

The threat of HIV Drug Resistance in low- and middle-income countries.

Antiretroviral therapy (ART) is one of the most effective tools available to fight HIV infection. Current ART combinations act by effectively blocking the replication of the virus at different steps of its replication cycle. This leads to durable suppression of HIV viremia, preservation of the immune system, and inability to transmit the virus. Today, there is ample evidence that the latter is one of the most powerful instruments we have to prevent the transmission of HIV infection. If a HIV-infected individual on ART has undetectable viremia, they will not transmit the virus to uninfected individuals, even after having unprotected sexual intercourse (*Rodger et al., Lancet 2019*).

However, the effectiveness of ART can be critically compromised by the emergence of HIV drug resistance (HIVDR). This occurs by selection of mutations in the viral genome at the sites of therapeutic targets, leading to uninhibited viral replication and the transmission of drug-resistant strains in the general population. In the high-income countries, the formula for successfully limiting HIV drug resistance has relied on using highly potent ART regimens with better safety profiles that are easy to take (e.g., one pill per day), which have improved treatment adherence by up to >95%, as well as putting in place the necessary health infrastructure to monitor the clinical response of patients with laboratory tests (i.e. CD4 counts, viral load monitoring and HIV drug resistance testing). As result, many of these countries are well on the way to meeting the WHO/UNAIDS 90-90-90 targets for people living with HIV.

In contrast, the situation is starkly different in the low- and middle income-countries. The latest WHO HIV Drug Resistance Report published in 2019 (<https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/>) revealed an alarming situation in the countries that reported survey data between 2014 and 2018. In 12 of 18 countries (i.e. Eswatini, Namibia, Uganda, South Africa, Zimbabwe, Argentina, Cuba, Guatemala, Honduras, Nicaragua, Nepal, Papua New Guinea), there were high rates of pre-treatment HIVDR (10-30%) to first line therapy (i.e. the NNRTIs efavirenz and/or nevirapine) and was usually twice as high among women than men. The figures for newly diagnosed infants (≤ 18 months) based on surveys conducted in 9 countries (i.e. Malawi, Zimbabwe, South Africa, Togo, Mozambique, Nigeria, Cameroon, Uganda, Eswatini) were devastating, with as many as half to 70% carrying HIVDR mutations, which huge implications for the success of prevention of mother –to –child HIV transmission programs. Moreover, increasing levels of pre-treatment HIVDR have being observed for other drugs that are always part of ART combinations (i.e. the NRTI emtricitabine, lamivudine, abacavir, or tenofovir), with rates ranging 10-20% in some countries.

In response to this catastrophic situation, WHO treatment guidelines have since 2018 recommended the use of dolutegravir as first line ART in low- and middle-income settings (<http://apps.who.int/iris>). Dolutegravir belongs to the class of integrase inhibitors and has already been widely used as first line therapy in high-income countries since 2013, with considerable treatment success due to its potency, fewer side effects, and lower chance of selection for drug resistance compared with the NNRTIs. However, the implementation of dolutegravir as the new first-line therapy in low- and middle-income countries will be met with many challenges. Perhaps the most important of these challenges is the lack of the necessary laboratory infrastructure in many of these countries to conduct HIVDR

surveys, in a setting of already high HIVDR prevalence rates at the population level, where many patients are failing treatment on the existing ART regimens in use.

To ensure long-term success of ART programs in limiting HIVDR and achieving the global 95-95-95 by 2030 targets (<https://www.unaids.org>) therefore, the current wave of transiting to dolutegravir in low- and middle-income countries will require engaging in a multi-sectoral approach, with the concerted effort of the scientific community, governments and the community working together to achieve common objectives. The prevailing challenges that are threatening the success of these efforts also present the unique opportunity to improve the quality of life for people living with HIV in resource-limited settings.

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