World Health Organization

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HIV drug resistance

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Key facts

- **The emergence of acquired resistance to Dolutegravir (DTG) – the preferred antiretroviral drug – may be higher than anticipated, especially in people with heavy prior treatment experience.**
- **Despite the emergence of resistance, DTG is a highly effective drug in HIV treatment, with more than 90% of patients achieving sustained viral suppression if adherent to treatment.**
- **DTG resistance amplifies the urgent need to implement standardized surveys to characterize the prevalence and patterns of DTG resistance mutations and their associated clinical determinants.**
- **As the use of dolutegravir-based antiretroviral treatment (ART) is scaled up, remaining vigilant in preventing and monitoring HIV drug resistance among infants newly diagnosed with HIV is imperative.**
- **The prevalence of pre-exposure prophylaxis (PrEP)-associated resistance (defined as resistance to tenofovir and/or lamivudine) is low for individuals who acquire HIV while receiving tenofovir-containing PrEP. However, the prevalence of tenofovir and or lamivudine resistance is more than 10-fold higher if PrEP is initiated during undiagnosed acute HIV infection.**
- **To stop HIV drug resistance: make optimal antiretroviral medicines available; retain patients in care and ensure adherence to treatment; increase access and use of viral load testing; and switch regimens rapidly in cases of confirmed treatment failure.**

Overview

Over the past decade, the world has witnessed an unprecedented increase in the use of antiretroviral therapy (ART), which has saved the lives of tens of millions of people living with HIV. At the end of December 2022, 29.8 million people were accessing ART, up from 7.7 million in 2010.

Increased use of HIV medicines has been accompanied by the emergence of HIV drug resistance, the levels of which have steadily increased in recent years.

HIV drug resistance is caused by changes in the genetic structure of HIV that affect the ability of medicines to block the replication of the virus. All antiretroviral drugs, including those from newer drug classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus. If not prevented, HIV drug resistance can jeopardize the efficacy of medicines used to treat HIV *(1)*, resulting in increased numbers of HIV infections and HIV-associated morbidity and mortality *(2)*.

Scope of the problem

Surveillance of HIV drug resistance provides countries with evidence that can be used to optimize patient- and population-level treatment outcomes. WHO recommends that countries routinely implement HIV drug resistance surveys in different populations, including adults, children and adolescents, and PrEP users diagnosed with HIV.

WHO's brief 2024 HIV drug resistance report summarizes recent information, with a focus on HIV drug resistance in the era of integrase-strand transfer inhibitors for HIV prevention and treatment.

Acquired HIV drug resistance

Viral load suppression – the goal of HIV treatment – significantly contributes to preventing the emergence of HIV drug resistance. When viral load suppression is achieved and maintained, drug-resistant HIV is less likely to emerge.

As documented in WHO's brief 2024 HIV drug resistance report, global data remain limited regarding emergence of HIV drug resistance to dolutegravir; however, in published cohorts DGT resistance has been observed in up to 4.8% of participants without viral suppression. Recent studies supported by the United States President's Emergency Plan for AIDS Relief in 4 low- and middle-income countries report prevalence estimates of DTG resistance among individuals receiving DTG-based ART with detectable viraemia ranging from 3.9% in

people without viral suppression on ART for at least 9 months to 19.6% in people with heavy prior treatment experience. More data from standardized surveys of acquired HIV drug resistance and from longitudinal observational cohorts are needed from countries in all regions to provide enhanced insight into risk factors and patterns of drug resistance emergence among individuals exposed to DGT-based ART regimens.

WHO recommends that countries implement routine surveillance of acquired HIV drug resistance in adults, children and adolescents receiving ART either using a viral load laboratory-based method, an ART clinic-based method, or a sentinel survey approach. Which method is used depends upon national viral load testing coverage, the availability of deidentified demographic information, and funding.

Pretreatment HIV drug resistance

Drug resistance can be found in some people before they begin treatment. This type of resistance can either be transmitted at the time of infection or acquired during previous treatments.

WHO recommends surveillance of HIV drug resistance in adults initiating or reinitiating ART and in treatment naive infants initiating ART to inform optimal selection of first-line regimens.

Eleven countries reported data to WHO on the prevalence of pretreatment HIV drug resistance to DTG among adults initiating ART. Only one country detected DTG at a very low prevalence of 0.2%, which was attributed to a rare non-polymorphic integrase mutation. However, these surveys were conducted before DTG was introduced or during the early stages of transition in these countries and thus cannot provide evidence of an absence of DTG resistance in populations initiating or reinitiating ART as scale-up and maintenance on DTG-based ART continues.

The levels of pretreatment rilpivirine (RPV) resistance among individuals initiating ART without previous exposure to ARV drugs ranged from 0.0% (95% CI 0.0–9.4%) in Tajikistan in 2016 to a high of 16.6% (95% CI 11.2–24.0%) in Eswatini. These data suggest that if RPV were to be used in combination with cabotegravir as a long-acting ART, pretreatment HIV drug resistance testing would be needed in some settings to identify those without RPV drug resistance because pretreatment RPV drug resistance mutations are a risk factor for failure to suppress viral load among people treated with long-acting cabotegravir in combination with RPV.

To date, only one country has reported data from a survey of HIV drug resistance among infants after introducing DTG-containing regimens. One infant with DTG resistance was identified whose mother had been receiving DTG-based ART.

The surveillance of HIV drug resistance among treatment-naive infants newly diagnosed with HIV remains highly relevant in the era of DTG-based ART, and accelerated implementation of these surveys is needed. Moreover, effective management of high viral loads among pregnant and breastfeeding women is critical to prevent transmitting HIV to infants.

Pre-exposure prophylaxis for HIV prevention

Many people living in situations considered high risk for exposure to HIV take medicines to reduce the chance of acquiring the disease. WHO recommends pre-exposure prophylaxis (PrEP) be offered as an additional choice for HIV prevention.

HIV infection is infrequent among individuals taking PrEP. However, among people becoming HIV infected despite the use of PrEP, the emergence of drug resistance is common. Drug resistance can reduce HIV treatment options due to the overlapping resistance profiles between antiretroviral drugs used for both PrEP and treatment.

In a literature review published in WHO's 2024 HIV drug resistance report, of 310 reported seroconversions occurring while on oral tenofovir-containing PrEP between 2020 and 2023 in clinical settings, 20% had tenofovir or lamivudine drug resistance, with the prevalence of drug resistance more than 10-fold higher if PrEP was initiated during undiagnosed infection.

Although the risk of acquiring HIV is substantially reduced among long acting cabotegravir PrEP users, to date, 10 cases of integrase inhibitor drug resistance have been reported among people who received long acting cabotegravir PrEP, and all 10 cases had mutations that confer cross-resistance to dolutegravir.

To monitor the effectiveness of HIV medicines used for both treatment and prevention, WHO recommends that countries implement nationally representative surveys to monitor the levels of HIV drug resistance among people initiating treatment, people receiving treatment and among people using PrEP who acquire HIV.

WHO response

Minimizing the emergence and spread of HIV drug resistance is a critical aspect of the broader global response to antimicrobial resistance and requires coordinated action across all government sectors and levels of society.

WHO's Global action plan on HIV drug resistance 2017–2021, aligned with the Global action plan on antimicrobial resistance resistance and the HIV drug resistance strategy, 2021 update outline key actions for country and global stakeholders to prevent, monitor and respond to HIV drug resistance and to protect the ongoing progress towards achieving the global targets for HIV epidemic control by 2030. The key actions are:

1. **prevention and response: implement high-impact interventions to prevent and respond to HIV drug resistance, including an emphasis on dolutegravir-based antiretroviral regimens, monitoring HIV care service delivery, and strategies to ensure uninterrupted drug supplies;**
2. **monitoring and surveillance: obtain quality data on HIV drug resistance and HIV service delivery from periodic surveys while expanding routine viral load and HIV drug resistance testing;**
3. **research and innovation: encourage relevant and innovative research that will have the greatest public health impact in minimizing HIV drug resistance;**
4. **laboratory capacity: support and expand use of viral load testing and build capacity to monitor HIV drug resistance; and**
5. **governance and enabling mechanisms: ensure country ownership, coordinated action, advocacy and sustainable funding are in place to support action on HIV drug resistance.**

WHO's Report on the Global action plan on HIV drug resistance 2017–2021 summarizes the plan's successes, impact and shortfalls using pre-established indicators qualitative interviews of key stakeholders at all levels. The report summarizes the findings of the assessment and paves the way for development of a unified Global Action Plan for HIV, viral hepatitis and sexually transmitted infection drug resistance.

References

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2. **Andrew N Phillips, John Stover, et al. Impact of HIV Drug Resistance on HIV/AIDS-Associated Mortality, New Infections, and Antiretroviral Therapy Program Costs in Sub–**

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