GEMS
GLOBAL EVALUATION OF MICROBICIDE SENSITIVITY

POLICY BRIEF

ART considerations for Individuals with Recent PrEP Use

Policy Context

By the end of 2018, antiretroviral therapy (ART) coverage among people living with HIV reached 62% worldwide, representing 23.3 million people on treatment[i]. At the same time, some low-income and middle-income countries are reporting increases in pretreatment HIV drug resistance (PDR)* rates, mainly in the form of increasing levels of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV) and nevirapine (NVP)[ii].

Individuals with prior antiretroviral (ARV) drug exposure who initiate or reinitiate first-line ART are at higher risk of having NNRTI-resistant HIV-1. According to the World Health Organization (WHO) 2019 HIV Drug Resistance Report[ii], the prevalence of PDR in several drug resistance surveys was 21.1%, compared to 7.8% among ARV-naive treatment initiators.

In 2017, the WHO presented recommendations for countries transitioning from EFV or NVP-based first-line ART regimens to regimens based on the integrase inhibitor dolutegravir (DTG), dependent on drug availability and levels of PDR[iii]. In 2019, WHO updated their guidance, strongly recommending a DTG-based regimen as the preferred first-line treatment option for all adults and adolescents[iv]. They also addressed concerns about small increased risk of neural tube defects among infants born to women who were taking DTG at conception and during the first eight weeks of pregnancy and recommended that effective contraception should be offered to adult women and adolescent girls of childbearing age. Women who wish to become pregnant or who are not using effective contraception can still be prescribed DTG as long as they have been fully informed of the potential increase in the risk of neural tube defects[iv]. Thus, the WHO 2019 guidelines support a woman-centered approach and autonomy to weigh the risks and benefits of using DTG to make an informed decision.

PrEP Use and Risk of PDR

- Using PrEP while having HIV can occur if an individual 1) starts PrEP during undiagnosed HIV infection (e.g. when tested during window period) or 2) becomes infected with HIV while on PrEP (e.g. due to poor adherence or being exposed to an HIV drug resistant strain).
- If HIV infection occurs while a person is using PrEP, that person can develop resistance to NRTIs/NtRTIs used in the PrEP regimen: Tenofovir (TDF), and emtricitabine (FTC) or Lamivudine (3TC)
- When drug resistance to any of these NRTIs/NtRTIs develops, EFV-based first-line ART regimens (which also include the NRTIs/NtRTIs in PrEP), may become particularly susceptible to virologic failure and NNRTI resistance emergence
- This risk is present but greatly diminished with first-line ART regimens containing DTG or protease inhibitors (PI)

ARVs used for pre-exposure prophylaxis (PrEP) are highly effective for HIV prevention, nevertheless those individuals who become HIV infected while using PrEP are at substantial risk of developing resistance to the ARVs used in the PrEP regimen including nucleotide reverse transcriptase inhibitor (NtRTI) TDF and nucleoside reverse transcriptase inhibitors (NRTIs) FTC and/or 3TC[v] (see Box). When a person with HIV drug resistance starts

* Pre-treatment drug resistance (PDR) is defined as resistance transmitted at time of infection or acquired due to prior ARV drug exposure (e.g. in women exposed to ARV drugs for the prevention of mother-to-child transmission of HIV, in people who have received pre-exposure prophylaxis, or in individuals reinitiating first-line ART after a period of treatment interruption without documented virological failure)[ii].

SEPTEMBER 2019

USAID FROM THE AMERICAN PEOPLE

PEPFAR U.S. President's Emergency Plan for AIDS Relief

This brief was made possible by the generous support of the American people by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID) (Cooperative Agreement No. AID-OAA-A-15-00031). The contents are the responsibility of GEMS and do not necessarily reflect the views of USAID or the United States Government.

a standard first-line regimen of EFV in combination with the same two drugs used in PrEP, NNRTI resistance may also emerge due to the high susceptibility of EFV to drug resistance development when not supported by other fully effective drugs. With PrEP expanding into more low- and middle-income countries, and concerns with rising PDR, it is essential to assess the risk of drug resistance in PrEP users.

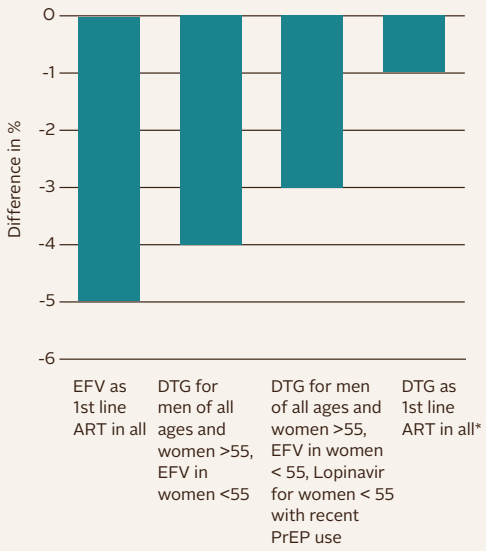
This brief provides an overview of key findings from modeling the impact of drug resistance with PrEP, conducted by the Global Evaluation of Microbicide Sensitivity (GEMS) project. It is intended to support policymakers as they develop the most appropriate first-line ART treatment recommendations during PrEP rollout.

Key Findings

The GEMS modeling analyses considered evidence based on the HIV epidemic with PrEP introduced to female sex workers and adolescent girls and young women, in KwaZulu Natal (KZN), South Africa, to predict the impact of PrEP use (TDF, FTC and/or 3TC), accounting for the effects on HIV drug resistance[vi]. While PrEP use has the potential to be a high impact HIV prevention method, the modeling analyses identified the following key findings regarding choice of ART regimens in the context of PrEP rollout:

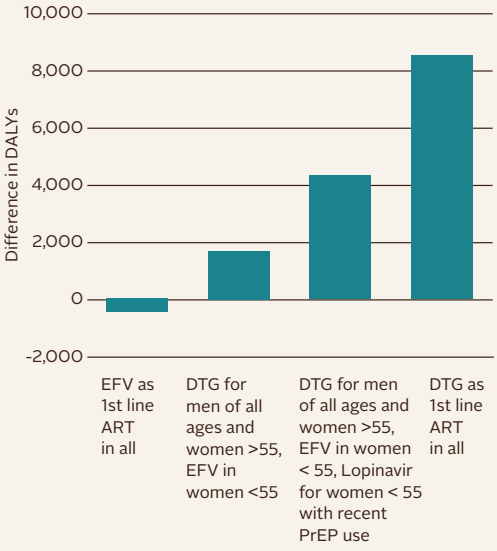
1. Introduction of PrEP use is predicted to lead to higher proportions of HIV positive people with drug resistance among those who seroconverted (although the risk of seroconversion while on PrEP is very low), and thus somewhat poorer future responses to first-line ART in the population compared with no PrEP rollout. The extent of this is dependent on the policy for first-line ART.
    a. Use of NNRTI-based first-line ART regimens is predicted to cause greater increases in drug resistance and result in lower levels of viral suppression compared with first-line ART regimens based on protease inhibitors or DTG (see Figure 1).
2. Increases in NNRTI resistance are predicted to lead to increased transmission of NNRTI drug resistant HIV strains (transmitted drug resistance), supporting WHO recommendations to transition to a DTG based first line regimen.
3. The differences in response to first-line ART regimens are mirrored by differences in the key health outcomes of disability adjusted life years (DALYs) in the population (see Figure 2).

Figure 1: Difference in percent of ART users (with PrEP introduction, compared with no PrEP introduction) who achieve viral load suppression by 12 months after ART initiation, according to first line ART regimen



* Further analyses (not shown here) demonstrate use of DTG as first line ART in all would be cost-effective.

Figure 2: Difference in DALYs* per year (with PrEP introduction, compared with no PrEP introduction) according to first line ART regimen



* Disability Adjusted Life Years (DALYs), is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. DALYs in this analysis is based on a 50-year time horizon with a 3% discount rate, based on a population size of 7.1 million in KZN, South Africa.

Policy Implications*

Monitoring systems should be established across various settings to identify changes in drug resistance rates with PrEP rollout. GEMS project findings can inform PrEP and ART programs, particularly in countries with rising PDR. Key implications include:

- Overall, ART programs should consider avoidance of NNRTI-based first-line ART regimen in recent PrEP users who were diagnosed with HIV
- Countries that have not transitioned to alternative non-NNRTI based first-line treatment regimens, should consider prioritization of non-NNRTI regimens for individuals diagnosed with HIV who recently used PrEP
- Regardless of treatment regimen, it is particularly important that recent PrEP users who were diagnosed with HIV be carefully monitored with viral load testing to inform future treatment approaches for the individual as well as potential changes to country ART policy and clinical guidance documents

* These findings are based on a model and in one specific region (KZN, South Africa), so it may not be applicable to all settings.

References

i. WHO Data and Statistics. https://www.who.int/hiv/data/en/ Accessed in September 2019.

ii. HIV Drug Resistance Report 2019. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.21). Licence: CC BY-NC-SA 3.0 IGO.

iii. Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. Geneva: World Health Organization; 2017 (WHO/HIV/2017.23). Licence: CC BYNC-SA 3.0 IGO.

iv. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.15). Licence: CC BY-NC-SA 3.0 IGO.

v. Parikh UM, Mellors JW. Should we fear resistance from tenofovir/emtricitabine preexposure prophylaxis?. *Curr Opin HIV AIDS.* 2016;11(1):49–55.

vi. Phillips A, Nakagawa F, et al. Potential effectiveness and cost effectiveness of condomless sex targeted PrEP in KwaZulu Natal, South Africa: considerations of drug resistance, ART regimen and HIV HIV testing frequency. AIDS, Jul 2018. Amsterdam, the Netherlands.

SEPTEMBER 2019

USAID FROM THE AMERICAN PEOPLE

PEPFAR U.S. President's Emergency Plan for AIDS Relief

This brief was made possible by the generous support of the American people by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID) (Cooperative Agreement No. AID-OAA-A-15-00031). The contents are the responsibility of GEMS and do not necessarily reflect the views of USAID or the United States Government.