Pre-Exposure Prophylaxis and HIV Drug Resistance: An Overview

FACT SHEET
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HIV Drug Resistance and PrEP

We know that PrEP works well to prevent HIV infection when taken correctly and consistently. However, if a person acquires HIV when using PrEP, there is a chance the virus in their body could mutate and become resistant to the antiretroviral (ARV) drug or drugs being used for PrEP. HIV drug resistance (HIVDR) could happen if a person has undetected HIV infection at the time they start PrEP, if they acquire HIV while using PrEP, or if drug-resistant HIV from a partner is passed on to them. Drug resistance related to PrEP could affect how well some drugs from the same drug class work to treat HIV. Data on the frequency of HIVDR in individuals who seroconvert on PrEP in programmatic settings can provide important information to public health programs.[1,2] See https://www.prepwatch.org/mosaic-hiv-drug-resistance-monitoring-program/ for information and tools to monitor PrEP and drug resistance.

Key Messages

- HIV drug resistance is when mutations in the virus cause one or more HIV drugs to not work as well to treat HIV infection.
- PrEP is effective at preventing HIV and individuals should be counseled to use PrEP products as indicated.
- The benefit of using PrEP to prevent HIV far exceeds the overall low risk of resistance.
- The risk of resistance is higher if an individual starts or continues PrEP without knowing they have acquired HIV. Individuals should be counseled to have routine HIV testing as per country guidelines.
- Monitoring for HIV drug resistance is important to preserve antiretrovirals (ARVs) used in both prevention and treatment.

Why are Drug Classes Important?

ARVs are grouped together in drug classes. Resistance to one drug may result in resistance to some drugs in the same drug class, or an entire drug class of ARVs. Current PrEP methods belong to three types of drug classes: nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI).

- Oral PrEP with tenofovir disoproxil fumarate/emtrictabine (TDF/FTC) or TDF/lamivudine (3TC) are part of the **NRTI class**. The success of dolutegravir-based ART among individuals on failing NRTI drugs offers reassurance on the limited effect of oral PrEP resistance on ART efficacy; however, long-term ART responses are still an important research gap.[3]
- The PrEP ring is part of the **NNRTI class**. The efficacy of the PrEP ring could be compromised in communities with high rates of transmitted NNRTI resistance.
- CAB PrEP is part of the **INSTI class**. HIVDR selected by CAB could have cross-resistance to dolutegravir or bictegravir, which could compromise INSTI effectiveness in ART.

Oral PrEP

Our early understanding about the frequency of drug resistance with oral PrEP came from five completed placebo-controlled clinical trials of TDF/FTC PrEP (FEM-PrEP, iPrEX, TDF2, Partners PrEP, VOICE).[4,5]

- HIV drug resistance was low (3%) for study participants who seroconverted while on PrEP in these clinical trials; all cases of resistance were associated with FTC.
- HIV drug resistance was more frequent (41%) for study participants who initiated PrEP while they were in the acute HIV infection phase; all but one case was associated with FTC.

Data from open-label and demonstration projects have showed similar patterns of resistance[2]:

- Among the seroconversions reported from individuals already on PrEP in open-label and demonstration studies, 6% developed TDF and/or FTC resistance.
- Of the individuals who initiated PrEP during acute HIV infection, 61% developed TDF and/or FTC resistance.
- The GEMS project, which monitored drug resistance in national PrEP rollout programs in several countries in sub-Saharan Africa, found that 23% (27/118) of individuals who became HIV positive during PrEP initiation or while on PrEP had PrEP-associated resistance mutations.[6]

Bottom line: Risk of HIVDR is highest when oral PrEP is started during acute HIV infection. The World Health Organization recommends that oral PrEP scale-up be accompanied by surveillance of HIV drug resistance through a cross-sectional, time-limited survey of all sites providing PrEP in a country.

PrEP Ring

Our understanding of HIV drug resistance and the monthly-inserted PrEP ring comes from two Phase 3 dapivirine ring studies, ASPIRE and The Ring Study, and two open-label trials, HOPE and DREAM.[7] In these studies, a high but similar rate of NNRTI resistance was observed in both the active and placebo ring arms, indicating that resistance was likely transmitted and not from PrEP ring use[2].

- In ASPIRE, eight of 71 seroconversions in the active ring arm (11%) and 10 of 97 seroconversions in the placebo arm (10%) had NNRTI resistance.
- In The Ring Study, 13 of 82 seroconversions in the active arm (16%) and eight of 57 seroconversions in the placebo arm (14%) had NNRTI resistance.
- The frequency of NNRTI resistance in the HOPE and DREAM open-label studies was seven of 38 seroconversions (18%) and five of 18 seroconversions (28%), respectively.
- Few participants initiated the ring during acute infection, and those infections did not result in drug resistance.

Bottom line: The risk of resistance selection from PrEP ring use is low and should not be a barrier to ring rollout. The efficacy of the PrEP ring could be compromised in areas with high rates of transmitted NNRTI resistance; however, there is no concern that this resistance would impact tenofovir, lamivudine, and dolutegravir (TLD) efficacy. Consider monitoring for HIVDR in countries with high background rates of transmitted NNRTI resistance.

CAB PrEP

Our understanding of HIV drug resistance in long-acting cabotegravir as an injectable PrEP method (CAB PrEP), comes from two Phase 2b/3 trials: HPTN 083, conducted with cisgender men and transgender women who have sex with men, and HPTN 084, conducted with cisgender women.[8, 9]

- In HPTN 083, 16 HIV infections occurred among the 2282 participants enrolled into the CAB PrEP arm.

  - Of the 16 participants, INSTI mutations were observed in 10 (63%) individuals: one was living with HIV at time of study enrollment, two acquired HIV during the oral product phase, six acquired HIV despite on time injections, and one restarted CAB injections after infection. The below focuses on two of these categories:
    - One of the four participants, who were living with HIV at the time of enrolment, had INSTI resistance (25% in this category)
    - Six of the six participants, who acquired HIV despite on-time injections, had INSTI resistance (100% in this category)
- In HPTN 084, of the 1614 participants enrolled into the CAB PrEP arm, only four seroconversions occurred and no INSTI mutations were detected.

Bottom line: HIVDR monitoring should be prioritized to better understand and mitigate the two major resistance concerns with CAB PrEP[10]:

1. CAB drug levels can persist for more than a year after the last injection (referred to as the pharmacokinetic "tail"). Drug resistance is a risk for individuals who become HIV positive after discontinuing CAB PrEP because the CAB levels may be too low to prevent infection but high enough to cause resistance.
2. Delayed detection of seroconversion may occur in individuals who become HIV positive while taking CAB PrEP because the injections may reduce the viral load and prolong the time that it takes to develop antibodies to HIV. This means that HIV will be present at levels too low to show up on a rapid test, and drug resistance can develop in the time between becoming HIV positive and testing HIV positive.

References

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