

TACKLING HIV DRUG RESISTANCE: TRENDS, GUIDELINES AND GLOBAL ACTION

JULY 2017



It is estimated that by the end of 2016, nearly 37 million¹ people were living with HIV, of whom 19.5 million were taking life-saving antiretroviral therapy (ART). This number highlights the incredible progress made in expanding access to treatment, but also underscores the effort still required to fully implement the World Health Organization's (WHO) "treat all" recommendation. Collective action is needed to provide ART to an additional 17.2 million people, and to ensure that current ART regimens and drugs used for pre- and post-exposure prophylaxis remain durable and effective over the long term.

Adoption of the United Nations' 2030 Agenda for Sustainable Development and WHO's *Global health sector strategy on HIV, 2016–2021* demonstrate the commitment of countries to end the AIDS epidemic by 2030. To track progress towards this goal, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have set the target of 90% of people living with HIV on ART to achieve virological suppression by 2020, rising to 95% by 2030.

The elimination of AIDS as a public health threat calls for accelerated efforts to expand the coverage and quality of treatment and ART services. This expansion needs to be balanced by well-coordinated efforts to ensure that ART remains effective, and that the risks and impact of HIV drug resistance (HIVDR) are minimized.

Minimizing the emergence and transmission of HIVDR is a critical component of the broader global response to antimicrobial resistance (AMR), which aims to provide effective prevention and treatment of infections caused by bacteria, viruses, parasites and fungi.

THE PROBLEM

WHO's *HIVDR report 2017* highlights concerning trends in the levels of HIVDR across several regions that need to be addressed. Pretreatment HIV drug resistance (PDR), detected in people starting ART, is increasing in low- and middle-income countries. This rise is observed more rapidly in Southern Africa and

Eastern Africa, where the estimated annual incremental increase of resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs has reached 23% and 29%, respectively (Fig. 1).

In six of the 11 countries reporting nationally representative survey data (2014–2016), over 10% of individuals who initiated ART had virus resistant to efavirenz (EFV) and/or nevirapine (NVP), the WHO-recommended and widely used NNRTI antiretroviral (ARV) drugs as part of first-line ART (Fig. 2). In two of the 11 countries, levels of resistance to EFV and/or NVP among people starting ART have reached 15%. Overall, among the countries reporting survey data, levels of pretreatment resistance to nucleoside reverse transcriptase inhibitors and protease inhibitors remain low.

Fig. 1: Estimated annual incremental increase of NNRTI pretreatment resistance across studies by calendar year

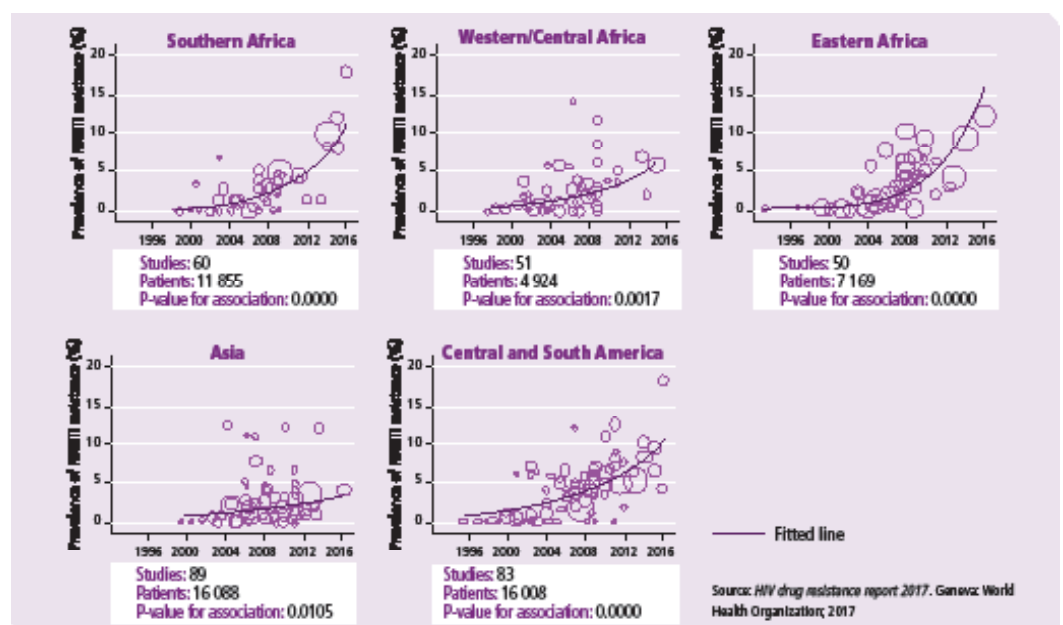
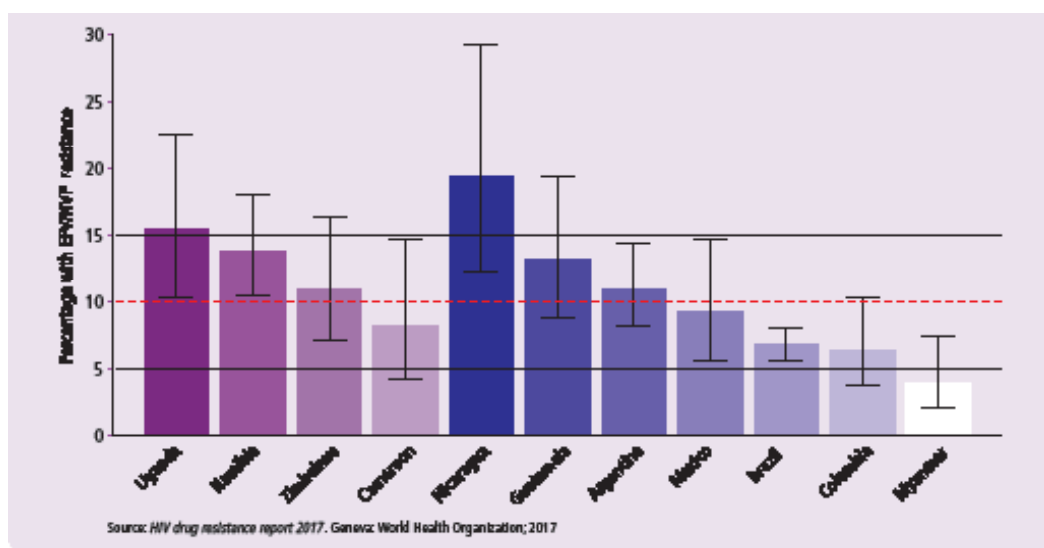
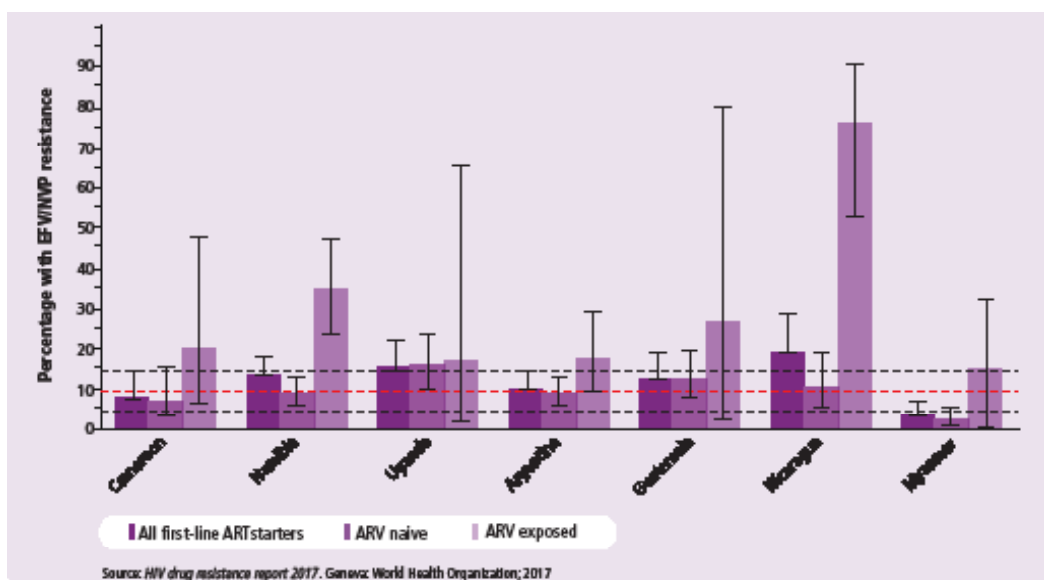


Fig. 2: Pretreatment HIV drug resistance to EFV or NVP in first-line ART initiators (pretreatment HIV drug resistance national surveys, 2014-2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3). Sequences with predicted low-, intermediate- or high-level resistance are considered resistant.

Fig. 3: Pretreatment HIV drug resistance to EFV or NVP in first-line ART initiators, by prior ARV drug exposure (pretreatment HIV drug resistance national surveys, 2014-2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3). Sequences with predicted low-, intermediate or high-level resistance are considered resistant.

Levels of drug-resistant HIV are significantly higher in people starting first-line ART who report prior ARV drug exposure (e.g. women exposed to ARV drugs for prevention of mother-to-child transmission (PMTCT) of HIV and people restarting first-line ART after an interruption), compared to people without prior ARV drug exposure (21.6% versus 8.3%; $p < 0.0001$) (Fig. 3). Data in children are limited, but suggest high levels of HIVDR, especially in those less than 18 months of age – a finding that requires urgent attention.

With the continued expansion of ART coverage, an increasing proportion of people initiating ART are likely to be infected with a virus that is resistant to one or more WHO-recommended first-line ARV drugs. A recent review of the published literature performed to support development of WHO's *Guidelines on the public health response to pretreatment HIV drug resistance* shows that

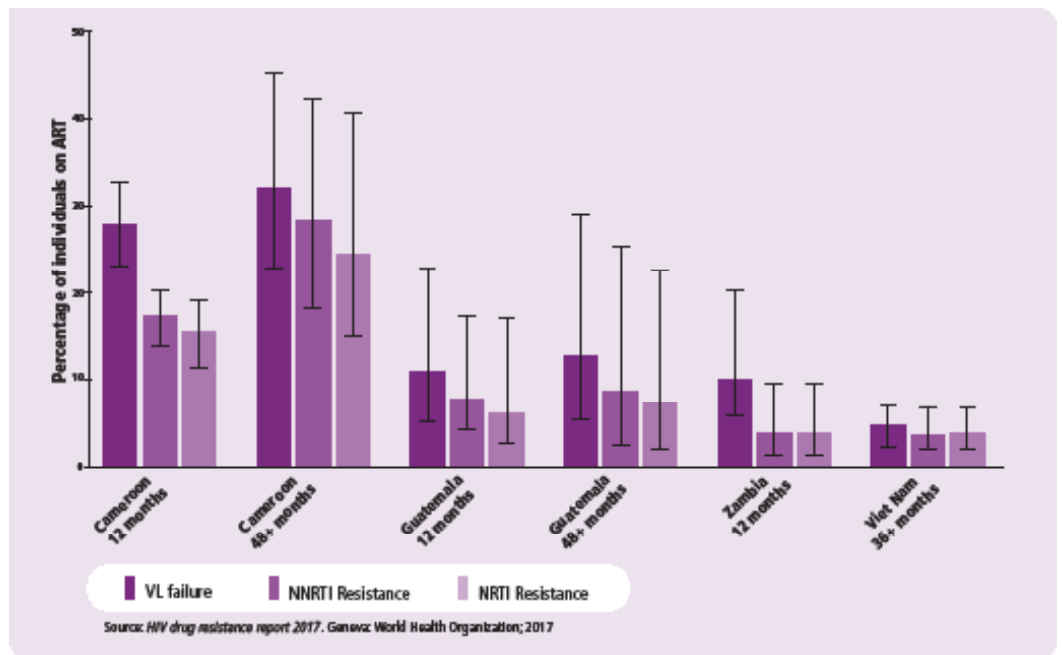
people with a virus resistant to EFV and/or NVP are more likely to fail to suppress and maintain viral load below 1000 copies/ml. People with drug resistant virus to EFV and/or NVP are also significantly more likely to experience virological failure or death, discontinue treatment, and acquire new HIVDR mutations. Similar poor outcomes were observed in children and adults.

WHO's *HIVDR report 2017* also presents the latest findings from countries reporting national data on viral load suppression in people retained in care and on treatment and acquired HIV drug resistance (ADR). Of the four countries that completed national surveys of ADR, two – Viet Nam and Zambia – reached the third 90-90-90 target: 90% of people on ART having undetectable virus levels. On the one hand, this demonstrates that “the third 90” target can be achieved; on the other, the remaining countries – Cameroon and Guatemala – reported levels

of viral load suppression below the 90 target, highlighting that gaps in the quality of HIV treatment service delivery need to be improved if global targets are to be achieved (Fig. 4).

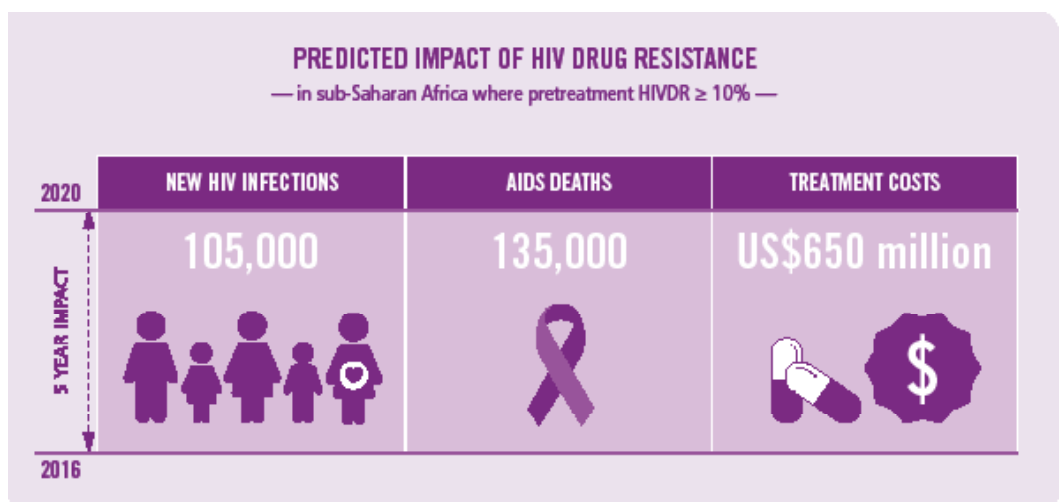
Levels of NNRTI resistance amongst individuals failing first-line ART ranged from 47.3% in Zambia to 89.5% in Cameroon. In some countries, a significant proportion (up to 28%) of people retained in care and on treatment had resistance to EFV and/or NVP. These people should promptly receive second-line ART regimens to suppress the virus and avoid transmission of drug-resistant virus to others. However, the proportion of individuals currently receiving second-line regimens remains below 5%, suggesting inadequate identification and switch of people failing first-line ART.

Fig. 4: HIV drug resistance in people on ART (acquired HIV drug resistance national surveys, 2014–2016)



Resistance is defined by the Stanford HIVdb algorithm (version 8.3). Sequences with predicted low- intermediate- or high-level resistance to any NRTI or to the NNRTI EFV or NVP are considered resistant.

Fig. 5: Predicted impact of pretreatment HIV drug resistance on new HIV infections, AIDS deaths and treatment costs



HIVDR has both human and financial consequences. Mathematical modelling predicts that if levels of NNRTI PDR exceed 10% in sub-Saharan Africa, and if NNRTI drugs continue to be used in first-line ART, between 2016-2020 PDR is predicted to be responsible for an additional 105 000 new HIV infections, 135 000 AIDS deaths, and US\$ 650 million in ARV drug costs² (Fig. 5).

THE SOLUTION: What the global community and countries should do

Effective action can be taken to prevent and manage the threat of HIVDR. WHO supports countries to prevent, monitor and respond to HIVDR. The *Global Action Plan on HIVDR, 2017–2021*, developed in collaboration with partners and stakeholders, provides a five-year framework for action centred on five strategic objectives (Fig. 6). The framework outlines key actions for all partners involved in the global response to HIVDR, and links to indicators to track implementation of the plan.

The Global Action Plan on HIVDR aims:

- to prevent HIVDR from undermining attainment of global targets on health and HIV; and
- to provide the most effective drugs, both for treatment for all people living with HIV and for prevention for all people at risk of HIV, including key populations, adults, pregnant and breastfeeding women, children and adolescents.

Fig. 6: Global Action Plan on HIVDR: five strategic objectives

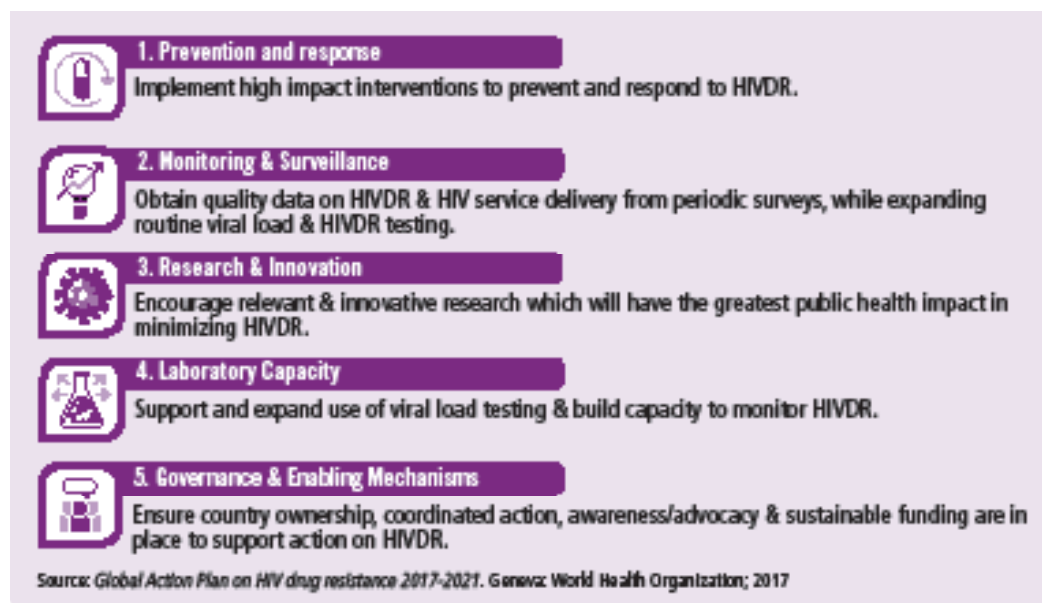
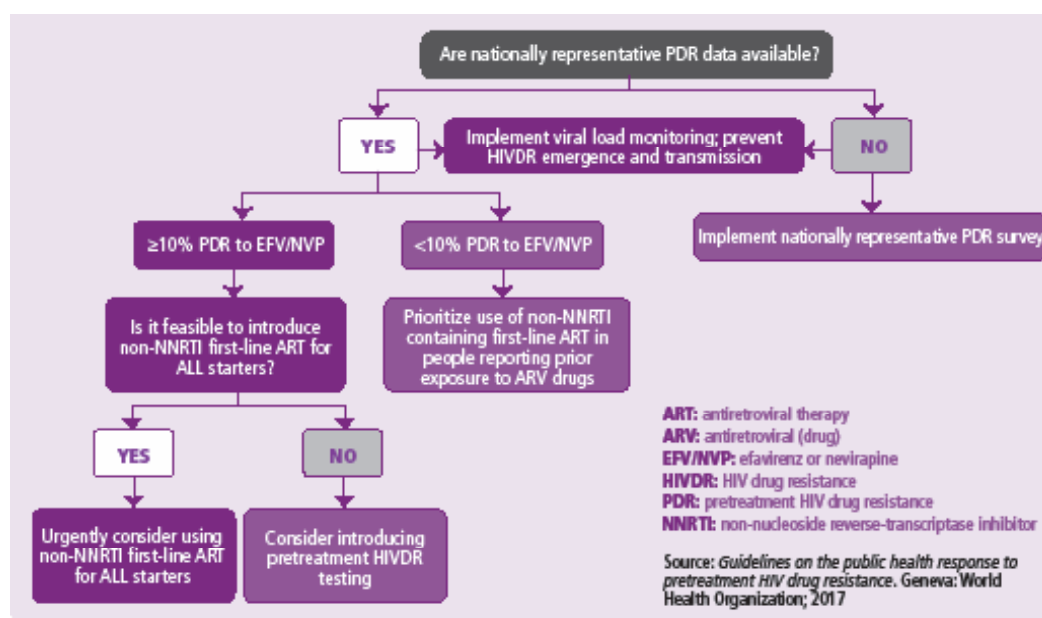


Fig. 7: WHO's recommended response to pretreatment HIV drug resistance³



WHO's *Guidelines on the public health response to pretreatment HIV drug resistance* is a key resource in the effective prevention and response to rising levels of HIVDR (strategic objective 1). The guidelines outline the need for countries to consider using an alternative first-line regimen that does not include NNRTIs when national levels of NNRTI drug resistance in people initiating ART reach 10% (Fig. 7). Dolutegravir (DTG), a potent integrase inhibitor with a high genetic barrier to selection of HIVDR, is recommended by WHO as an alternative option in first-line ART. DTG is becoming increasingly affordable and available in many low- and middle-income countries. Its use can be prioritized in countries with levels of pretreatment NNRTI resistance above 10%. These guidelines, when implemented, will save and improve the lives of people living with HIV,

and can also reduce the overall costs of ART, ensuring that more individuals receive optimum treatment. They also advise countries to prioritize, when feasible, initiation of ART regimens that do not contain NNRTIs for individuals initiating first-line ART who are at higher risk of resistance (i.e. people reporting prior exposure to ARV drugs and people who restart ART after a period of interruption, including women exposed to ARV drugs for PMTCT).

Rising levels of NNRTI resistance could threaten to reverse decades of hard-won gains in HIV-related morbidity and mortality. There is an urgent need to collectively implement the *Global Action Plan on HIVDR* and to support a collaborative approach to monitor, prevent and respond to HIVDR. Focused research

and laboratory capacity-strengthening are fundamental to ensuring that innovative and effective tools are available to maximize impact. Through well-coordinated collective action, we can accelerate achievement of the Fast-Track global targets of 90-90-90 by 2020, and help ensure future generations are free of AIDS.

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POLICY BRIEF

HIV DRUG RESISTANCE