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Resistance Data Revolution: Insights, Challenges and FDA Compliance Implementation

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ABSTRACT

HIV treatment, also known as antiretroviral therapy (ART), is a combination of medications that help control the progression of the virus. Currently, millions of people worldwide receive ART. Resistance data is a key component in HIV therapy, playing a crucial role in optimizing ART, enhancing viral suppression, and preventing the transmission of drug-resistant strains. It helps tailor effective regimens, particularly for patients experiencing treatment failure. This poster highlights the end-to-end data flow of resistance data, detailing its complex processes, including data collection, standardization, and analysis in one of our studies. It also addresses the challenges faced during implementation. Additionally, the poster provides insights into patient treatment optimization using resistance data.

INTRODUCTION

The world has embarked on a fast-track strategy to achieve the Joint United Nations Program on HIV/AIDS 90-90-90 target and reduce the number of new HIV infections to 500,000 per year by 2020. Achieving the 90-90-90 target requires that 90% of all people living with HIV will be diagnosed, 90% of all people with known HIV infection will be receiving antiretroviral (ARV) therapy, and 90% of all people receiving ART will have a suppressed viral load. While the successful implementation of these recommendations will reduce the number of new HIV infections, the dramatic increase in ARV use will likely increase the prevalence of acquired drug resistance (ADR) in treated individuals and transmitted drug resistance (TDR) in newly infected individuals.

Whereas the principles of drug resistance are similar in all populations, differences in access to diagnostic testing and to many ARVs in low- and middle-income countries (LMICs) necessitate different approaches to the management of TDR and ADR. In most LMICs, HIV drug resistance (HIVDR) testing is neither feasible nor routinely recommended for patients receiving ART.

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HIV Medicine classification:

The goal of HIV medicines is to prevent HIV from multiplying. There are 6 classes of drugs used in antiretroviral therapy. These drugs generally fall into classes according to the phase of the HIV life cycle they inhibit. More common combinations include 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase inhibitor (II). The drugs are listed below according to their class and generic names.

HIV-1 Drug Resistance Testing:

HIV-1 drug resistance testing can be performed phenotypically or genotypically. Phenotypic in vitro susceptibility assays measure ARV susceptibility in cell culture. Due to cost and lengthy turnaround time, phenotypic resistance testing is typically reserved for drug development, drug resistance research, or complex clinical cases. Standard genotypic resistance testing (SGRT) involves the use of dideoxyterminator Sanger sequencing of protease, RT, and/or integrase to identify established clinically significant DRMs. SGRT is performed on PCR products directly amplified

from cDNA that has been reverse-transcribed from plasma RNA. Although the lower limit of SGRT detection is generally agreed to be around 20%, both point mutation assays (PMAs) and next generation deep sequencing (NGS) technologies often detect drug-resistant variants at levels well below a 20% threshold. Due to the high number of sequences obtained with NGS, the cost per sequence obtained with this platform is lower than with SGRT. In NGS deep sequencing the depth of coverage refers to the number of viral variants sequenced, typically several hundred.

Drug Resistance Test Interpretation:

Understanding the results of drug resistance tests is one of the most difficult tasks facing HIV care providers. There are many DRMs and they arise in complex patterns that cause varying levels of drug resistance. Some DRMs are responsible for just low levels of resistance to a drug but it would not be a contraindication to using that drug if the remaining components of a patient's regimen were fully active. Further complicating genotypic resistance test interpretation is the recognition that SGRT and even NGS deep sequencing may not detect all the resistant variants within an individual patient and that inference into the possible presence of these variants will depend on a patient's past treatment regimens.

The predictive value of specific mutations on the response to a new ARV has been shown most convincingly in large clinical trials in which individuals were randomly assigned to receive a new ARV or placebo in combination with an optimized background regimen. Additionally, observational studies have also shown that the predicted activity of a new ARV regimen (often called the genotypic susceptibility score) is a strong independent predictor of the response to that regimen.

The Stanford HIV Drug Resistance Database (HIVDB) provides an online genotypic resistance interpretation program to help clinicians and laboratories interpret HIV-1 genotypic resistance tests (http://hivdb.stanford.edu).

The estimate of reduced susceptibility for each ARV is obtained by adding each of the DRMs' penalty scores for the ARV. The DRM penalty scores (http://hivdb.stanford.edu/DR/) are based upon the DRM characteristics and the consensus on the clinical significance of a DRM among experts in the field, such as the IAS-USA Drug Resistance Mutations Group.

FDA recommendation on data submission standards:

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended but not required.

Efficacy Outcomes Data Set (ADEFFOUT):
This is a one-record-per-subject data set that contains a comprehensive set of variables pertaining to the subject and their measures of efficacy. The specification for ADEFFOUT organizes these variables into groupings of subject demographics, baseline characteristics (including prior therapies and genotypic and phenotypic data), subject disposition, measures of efficacy over the time span of the trial, exposure, and important covariates.

CONCLUSION
An unprecedented scale-up of ART has been observed in the last 10 years: at the end of 2015, 17 million people were receiving antiretroviral therapy. However, the HIVDR emergence associated with increased ART use can compromise the effectiveness of antiretroviral drugs. Resistance is an inevitable consequence of any interventions that, through the use of ARVs, aim to reduce mortality, morbidity and HIV transmission. While concern for resistance should never limit ARV access for all HIV-infected individuals, the long-term implications of earlier initiation on adherence and drug resistance need to be closely monitored. Knowledge of the mechanisms, implications, and patterns of HIVDR can be harnessed to both select effective SGRT-guided therapy for individuals and/or to adapt national treatment guidelines according to surveillance findings following the public health approach to HIV treatment.

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