HIV in Podcast USA

Episode title: Archive Resistance

Episode length: 10:46

Intro music

Rachel Rogers: Hi there and welcome to HIV in Podcast, brought to you by Gilead Sciences. This episode on archived HIV resistance has been adapted from a video that was filmed on August 26, 2024. The discussion was based on data available at the time of recording. I'm Rachel Rogers, Director of US Medical Affairs at Gilead Sciences and in this episode, you'll hear from Dr Michelle D'Antoni, a Gilead researcher in clinical virology. Thanks for listening to HIV in Podcast - we hope you enjoy it!

Introduction

- Hi, I'm Michelle D'Antoni, and through my research on HIV treatment, I hope to help communities impacted by the virus.
- Today, we'll explore the topic of archived HIV resistance and its impact on antiretroviral therapy.
- Significant progress has been made in ending the HIV epidemic with the use of antiretrovirals.
- Early in the epidemic, treatment options and combinations were limited due to their toxicities, high pill burdens, inconvenient dosing and incomplete viral suppression.
- Sequential monotherapy and incomplete viral suppression contributed to the emergence of HIV drug resistance mutations in the individual and community, which compromised the choice of future treatment.
- Compared with older regimens, today's regimens use combinations of antiretrovirals that provide more effective viral suppression and have more tolerable safety profiles, all the while drug development continues to innovate regarding future treatment options.
- However, HIV drug resistance remains a threat to ending the HIV epidemic and can occur during periods of viremia, arising either through transmission or acquired during suboptimal adherence and virologic failure.

- Therefore, effective suppression of viral load and management of antiretroviral resistance is key to ensuring successful treatment outcomes for the patient and preventing onward transmission of HIV.

Brief overview of HIV life cycle and HIV treatment

- Each class of antiretroviral drug used to treat HIV is designed to target a specific step in the HIV life cycle, the process whereby HIV uses the machinery of $CD4^+$ T cells to multiply and spread throughout the body.
- Current classes of antiretrovirals include CCR5 antagonist or post-attachment inhibitors, NRTIs, NNRTIs, INSTIs, PIs and capsid inhibitors.

Brief overview of drug resistance mutations and transmitted drug resistance prevalence data

- HIV undergoes many rounds of replication each day. However, HIV replication is error-prone and mutations occur at a high rate, including those that arise in the target proteins of antiretrovirals, which may lead to drug resistance.
- The likelihood of developing resistance is highly dependent on active viral replication and the level of antiretrovirals in the plasma:
    - In the absence of drugs or at low antiretroviral plasma levels, HIV replicates and remains wild type.
    - At optimal therapeutic drug levels, HIV is suppressed and resistance rarely emerges.
    - Suboptimal or inconsistent antiretroviral levels allow for selective pressure to occur at the same time as HIV replication, leading to the emergence of drug-resistance mutations.
    - Inadequate treatment adherence may cause inconsistent antiretroviral levels. A retrospective claims database analysis found that adherence to antiretrovirals was suboptimal across the United States and varied by region.
- Antiretroviral resistance strains can also be transmitted person to person.
- Although the prevalence of transmitted drug resistance has decreased over time, drug resistance mutations in certain antiretroviral classes are more prevalent than others.
- Based on current rates of transmitted resistance, the HIV reverse transcriptase and protease genes are the focus of resistance testing.

- Drug resistance testing data from the US National HIV Surveillance System between 2014 and 2018 found that:
  - the prevalence of any transmitted drug resistance mutation was 18.9%
  - NNRTI and NRTI resistance were the drug classes with the highest prevalence of transmitted drug resistance mutations, at 12.0% and 6.9%, respectively
  - transmitted PI resistance was much less common, with a prevalence of 4.2%
  - and transmitted INSTI resistance was rare, with a prevalence of 0.8%.

Viral reservoirs and archive resistance

- Resistance-associated mutations that are present during a period of viremia, either due to transmission or development during treatment failure, can be archived in the latent HIV reservoir.
- This viral reservoir is mainly comprised of $CD4^+$ T cells harboring HIV but which are not actively producing new virus particles.
- Resistance-associated mutations may revert to wild type in the plasma in the absence of selective drug pressure, but resistant virus may persist in the latent HIV reservoir even when viral load is undetectable.
- The latent HIV reservoir is heterogenous, containing a range of variants, from a minority of HIV infected cells that are transcriptionally active to those that are not replication competent because of the deep latency of the cell or the virus being defective.
- The reservoir is dynamic, expanding and contracting over time as the pool of memory $CD4^+$ T cells latently infected with HIV variants is modulated in response to stimuli, including cytokines and antigenic exposure. This means that the frequency of HIV variants will be modulated over time.
- Current antiretroviral drugs don't eliminate virus found in cells in the latent HIV reservoir. Therefore, if antiretrovirals are stopped, virus can rebound, allowing mutant virus populations to reemerge and become the dominant variant under the appropriate selective drug pressure.

Resistance testing overview

- Genotypic and phenotypic assays can be used to predict or detect HIV drug resistance.
- Phenotypic assays measure the ability of virus to grow in different concentrations of antiretrovirals and can identify which drugs will work and which viruses will no longer

respond to the current regimen. Phenotypic assays are labor-intensive and relatively more expensive than genotypic testing.

- Genotypic assays make a prediction of drug susceptibility based on genetic mutations found in virus sequences. Assay types include plasma RNA testing and proviral DNA testing.
- Plasma RNA testing, which generally requires a plasma viral load of at least 500 copies/mL, may not identify minor resistance variants that comprise less than 10–20% of the viral population.
- Proviral DNA testing can be performed in people with undetectable or low viral loads and identifies archived resistance.
    - Proviral DNA testing may fail to detect some drug resistance mutations as the assay is insensitive, partly due to sampling small numbers of latently infected peripheral $CD4^+$ T cells.
    - Long periods of viremia and high plasma HIV RNA levels increase the likelihood of detecting drug resistance mutations in proviral DNA, compared with shorter episodes of viremia or low viral loads.
    - Additionally, standard proviral genotypic testing methods cannot discriminate between intact and defective virus, complicating interpretation of testing results.
- A longitudinal analysis of preexisting drug resistance mutations found that almost half of mutations had variable detection across the sample timepoints in genotypic testing assays.
- This and other studies suggest that failure to detect a drug resistance mutation at a given timepoint does not mean that it will not be detected in the future or negate a previously detected result.
- Consequently, when selecting a new antiretroviral regimen for a patient, it is important to obtain a complete treatment history and the results of prior resistance tests, if available.

Archive resistance testing guidelines

- Use of proviral resistance testing is suggested by the DHHS in patients with a history of multiple prior virologic failures or multiple antiretroviral regimens.
- Proviral testing may also be useful when switching antiretroviral regimens in people with low level viremia, according to the IAS-USA guidelines.
- Both guidelines highlight that proviral testing may not detect all drug resistance mutations, therefore results must be interpreted with caution.

Future directions

- While current antiretroviral therapy effectively prevents disease progression, it does not eliminate the latent HIV reservoir.
- Potential curative strategies to target the HIV reservoir include a “shock and kill” approach to activate gene transcription in latent HIV and then kill the virus using the body’s immune system and a “block and lock” approach to prevent the reactivation of HIV in the latent reservoir.
- Further research into the HIV reservoir is required to push forward these potentially curative strategies.

Conclusion

- To conclude, thanks to effective antiretroviral therapy, people living with HIV may have a normal lifespan.
- However, drug resistance mutations can occur during periods of viremia and can be subsequently archived in the latent HIV reservoir, reemerging under the appropriate selective drug pressure.
- The detection of resistance mutations using genotypic assays can be variable over time.
- Therefore, when selecting a new antiretroviral regimen for a patient, it is important to consider the patient’s complete treatment history as well as the results of any prior resistance tests, because drug resistance can jeopardize the efficacy of antiretrovirals, increasing HIV acquisition rates and HIV-associated morbidity and mortality.

Rachel Rogers: And this brings us to the end of this episode. Many thanks to Gilead Sciences, who have supported this podcast, and to Oxford PharmaGenesis for their assistance in editing and production. Listeners should note that our discussions in this episode are relevant to the USA only and may not be appropriate for other regions. If you would like to learn more about the topics covered today, our references will be in the show notes. If you enjoyed this podcast, spread the word and join us again next time. I'm Rachel Rogers and thanks for listening to **HIV in Podcast**.

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Supplementary information

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Episode description

Dr Michelle D'Antoni discusses archived HIV resistance and its impact on antiretroviral therapy. The views expressed are those of the speakers and not necessarily Gilead Sciences, Inc.

Speakers

Rachel Rogers (Introductions)

Dr Michelle D'Antoni is a Principal Scientist in Clinical Virology at Gilead Sciences, Inc.

Declaration of interests

- Michelle D'Antoni is a full-time employee of Gilead Sciences, Inc.

Abbreviations

CCR5, C-C chemokine receptor type 5; CD4, cluster of differentiation 4; DHHS, Department of Health and Human Services; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; IAS-USA, International Antiviral Society–USA; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RNA, ribonucleic acid.

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