The HIV-1 Non-subtype B Workgroup: An International Collaboration for the Collection and Analysis of HIV-1 Non-subtype B Data

Rami Kantor*1, Robert W Shafer2, David Katzenstein3 for the HIV-1 Non-subtype B Workgroup*

Address: 1Assistant Professor (Research), Division of Infectious Diseases, Brown University, Providence, Rhode Island, 2Assistant Professor, Division of Infectious Diseases, Stanford University, Stanford, California and 3Professor, Division of Infectious Diseases, Stanford University, Stanford, California
* Corresponding author

HIV Diversity and Drug Resistance
HIV-1 group M, the major pathogen responsible for the AIDS pandemic, is characterized by a wide range of genetic diversity among distinct subtypes (A-K), sub-subtypes (A1, A2; F1, F2), and circulating recombinant forms (CRF01_AE, CRF02_AG, and more). The different variants are approximately equidistantly related, and are distinct from one another across the entire genome.[1]

Current FDA-approved antiretroviral medications include 18 drugs targeted against 2 pol gene enzymes, the reverse transcriptase (RT) and the protease. Antiretroviral drug resistance is common as treatment efforts intensify, and is both a cause and a result of virologic treatment failure and incomplete virus suppression. Drug resistance is an adaptive viral response, and once virologic failure occurs, it is necessary to change drug therapy, substituting to new drugs to which the virus is susceptible for suppression of virus replication. The larger body of experience with treatment of subtype B virus infection has provided considerable data on the patterns of resistance which may emerge following virologic failure.[2]

The Global Paradox
Most of our current knowledge of HIV-1 drug susceptibility and resistance, and interpretations of genotypic changes in HIV-1 RT and protease, are based on data obtained from HIV-1 subtype B viruses prevalent in North America, Western Europe, and Australia. Worldwide, however, the majority of people with HIV are infected with non-B subtypes, which differ from subtype B by as much as 30% in env and 15% in pol.[3] With growing treatment and access to antiretroviral therapy in resource-limited settings, the non-subtype B viruses prevalent in the African and Asian epidemics are only now becoming the targets of widespread antiretroviral therapy. As the epidemic and treatment efforts mature, there is the expectation that differences in resistance patterns may emerge between divergent subtypes.

There is extensive literature on sequence data from untreated and treated persons infected with subtype B virus. This has led to increasingly accurate, albeit complex, interpretations of subtype B drug resistance. Patterns of mutations arising during virologic failure with specific drugs have become increasingly recognizable, making it possible to improve the response to second-line treatment through genotypic resistance testing.[4] However, the data to accurately interpret resistance are generally not available for non-B subtypes, and frequency and patterns of specific mutations and response to antiretroviral drug therapies have not been well characterized.

For persons initiating drug therapy, the presence of known drug-resistance mutations and polymorphic residues that differ from the consensus sequence of subtype B may drive treatment response. For persons failing drug therapy, as in subtype B, assessment of the drugs to which their virus is susceptible may improve subsequent treatment. Through clinical trials and practice, there are
increasing data on the genotype of B and non-B viruses among drug-naive and -experienced patients. Although the overall response to drugs appears to be similar, differences between subtypes in terms of specific mutations and drug resistance may emerge as antiretrovirals are widely applied to treatment throughout the world.

Potential Implications of HIV Diversity
Despite intensive studies, it has been difficult to identify clear differences between the group M subtypes and CRFs with respect to pathogenesis, transmission, or drug susceptibility. Host genetics, which include chemokine receptor polymorphisms, pharmacogenomic markers, and immune response diversity (HLA), each contribute to the natural history and response to treatment within an individual. In general, subtype B and non-B treated patients have shown relatively similar rates of overall response to drug treatment.[5,6] However, the pol genes of each subtype are phylogenetically distinct, contain distinct amino acids at variable sites, and may use different nucleic acid triplets, even to encode the same amino acid.[7-9]

Protease and RT variation between subtypes is increasingly linked to differences in disease progression and the potential for infection transmission. Such differences also affect enzymatic properties of protease and RT, phenotypic susceptibility to antiretroviral drugs, and evolution of subtype-specific genotypic patterns of drug resistance. Despite subtle differences that have been identified in small cohorts, the response to antiretroviral therapy among non-B infected persons is adequate and certainly comparable to subtype B infected persons. Several groups[10-13] have described the likely effect of specific mutations on antiretroviral susceptibility in subtype B viruses. Although this will support increased global access to antiretroviral therapy, it is not known how well these known subtype B mutations encompass resistance in non-subtype B viruses. As treatment access is extended to increasing numbers of individuals with non-subtype B infection, the potential for inter-subtype differences in drug response and drug resistance is enhanced. As knowledge increases and new mutations are identified,[14] algorithms to interpret drug resistance will need to be continuously updated.

The International Non-subtype B Workgroup
We have established an international workgroup for the collection and analysis of RT and protease sequences and data from persons infected with non-B HIV-1 subtypes. Currently, the workgroup consists of investigators from 15 sites in 13 countries. The goal of the workgroup is to collect and analyze a robust database of sequences and clinical data to identify similarities and differences among HIV-1 subtypes with respect to drug resistance. As treatment efforts increase, data on non-B resistance patterns will be useful to test the hypothesis that the knowledge acquired in subtype B can be implemented in persons infected with non-B subtypes.[15] The collected data are intended to be publicly available, and can serve as a reference dataset and as a watch list for resistance surveillance programs and epidemiologic studies (see poster MoPeC3446 from the 15th International AIDS Conference).

Conclusion
Thousands of well-characterized sequences within each subtype will likely be required for definitive conclusions regarding different resistance patterns and clinical response among non-B HIV-1. For new drugs and certain combinations, there are insufficient data, even in subtype B HIV-1. Worldwide collaboration, using common data collection instruments and uniform protocols, is essential to the analysis of non-B resistance. This is crucial as access to antiretroviral therapy in the developing world increases within the next few years, and as migration and travel lead to a rise in non-B infected persons in the developed world. Extensive interlaboratory collaboration will enable better understanding of the potential implications of HIV-1 diversity and effective antiretroviral treatment.

Authors and Disclosures
Rami Kantor, MD, has disclosed no significant financial interests or relationships.

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