure [7], and M184 V or I, abrogating lamivudine efficacy, results in dolutegravir monotherapy with the outcome of substantial rates of treatment failure with drug resistance [8]. DNA genotyping of a PBMC sample when contemplating a switch in a well suppressed patient might make some sense if transmitted or acquired is suspected, although the FDA approval for these two drug combinations excludes suspected drug resistance mutations. With the encouraging diminution of acquired drug resistance to the newer recommended regimens throughout the resource-rich countries [9,10] and the remarkable efficacy of these regimens, much less drug resistance testing has been needed for patient management and the primary role of drug resistance has become the detection of transmitted drug resistance in newly diagnosed (viraemic) individuals. This resistance is predominantly to NNRTIs and confers little threat to currently recommended drug regimens with perhaps the exception of the two drug regimens mentioned above.

Finally, although cellular DNA sequencing can clearly document the accumulation of resistance mutations selected by drug treatment (or hypermutation), no studies to this author's knowledge have demonstrated clinical value of testing for archived drug resistance to improve treatment outcomes of ART regimen selection. DNA genotyping during effective suppression with ART has been shown to identify archived drug resistance mutations when testing plasma is not feasible in well suppressed subjects; nevertheless, the utility of this genotyping information remains to be documented, especially with the currently approved drug regimens. In summary, the results from Li *et al.* [1] convincingly demonstrate that APOBEC editing of HIV reverse transcripts can generate enrichment of certain drug resistance mutations in proviruses that have not benefitted from the shunting of this virus restriction factor to proteasomal degradation by *vif*. The lesson for patient management is that the analysis of HIV DNA sequencing for drug resistance needs to filter out sequences that have been hypermutated, a step that is part of the GenoSure Archive assay. Studies to document the utility of such assays will still be needed to prove their benefit for effectively selecting new ART regimens.

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Conflicts of interest

There are no conflicts of interest.

References

1. Li Y, Etemad B, Dele-Oni R, Sharaf R, Gao C, Lichterfeld M, Li JZ. **Drug resistance mutations in HIV provirus are associated with defective proviral genomes with hypermutation.** *AIDS* 2021; **35**:1015–1020.
2. Sheehy AM, Gaddis NC, Choi JD, Malim MH. **Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein.** *Nature* 2002; **418**:646–650.
3. Bishop KN, Holmes RK, Sheehy AM, Malim MH. **APOBEC-mediated editing of viral RNA.** *Science* 2004; **305**:645.
4. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel.** *JAMA* 2020; **324**:1651–1669.
5. Olearo F, Nguyen H, Bonnet F, Yerly S, Wandeler G, Stoeckle M, *et al*. **Impact of the M184 V/I mutation on the efficacy of abacavir/lamivudine/dolutegravir therapy in HIV treatment-experienced patients.** *Open Forum Infect Dis* 2019; **6**:ofz330.
6. Andreatta K, Willkom M, Martin R, Chang S, Wei L, Liu H, *et al*. **Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184 V/I.** *J Antimicrob Chemother* 2019; **74**:3555–3564.
7. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, *et al*. **Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression.** *N Engl J Med* 2020; **382**:1112–1123.
8. Wijting I, Rokx C, Boucher C, van Kampen J, Pas S, de Vries-Sluijs T, *et al*. **Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised noninferiority trial.** *Lancet HIV* 2017; **4**:e547–e554.
9. Scherrer AU, von Wyl V, Yang WL, Kouyos RD, Böni J, Yerly S, *et al*. **Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: a 15-year prospective cohort analysis.** *Clin Infect Dis* 2016; **62**:1310–1317.
10. Bajema K, Nance R, Delaney J, Eaton E, Davy-Mendez T, Karris M, *et al*. **Substantial decline in heavily treated therapy-experienced persons with HIV with limited antiretroviral treatment options.** *AIDS* 2020; **34**:2051–2059.