Special Contribution

2014 Update of the Drug Resistance Mutations in HIV-1

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This July 2014 edition of the IAS–USA drug resistance mutations list updates the figures last published in March 2013.[1]

The following mutations have been added to existing classes or drugs: K65E/N has been added to the bars for the nucleoside and nucleotide analogue reverse transcriptase inhibitors (nRTIs) abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir[2]; L100I has been added to the bar for the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) rilpivirine[3,4]; and F121Y has been added to the bars for the integrase strand transfer inhibitors (InSTIs) dolutegravir, elvitegravir, and raltegravir.[5,6] With regard to protease inhibitors (PIs), it cannot be excluded that drug resistance may be selected for outside the protease encoding region.[7,8]

Methods

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As with all IAS–USA volunteer panels, members are rotated on a structured, planned basis. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

In addition, the group considers only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (FDA) as well as any drugs available in expanded access programs are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Identification of Mutations

The mutations listed are those that have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from patients in whom the drug is failing; (4) association studies between genotype at baseline and virologic response in patients exposed to the drug.

The development of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in otherwise wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in making therapeutic decisions. In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance develops most commonly to lamivudine or emtricitabine or the NNRTIs).

The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, nonadherence to medications, laboratory error, lack of current knowledge of the association

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of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing[9] and 2014 IAS–USA panel recommendations for antiretroviral therapy.[10] Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to the **journal"at"iasusa.org** or by fax to 415-544-9401.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and **no alterations in format or the content can be made.**

Requests to reprint the material should include the name of the publisher or sponsor, the name or a description of the publication in which you wish to reprint the material, the funding organization(s), if applicable, and the intended audience. Requests to make any minimal adaptations of the material should include the former, plus a detailed explanation of the adaptation(s) and, if possible, a copy of the proposed adaptation. To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted.

Permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted at www.iasusa.org. Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact the IAS–USA.

Financial affiliations in the past 12 months: The authors (listed alphabetically) disclose the following affiliations with commercial organizations that may have interests related to the content of this article: Dr Calvez has served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Janssen Pharmaceuticals, Inc, Pfizer, Inc, Roche, and ViiV Healthcare. Dr Günthard has served as an advisor and/or consultant for Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Novartis, Pfizer, Inc, Roche, and Tibotec Therapeutics, with all compensation going to his institution, University Hospital of Zurich. He has received unrestricted research and educational grants to his institution from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Merck Sharp & Dohme, and Roche; has served on a data and safety monitoring board for Merck Sharp & Dohme; and has received travel grants from Bristol-Myers Squibb and Gilead Sciences, Inc. Dr Johnson has received research support from Abbott Molecular, Roche Molecular Diagnostics, and Siemens Healthcare Diagnostics, Inc. Dr Paredes has received research grants awarded to IrsiCaixa and Lluita Contra la SIDA Foundations from Gilead Sciences, Inc, and ViiV Healthcare. Dr Pillay has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gen-Probe Inc, Gilead Sciences, Inc, Sirenas, Prism, and Monogram Biosciences, Inc. He owns stock from Chimerix. Dr Shafer has served as a consultant or advisor for Celera and has received grants from Bristol-Myers Squibb F. Hoffmann-La Roche, Ltd, Gilead Sciences, Inc, and Merck & Co, Inc. Dr Wensing has served on advisory boards for Bristol-Myers Squibb and Gilead Sciences, Inc; has received grants from Janssen Pharmaceuticals, Inc, and ViiV Healthcare; and has received travel, accommodation, or meeting expenses from Bristol-Myers Squibb and Virology Education.

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