Special Contribution

2015 Update of the Drug Resistance Mutations in HIV-1

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The 2015 edition of the IAS–USA drug resistance mutations list updates the figures last published in July 2014. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The figures are designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs and, therefore, in making clinical decisions regarding antiretroviral therapy.

The 2015 edition of the IAS–USA drug resistance mutations list updates the figures last published in July 2014.[1] The following mutations have been added to the bars for the integrase strand transfer inhibitors: Q148R, N155H, and R263K for dolutegravir, and R263K for elvitegravir and raltegravir.[2-5] The G140S mutation for dolutegravir is no longer bold, and the Q148H/K mutations for elvitegravir are now bold.[6]

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 drug resistance–associated mutations for HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV-1. 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 as well as any drugs available in expanded access programs are included (listed in alphabetic 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 emerges most commonly to lamivudine or emtricitabine or nonnucleoside analogue reverse transcriptase inhibitors).

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 of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions

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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[7] and 2014 IAS–USA panel recommendations for antiretroviral therapy.[8] Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to **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 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 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 as an advisor or consultant to and has received research grants from Bristol-Myers Squibb, Gilead Sciences, Inc, Johnson and Johnson, and ViiV Healthcare. Dr Günthard has served on a data and safety monitoring board for Merck & Co, Inc, and has received grants for travel from Gilead Sciences, Inc, and Janssen Therapeutics. Dr Johnson has no relevant financial affiliations to disclose. Dr Paredes has served as a consultant or advisor to Gilead Sciences, Inc, and ViiV Healthcare and has recieved research grants from ViiV Healthcare. Dr Pillay has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gilead Sciences, Inc, Hera Therapeutics, and Monogram Biosciences, Inc. Dr Shafer has served as a consultant or advisor for Celera and has received grants from Bristol-Myers Squibb, Celera, Gilead Sciences, Inc, Merck & Co, Inc, Roche Molecular, and Siemans Health Care. Dr Wensing has served on advisory boards for Bristol-Myers Squib, Gilead Sciences, Inc, and ViiV Healthcare; has received grants from Janssen Pharmaceuticals, Inc, and Gilead Sciences, Inc; and has received travel, accommodation, or meeting expenses from Gilead Sciences, Inc, and Virology Education.

Funding/Support: This work was funded by IAS–USA. No commercial company or government funding was used to support the effort. Panel members are not compensated.

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