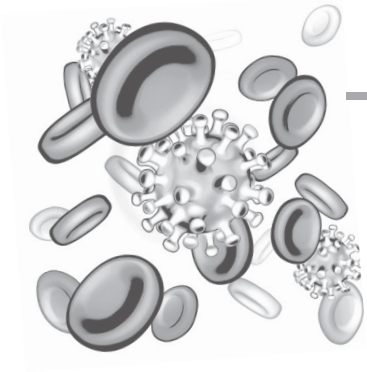

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HIV Treatment Failure and Resistance

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INTRODUCTION

Among the goals of antiretroviral therapy (ART) is to achieve maximal and durable suppression of human immunodeficiency virus (HIV) replication and prevent the emergence of drug resistance.[1] Treatment failure occurs when patients on ART do not achieve virologic suppression or experience virologic rebound. These patients are at risk of developing resistance mutations to one or more components of their regimen. Pharmacists can help patients achieve virologic suppression, identify patients with treatment failure, assess for the presence of resistance, aid in interpreting HIV resistance testing, and assist in selecting new ART regimens in patients with treatment failure and resistance.

TREATMENT FAILURE TERMS AND DEFINITIONS

Virologic Failure

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents defines *virologic failure* as HIV RNA level consistently >200 copies/mL, indicating the inability to attain or sustain suppression of viral replication.[1]

Incomplete Virologic Response

Based on the DHHS guidelines, *incomplete virologic response* is defined as having two sequential plasma HIV RNA levels ≥200 copies/mL without documented viral suppression in a person who has been treated with at least 24 weeks of ART.[1] Persistent HIV RNA ≥200 copies/mL is associated with accumulation of drug resistance and virologic failure.[2]

Virologic Blips

The DHHS guidelines define *blips* as the occurrence of a single detectable HIV RNA level and subsequent return to levels below the limit of quantification. Blips are often low levels of virus and are not usually an indication of virologic failure.[1]

Low-Level Viremia

These are HIV RNA levels that persistently fall between undetectable and <200 copies/mL in individuals on ART. Studies have reported conflicting results as to whether low-level viremia can result in virologic rebound and evolution of drug resistance.[2-4] One long-term study found a correlation between the risk of virologic failure and an increasing level of viremia, while results from another study showed that, as a threshold for virologic failure, HIV RNA levels of 200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound to >200 copies/mL.[3,4]

Suboptimal CD4+ Cell Count Response

ART initiation and viral suppression will result in an increase in CD4+ cell count in most individuals.[1] However, in about 15% to 20% of individuals who start ART at CD4+ cell counts <200 cells/mm^3, CD4+ count recovery may plateau at these low levels.[5,6] Persistently low CD4+ cell counts despite ART use and viral suppression have been related to an increased risk of morbidity and mortality.[7]

RESISTANCE

Basic Principles

Transmitted HIV resistance occurs when an individual is infected with a virus that is already resistant to one or more drugs. The probability that an individual will acquire a drug-resistant virus can be associated with the prevalence of drug resistance among the population of individuals participating in high-risk behaviors. In the United States, a study conducted between 2003 and 2008 by the U.S. Center for AIDS Research showed a prevalence of genotypic resistance to at least one antiretroviral (ARV) to be 14.2% (8.3% non-nucleoside reverse transcriptase inhibitor [NNRTI], 8.2% nucleoside/tide reverse transcriptase inhibitor [NRTI], and 4.2% protease inhibitor [PI]).[8] Importantly, the prevalence of drug resistance reported in this study varied by geographic region.[8]

In contrast to transmitted resistance, *acquired resistance* emerges while a person is receiving ART and can occur for a variety of reasons, including suboptimal medication adherence, suboptimal virologic potency of the ART regimen, or interactions that negatively influence ART drug concentrations.[9] Innately drug-resistant viruses that have not been exposed to selective drug pressure are rare.[10]

Genetic Barriers to Resistance

Genetic barrier to resistance refers to the number of HIV mutations required for the development of resistance to a specific ARV medication. High barrier to resistance is considered when a greater number of critical mutations are necessary to render treatment ineffective. In contrast, ARVs that require fewer mutations before they are no longer effective are considered to have a lower barrier to resistance.[9]