GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017-2021

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HIV DRUG RESISTANCE

World Health Organization
GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE
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PLHV, COMMUNITY ORGANIZATIONS AND CIVIL SOCIETY

Edwina Pereira ADOLESCENTS LIVING WITH HIV, INDIA Alex Dane Fraser ARTISTES IN DIRECT SUPPORT Jonas Bahas, R.D. Marie ASIA PACIFIC COUNCIL OF AIDS SERVICE ORGANIZATIONS Shiba Phurailatpam ASIA PACIFIC NETWORK OF POSITIVE PEOPLE Nicolette Burrows Steve Maibel UN ESCAP

Kraipet ASIA PACIFIC TRANSGENDER NETWORK Belal Hossain Carole Treston ASSOCIATION OF NURSES IN AIDS CARE Carla Bingham-Ledgister CIVIL SOCIETY FORUM OF JAMAICA

Khalil Elouardighi COALITION PLUS Aliou Sylla COALITION PLUS AFRIQUE

Ernest Norenga UNDP Tristam Price Network 1 UN ESCAP

Marianela Bavinchi-Lemer Catherine Bilger Patricia Bramacoton David Bridger Miriam Chimpio Ruben del Prado Maria Elena G. Filo-Borromoe Sun Gang Michael Glees Benjamin Goneet Vera Itayenkov Pradeep Kakkattil Fathima Khan Saima Khan Isabelle Kounane Hugues Lapa Tony Lisle Luiz Laureu Mary Mahy Eamon Murphy Bizwilwiek Michweye Dayanath Ramatane Vinay Saldanha Naira Sangsang Tatsiana Shouminina Dussama Tawil Thomas Tchetmi Claire Mulanga Tshididi Aires Valeriano Ian Wayniki UNAIDS Werning Tang UNC CHAPEL HILL INSTITUTE FOR GLOBAL HEALTH & INFECTIOUS DISEASES, CHINA

Ernest Norenga UNDP Tristam Price Network 1 UN ESCAP

Marianela Bavinchi-Lemer Catherine Bilger Patricia Bramacoton David Bridger Miriam Chimpio Ruben del Prado Maria Elena G. Filo-Borromoe Sun Gang Michael Glees Benjamin Goneet Vera Itayenkov Pradeep Kakkattil Fathima Khan Saima Khan Isabelle Kounane Hugues Lapa Tony Lisle Luiz Laureu Mary Mahy Eamon Murphy Bizwilwiek Michweye Dayanath Ramatane Vinay Saldanha Naira Sangsang Tatsiana Shouminina Dussama Tawil Thomas Tchetmi Claire Mulanga Tshididi Aires Valeriano Ian Wayniki UNAIDS Werning Tang UNC CHAPEL HILL INSTITUTE FOR GLOBAL HEALTH & INFECTIOUS DISEASES, CHINA

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RESEARCHERS

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Gayane Ghukasyan ARMENIA
Kamar Rezwan BANGLADESH
Vatcheslav Grankov BELARUS
Telephone Housansou BENIN
Ugney Wangchuk BHUTAN
Tohgo Madimakoe BOTSWANA
Bazie Babou Kouadio
Yebozu Souleymane Zan BURKINA FASO
Jean Francis Bosogoro Denise Niezimana BURUNDI
Carolina Gomes CAPE VERDE
Barbara Etoa Elleine Hembou Irene Yakana Emah CAMEROON
Niel Djemadi Outji CHAD
Francoise Bigirimana Omar Coulibaly Frank John Luke Jeschah Miike Mireille Moure Lolo Jean Bosco N’Dokoumbeo Harilata Nina Razakosea Magda Robalo REGIONAL OFFICE FOR AFRICA,
CONGO
Marie Catherine Barouan CÔTE D’IVOIRE
Jeane Bolivicevic CROATIA
Casimir Mamzengo Bemadette Mbu Nkolomonyi DEMOCRATIC REPUBLIC OF THE CONGO
Elena Chukova Tiffen
Humbert Lai Khotenashvili Anthon Mazzalowski Elena Raagaugov REGIONAL OFFICE FOR EUROPE, DENMARK
Alaa Hashish Wanis Imran EGYPT
Fekade Adugna Aschalew Endale Fita Aminch Gebregiorgis
Ghon T Mengistu Silemoneggel Negussie ETHIOPIA
Dinny Konbate Noudsi Saligues Sanni Henriette Wembyamamm GABON
Nana Mamutasheri GEORGIA
One Roseline Dansowa Felicia Onwu-Achib GHANA
Macaca Alvarenga GUINEA-BISSAU
Khurshid Alam Hyder Razia Narayan Pendze B.b. Rewan REGIONAL OFFICE FOR SOUTH-EAST ASIA, INDIA
Bhattacharya Iwaro Tiara Nisa INDONESIA
Brian Chimbombo Christine Kissi KENYA
Susan Tembo LESOTHO
Richard Banda Ishamel Nyassou Ellen Thom MALAWI
Mohamed Abdel Aziz Boubacarat Mohamed Mohamed Cheiki MAURITIUS
Silvia Giobanu MOLDOVA
Alcina Carbonel MOZAMBIQUE
Pharady Bollen Masami Fujita MYANMAR
Sirak Hali Desta Tiruneh NAMIBIA
Nikhil Singh Nepal Rex Muzenje NIGERIA
Khaliduddin Kakak PAKISTAN
Shimuske Miyano PAPUA
NEW GUINEA
Naoko Ishikwan Limb-V Le Ying-Ru Jacqueline Lo REGIONAL OFFICE FOR THE WESTERN PACIFIC, PHILIPPINES
Claudia Augusto Da Cruz Maria Quanmassa G Dos Arjos SAO TOME AND PRINCIPE
Sarah Barber Augustin Ntivomunza SOUTH AFRICA
Benjamin Chemedo Moses Mokhla Ngandu SOUTH SUDAN
Sheikh Abdallah Eshkebi Ali SUDAN
Sithembile Dlamini-Mnqkelo SWAZILAND
Pedro Alonso Annabel Badalely Naye Bah Andrew Ball Rachel Beanland Silva Bertagnolio Michel Buesenberg Mq Doherty Philippa Easterbrook Shaflq Essajee Carmen Figueroa Nathan Ford Vincent
Habibamure Hkwat Hlaile-Selassie Gottfried Henschall Yvan Hutin Daniel Low-Beer Virginia Macdonald Chantal Magnone Oyeyeng Eshikeo Namijasuerei Martha Penazzato Carine Pessa Da Silva Pascal Ringwald Mubashar
Sheikh Vindi Singh Marcus Sprenger David Sunderland Liz Taylor Elvira Teodora Marco Viteria Lara Yjpoov Karin Weyer HEADQUARTERS, SWITZERLAND
Firdavs Kurbonov TAJIKISTAN
Mula Shaharma Senam Wangdi Dongbao Yu THAILAND
Koko Lawson-Eni TOGO
Muzagga Kaggwa Olive Sembumbwe-Mugasa UGANDA
Alessy Dubiru UKRAINE
Theopista John Kabuteni UNITED REPUBLIC OF TANZANIA
Massimo Ghidinelli Giovanni Ravasi REGIONAL OFFICE FOR THE AMERICAS, UNITED STATES OF AMERICA
Jamshid Gadov UZBEKISTAN
Lastore Chilomba Sarai Manja Maloumu ZAMBIA
Christine Chakanyuka Musanhu, Trevor Kanyowa, Buhle Ncube, Fabian Ndenzako, Morkor Newani ZIMBABWE
Combatting antimicrobial resistance (AMR) is a global priority that needs coordinated action across all government sectors and levels of society. Minimizing the emergence and transmission of HIV drug resistance (HIVDR) is a vital part of the global commitment to address the challenges of AMR. Increasing levels of resistance to commonly used antiretroviral (ARV) drugs could jeopardize the success of the scale-up of antiretroviral therapy (ART), and the broader HIV response, if not urgently addressed.

WHO’s Report on HIV drug resistance 2017 demonstrates a steady increase in the prevalence of HIVDR in individuals initiating first-line ART since 2001, most notably in Southern and Eastern Africa. The prevalence of HIVDR in people initiating first-line ART (pretreatment resistance: PDR) was 6.8% in 2010, and estimates from recent nationally representative surveys indicate levels of PDR above 10% to the WHO-recommended and widely used first-line ARV drugs in many countries.

At the end of 2016, 19.5 million people were taking life-saving ART. WHO’s recommendation to “treat all” will result in an additional 17.2 million individuals starting ART, to reach a total of 36.7 million people who must be successfully maintained on treatment for life. HIVDR is associated with poor clinical outcomes and reduced effectiveness of ARV drugs. As HIV treatment continues to be scaled up, the global community needs to be vigilant about the emergence of HIVDR and the urgent need to protect the effectiveness of currently available and new ARV drugs.

Preventing and managing the emergence of HIVDR is a key component of a comprehensive and effective HIV response, and should be integrated into broader efforts to ensure sustainability and greatest impact. It is essential that actions to monitor, prevent and respond to HIVDR are implemented at the clinical, programme and policy levels to address the many drivers of HIVDR.

The goal of this Global Action Plan is to articulate synergistic actions that will be required to prevent HIVDR from undermining efforts to achieve global targets on health and HIV, and to provide the most effective treatment to all people living with HIV including adults, key populations, pregnant and breastfeeding women, children and adolescents. The Global Action Plan has five strategic objectives: 1) prevention and response; 2) monitoring and surveillance; 3) research and innovation; 4) laboratory capacity; and 5) governance and enabling mechanisms. It is built on the guiding principles of a public health approach; comprehensive, coordinated and integrated action; country ownership; a focus on high-impact countries; sustainable investment; and use of standardized methods to monitor resistance and achieve impact from actions.

The Global Action Plan was developed with the full involvement of key partners (e.g. CDC, the Global Fund and PEPFAR). It provides countries and national and international partners with a framework, which – when implemented collectively between 2017 and 2021 – will contribute to the achievement of the Fast-Track global targets of 90-90-90 by 2020 (90% of all people living with HIV will know their HIV status; 90% of all people diagnosed with HIV infection will receive ART; and 90% of all people accessing ART will have viral load suppression), and to ending the AIDS epidemic as a public health threat by 2030.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>acquired HIV drug resistance</td>
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<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
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<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral (drugs)</td>
</tr>
<tr>
<td>DBS</td>
<td>dried blood spot</td>
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<tr>
<td>EFV</td>
<td>efavirenz</td>
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<tr>
<td>EWI</td>
<td>early warning indicator</td>
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<td>GAP</td>
<td>Global Action Plan</td>
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<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>HIVDR</td>
<td>HIV drug resistance</td>
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<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse-transcriptase inhibitor</td>
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<tr>
<td>NRTI</td>
<td>nucleoside reverse-transcriptase inhibitor</td>
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<td>PDR</td>
<td>pretreatment HIV drug resistance</td>
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<td>PEP</td>
<td>post-exposure prophylaxis</td>
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<td>PEPFAR</td>
<td>United States President’s Emergency Plan for AIDS Relief</td>
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<tr>
<td>PI</td>
<td>protease inhibitor</td>
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<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child transmission of HIV</td>
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<tr>
<td>PrEP</td>
<td>pre-exposure prophylaxis</td>
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<tr>
<td>TDF</td>
<td>tenofovir</td>
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<td>TDR</td>
<td>transmitted HIV drug resistance</td>
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<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

The Global Action Plan on HIV drug resistance (HIVDR) builds on the new global commitment of the 2030 Agenda for Sustainable Development to end the AIDS epidemic by 2030. The Global Health Sector Strategy on HIV, 2016–2021 (1), adopted by the 69th World Health Assembly in May 2016, and the Political Declaration of the United Nations High-Level Meeting on Ending AIDS 2016 (2) commit countries to meeting the 90-90-90 targets by 2020. These targets envisage 90% of people with HIV knowing their status, 90% of people diagnosed with HIV infection receiving antiretroviral therapy (ART), and 90% of people with HIV on ART achieving sustained viral load suppression. HIVDR threatens to undermine efforts to achieve these targets. The Global Action Plan on HIVDR defines the problem and outlines roles for, and actions to be undertaken by, countries, WHO and other stakeholders. It aligns itself with the broader Global Action Plan on antimicrobial resistance (AMR) (3) and aims to re-energize and build action to address HIVDR across all levels of the HIV response.

The plan has been developed through an extensive consultation process over more than 12 months (2015–2017) with inputs from nearly 800 people, from over 100 countries, and over 350 organizations. Key partners such as CDC, the Global Fund and PEPFAR provided full inputs. The process included six regional consultations (between April and September 2016) with participation from ministry of health representatives from 69 countries; numerous expert meetings; and one-on-one consultations with stakeholders. A draft consultation version of the plan was released at the International AIDS Conference in July 2016 in Durban, and was made available online for open web-based consultations between July and October 2016. Fifty-two civil society representatives from 25 countries were consulted, and two webinars with over 100 participants were organized in December 2016 for further inputs.

The Global Action Plan on HIVDR provides a comprehensive framework for global and country action by countries, WHO and other stakeholders, and describes a package of interventions and resources to guide the response to HIVDR. This includes:

- **Report on HIV drug resistance** – produced by WHO to disseminate data on global HIVDR prevalence, it will be used to report on progress in implementation of the Global Action Plan and on the global and country responses to HIVDR;
- **HIVDR guidelines and implementation tools** – these will provide authoritative guidance to countries and programme implementers on the selection and implementation of interventions to monitor, prevent and manage HIVDR, as outlined in the Global Action Plan.
Over the last 15 years, scale-up of HIV treatment has had a major impact on HIV-related illness, averting AIDS-related deaths, preventing new HIV infections, and resulting in cost savings (4) that will contribute to realization of the Sustainable Development Goals (5). Despite significant advances in the prevention and treatment of HIV, countries continue to experience serious gaps in ART service delivery, including suboptimal retention in treatment and care services, drug stock-outs, suboptimal use of viral load testing, and inadequate support for population adherence to ART, which favour the emergence and transmission of HIVDR (6). As efforts to scale up treatment continue, and more individuals receive antiretroviral (ARV) drugs for the treatment or prevention of HIV, it is likely that a further increase in levels of HIVDR (Box 1) will compromise the substantial gains already achieved in the HIV response, and threaten efforts to expand treatment further and achieve even greater impact globally.

Box 1: Definitions of HIV drug resistance

HIVDR is caused by a change (mutation) in the genetic structure of HIV that affects the ability of a particular drug or combination of drugs to block the replication of the virus. All current ARV drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of resistant virus. Broadly speaking, there are three main categories of HIVDR:

1. **Acquired HIVDR (ADR)** develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs.

2. **Transmitted HIVDR (TDR)** is detected in ARV drug naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations.

3. **Pretreatment HIVDR (PDR)** is detected in ARV drug naive people initiating ART or people with prior ARV drug exposure(s) initiating or reinitiating first-line ART. PDR is either transmitted or acquired drug resistance, or both. PDR may have been transmitted at the time of infection (i.e. TDR), or it may be acquired by virtue of prior ARV drug exposure(s), such as in women exposed to ARV drugs for the prevention of mother-to-child transmission (PMTCT) of HIV, or in people who have received pre-exposure prophylaxis (PrEP), or in individuals reinitiating first-line ART after a period of treatment interruption without documented virological failure.

**ARV drug naive.** This term is applied to people with no history of ARV drug exposure(s).

**Pretreatment HIV drug resistance**

WHO’s Report on HIV drug resistance 2017 presents data from countries that conducted nationally representative surveys of PDR between 2014 and 2016. Seven of the 11 countries surveyed estimated a prevalence of PDR greater than 10% in adults initiating ART (Argentina, Guatemala, Mexico, Namibia, Nicaragua, Uganda and Zimbabwe) (7) (Fig.1) PDR to non-nucleoside reverse transcriptase inhibitors (NNRTI) of greater than 10% was reported by six of the 11 countries.
Globally, the prevalence of PDR to NNRTI drugs has significantly increased since 2001, concurrent with the expansion of ART coverage (7). This rise has been observed more rapidly in published studies from Eastern Africa (estimated annual incremental increase of 29%) and Southern Africa (23%), compared to Western and Central Africa (17%), Latin America (15%), and Asia (11%) (7) (Fig.2).

1. Component of the WHO-recommended first-line ART regimens
In WHO’s national survey of PDR conducted in 2014–2016, NNRTI PDR was significantly higher among individuals initiating first-line ART with prior ARV drug exposure (21.6%), compared to ARV drug naive individuals (8.3%) (P < 0.0001). Similarly, a higher pooled prevalence of NNRTI PDR among PMTCT-exposed children compared to PMTCT-unexposed children (43% versus 13%, P=0.004 respectively) was reported by a systematic review of PDR in children in sub-Saharan Africa (8).

Data on the levels of HIVDR in key populations is limited, with some evidence of higher prevalence of NNRTI and protease inhibitor (PI) resistance in men who have sex with men, compared to other population groups, particularly in Oceania (Australia), Eastern Europe/Central Asia, and East Asia (9).

WHO’s new recommendations on the public health response to PDR (10) indicate that in countries where population-levels of PDR to NNRTI reach the threshold of 10%, a change in the first-line ART regimen (from NNRTI-based to non-NNRTI based, such as integrase inhibitors) should be urgently considered (Fig. 3).

As yet, the risk of emerging resistance to newer classes of ARV drugs is unknown. However, as countries with high levels of NNRTI resistance modify their first-line ART regimens to include new drugs such as dolutegravir (DTG), despite its higher genetic barrier to resistance when compared with efavirenz (EFV), it is expected that resistance to DTG will invariably emerge, and there is a need to closely monitor this.

**Fig. 3: WHO’s recommendations on country response to pretreatment HIVDR to NNRTIs**

Are nationally representative PDR data available?

- **YES**  
  - Implement viral load monitoring; prevent HIVDR emergence and transmission
  - Is it feasible to introduce non-NNRTI first-line ART for ALL starters?
    - **YES**  
      - Urgently consider using non-NNRTI first-line ART for ALL starters
    - **NO**  
      - Consider introducing pretreatment HIVDR testing
  - <10% PDR to EFV/NVP

- **NO**  
  - Implement nationally representative PDR survey
  - Prioritize use of non-NNRTI containing first-line ART in people reporting prior exposure to ARV drugs

**ART**: antiretroviral therapy  
**ARV**: antiretroviral (drug)  
**EFV/NVP**: efavirenz or nevirapine  
**HIVDR**: HIV drug resistance  
**PDR**: pretreatment HIV drug resistance  
**NNRTI**: non-nucleoside reverse transcriptase inhibitor


**Acquired HIV drug resistance**

The prevalence of NNRTI resistance among all people on ART is estimated to be between 5% and 28%, and from 50% to over 90% in people failing ART (7) (Fig. 4). Patterns and predicted susceptibility to NNRTIs and nucleoside reverse transcriptase inhibitors (NRTIs) in low- and middle-income countries (LMIC) do not appear to differ significantly between adults, adolescents and children failing first-line ART (11,12). At the time of an individual’s first virological failure (viral load greater than 1000 copies per mL while taking ART), NNRTI susceptibility is already severely reduced due to HIVDR, and will decrease significantly after continued maintenance on the same ARV drugs in the presence of active viral replication (7,11,13).

Estimates of viral load suppression in individuals on ART, generated by national surveys of ADR, range from 68% to 90% (Fig. 4). Globally, the pooled prevalence from cohort data of viral load suppression in the first 12 months after ART initiation is estimated to be 82.1% (range 11–90%) in individuals initiating first-line NNRTI-based therapy (7).

2. Adults restarting first-line ART after treatment interruption or women with prior exposure to ARV drugs from PMTCT.
3. Men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers, and transgender people.
Resistance to NNRTIs at the time of failure (defined as the proportion of those with a resistance mutation to NNRTIs among those with a viral load greater than 1000 copies per mL) is significantly higher among individuals monitored with viral load testing less frequently then every three months, compared to more frequently monitored patients (88.3% compared to 61.0%) (13).

**Fig.4: Prevalence of acquired HIVDR among individuals on ART (early and late time points)**

![Graph showing prevalence of acquired HIVDR](source)

High levels of ADR observed in cohorts of children failing ART are consistent globally. Importantly, up to 98% of children identified as failing first-line ART harbour dual-class resistance, and half have multiple thymidine analogue mutations (14), reducing the virus’ susceptibility to NRTIs and jeopardizing the recycling of NRTIs in second-line ART.

A recent multicentre cohort reported higher rates of tenofovir (TDF)-associated drug resistance mutations in individuals failing TDF-containing first-line ART in sub-Saharan Africa (57–60%), compared to individuals failing the same regimen in high-income countries (20–22%) (15). This difference highlights the need for ongoing surveillance of TDF resistance in all population groups, as transmission of TDF-associated resistance mutations can hamper the effectiveness of both first-line ART regimens and PrEP.

**The impact of HIV drug resistance and the way forward**

Attainment of the Global Health Sector Strategy on HIV targets (1) and the UNAIDS Fast-Track targets (16) is dependent on functional health systems and highly effective, well-tolerated HIV treatment, including expanded access to second- and third-line ART regimens. The emergence of HIVDR threatens to reduce gains in morbidity and mortality anticipated by a “treat all” approach and the scale-up of PrEP (17).

Should levels of NNRTI PDR exceed 10% in sub-Saharan Africa, and NNRTI-based ART continue to be used in first-line ART, mathematical modelling predicts that over the next 15 years, PDR could be responsible for cumulatively 16% of AIDS deaths (890 000 deaths) and 9% of new HIV infections (450 000) in sub-Saharan Africa alone (18). Over a five-year period, these estimates are 135 000 AIDS deaths and 105 000 new HIV infections (Table 1).

Individuals with NNRTI PDR who initiate an NNRTI-based regimen are less likely to achieve viral load suppression compared to those who initiate a non-NNRTI based regimen. In addition, they are 23 times more likely to experience virological failure or death, and nine times more likely to discontinue treatment (7). This pattern is also observed in treatment outcomes for children (7). For women living with HIV initiating ART during pregnancy, resistance poses a significant challenge to the elimination of mother-to-child transmission of HIV and to maternal and child health outcomes (19).
Table 1: Projected impact of HIV drug resistance on AIDS deaths, new infections and ART costs in sub-Saharan Africa (pretreatment HIVDR > 10% in Fast-Track countries) during 2016–2020 and 2016–2030, assuming the use of NNRTI-based regimen in first-line ART

<table>
<thead>
<tr>
<th></th>
<th>AIDS deaths</th>
<th>New HIV infections</th>
<th>ART costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount attributable to HIVDR</td>
<td>135 000</td>
<td>890 000</td>
<td>105 000</td>
</tr>
<tr>
<td>Percentage attributable to HIVDR</td>
<td>5.7%</td>
<td>16%</td>
<td>3.5%</td>
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If not addressed, rising levels of PDR to NNRTIs may reduce the durability and effectiveness of currently recommended first-line ART regimens for a significant proportion of individuals. This is particularly true in LMIC, where NNRTIs provided to all first-line starters, regardless of the presence of HIVDR or prior exposure to ARV drugs. In addition, the significant loss in susceptibility of the NRTI class is of particular concern for young children, for whom the number of licensed NRTIs is limited.

When PDR to NNRTI reaches 10%, for every 100 000 people initiating ART, an additional 2510 individuals fail to reach and maintain viral load below 1000 copies per mL; these individuals will require second-line ART. This translates to an annual increase of US$ 502 000 to purchase second-line drugs per 100 000 people starting ART, and a yearly increase of US$ 4 250 000 to the annual drug procurement cost for second-line regimens.

Despite the high levels of ADR seen in national surveys and published data, the mutations and mutation patterns observed among individuals failing ART suggest that the currently recommend PI-based second-line ART is still an effective option for the vast majority of people failing first-line ART. However, access remains limited, with less than 5% of people on ART receiving a PI-based ART regimen in most LMIC. The cost of second-line regimens in LMIC is, on average, three times higher than first-line regimens (US$ 263 mean cost per patient per year, compared to US$ 85) (20) (Fig.5). Treatment options beyond second-line are even more costly: at present, the lowest possible price for a third-line regimen is around US$ 1235 per patient per year, 14 times more than the lowest price for a first-line regimen (20). If levels of NNRTI PDR reach 10% in sub-Saharan Africa, NNRTI drugs continue to be used in first-line ART, the treatment cost attributable to HIVDR is predicted to rise to 8% of total ART costs, representing US$ 650 million by 2020, and US$ 6.5 billion between 2016 and 2030 (18). (Table 1).

Nevertheless, there are appropriate and potentially cost-effective responses to address the risk of NNRTI PDR. If countries transition to using a DTG-based ART regimen in first-line initiators (compared to using EFV-based ART) when levels of NNRTI PDR reach 10%, mathematical modelling predicts better health outcomes. In particular, when compared to EFV-based regimens, DTG in first-line ART initiators is predicted to lead to: increased prevalence of viral load suppression (from a mean of 77% to 86%); reduced mortality (from 4.5 to 3.5 persons per 1000 person/year); and reduced HIV incidence (from 0.79 to 0.72 new HIV infections per 100 person/year) (10). This model predicts that in the context of sub-Saharan Africa, and in settings where the cost of a DTG-containing regimen is similar to the cost of an EFV-based regimen, use of DTG in first-line will be cost-effective, and could even be cost-saving, at any level of PDR to NNRTI observed at country level, due to the beneficial properties of DTG also conferred upon individuals without drug-resistant virus.

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4. Using the Spectrum Goals Model, by applying the impact of drug resistance, as estimated using the HIV Synthesis Model. Estimating the current level of PDR in all ART initiators (including re-initiators) to be above 10%. Estimates based on adults only. Higher levels of drug resistance are seen in children, due to use of drugs aiming to prevent acquisition and higher levels of resistance acquisition on ART.
Fig. 5: Annual cost of ARV drugs per person in low-income countries

- **US$85** 1st LINE
- **US$263** 2nd LINE
- **US$1,235** 3rd LINE

Costs increase by factors of 3.1x and 14.5x respectively.
The Global Action Plan on HIVDR is a five-year plan (2017–2021), aligned with WHO’s Global Action Plan on AMR (3) and Global Health Sector Strategy on HIV (2016–2021) (1) (Fig. 6).

Vision
The Global Action Plan on HIVDR supports the commitment of the United Nations High-Level Meeting on Ending AIDS to “establish effective systems to monitor for, prevent and respond to the emergence of drug-resistant strains of HIV in populations and AMR among people living with HIV”.

Goals
The goals of the Global Action Plan on HIVDR are:

• to prevent HIVDR from undermining attainment of global targets on health and HIV; and

• to provide the most effective drugs, for treatment for all people living with HIV and for prevention for all people at risk of HIV, including key populations, pregnant and breastfeeding women, children and adolescents.

Targets
By supporting the Global Action Plan, the global community has an opportunity to contribute to the 2020 global targets to:

• reduce global HIV-related deaths to below 500 000;

• ensure 90% of people living with HIV, who are on treatment, achieve viral load suppression;

• increase research into, and development of, HIV-related medicines for use in treatment and prevention;

• ensure all countries integrate essential HIV services into national health financing arrangements; and

• ensure overall financial investments for the AIDS response in low-and middle-income countries reach at least US$ 26 billion, with continued increases from the current levels of domestic public sources.

The monitoring and evaluation framework (Web Annex 1) will track implementation of the Global Action Plan by countries and stakeholders.
Scope

This plan outlines the key roles and actions for countries, global and national partners, and WHO over the next five years, structured around five strategic objectives. Although actions are relevant to all countries in their response to the HIV epidemic, there is a special focus on the 35 Fast-Track countries (21), which together account for the vast majority of all new HIV infections worldwide, as results in these countries5 the Global Action Plan on HIVDR have a large effect on the prospects for ending the epidemic.

Guiding principles

The Global Action Plan relies on the following principles and approaches.

A public health approach aims to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized interventions, and services that can readily be brought to scale in resource-limited settings.

Comprehensive, coordinated and integrated action allows for patient-centred care; improved service delivery; greater and more sustained impact; more efficient mobilization and use of resources; greater sharing of information; and enhanced research into innovative approaches to tackle HIVDR and broader HIV and AMR challenges. The collaboration at global and national levels and between key partners (i.e. countries, nongovernmental organizations, people living with HIV and their communities, civil society organizations, United Nations programmes and agencies, and international implementing partners and donors) can increase awareness, advocacy, and political and programmatic commitment to tackle HIVDR. WHO provides strategic leadership and coordination, as well as a platform to support implementation and monitoring of the global response to HIVDR.

Country ownership of the monitoring, prevention and response to HIV, including HIVDR, will ensure that high-quality patient-centred care is provided equitably to all citizens in a sustainable manner.

Focus on high-impact countries, specifically UNAIDS’ 35 Fast-Track countries (21), which account for approximately 90% of new HIV infections.

Sustainable investment in HIVDR is a moral responsibility and cost-saving intervention. Resources should be allocated to combinations of interventions that will achieve the greatest impact, be aligned with national programmes, and maximize the investments of major development agencies and donors in the global response to HIV.

Standardized methods to assess HIVDR enable robust estimates which facilitate their interpretation, comparison, assessment of national and global trends, and appropriate responses to increasing levels of resistance.

Strategic objectives

The Global Action Plan is structured around five strategic objectives that are consistent with the Fast-Track actions outlined in WHO’s Global Health Sector Strategy on HIV, 2016–2020:

For countries:

Implement strategies and services to minimize HIVDR, and use data to inform national ARV policies and guidelines.

For WHO:

Provide guidance on HIVDR surveillance, prevention and management, and regularly report on global HIVDR prevalence and trends.

Strategic objective 1: Prevention and response

Implement high-impact interventions to prevent and respond to HIVDR.

Prevention of HIV drug resistance

Prevention of HIVDR is a critical component of any national AIDS programme and is achieved through optimization of ART service delivery and elimination of programmatic gaps along the cascade of HIV testing, treatment and care services. The implementation of WHO “treat all” and PrEP recommendations provides an opportunity for ART programmes to deliver ARV drugs in ways that minimize treatment interruptions and maximize adherence.

Quality programmes implement WHO normative standards and guidelines for HIV prevention, testing, care and treatment, to ensure:

i. adequate adherence support (particularly for adolescents, postpartum women and key populations);

ii. appropriate use of recommended ARV drugs; and

iii. effective strategies to maximize retention in care and limit loss to follow-up. National AIDS programmes should ensure HIVDR interventions are integrated into their comprehensive HIV responses.

5. Angola, Botswana, Brazil, Cameroon, Chad, China, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Haiti, India, Indonesia, Islamic Republic of Iran, Jamaica, Kenya, Lesotho, Malawi, Mali, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Russian Federation, South Africa, South Sudan, Swaziland, Uganda, Ukraine, United Republic of Tanzania, United States of America, Viet Nam, Zambia, Zimbabwe.
Actions to prevent HIVDR in people on ART should be intensified to minimize the emergence of HIVDR and its transmission to others. Procurement and supply chain systems for ARV drugs and viral load testing reagents should be strengthened to ensure that quality (prequalified) medicines and diagnostics are procured and the risk of stock-outs is avoided. Continued efforts to expand access to viral load will enable viral load testing to be offered to all eligible people living with HIV in all ART clinics at six-months, 12 months and annually thereafter; turnaround time to return viral load test results to providers should be minimized, and viral load results effectively used to inform decisions for the management of HIV infection. Individuals failing first-line ART should be promptly switched to second-line ART to obtain viral load suppression and avoid accumulation of resistance mutations. When feasible, HIVDR testing should be offered to individuals failing second-line ART to select an optimal third-line ART regimen.

Response to HIV drug resistance

Monitoring levels of HIVDR and factors associated with HIVDR emergence should be combined with a systematic country-led response. The overall aim should be to attain and maintain the treatment target of 90% virological suppression in all people receiving ART, and gradually increase to the longer-term goal of 95% virological suppression. Countries need to respond promptly to rising levels of HIVDR and suboptimal performance of programmatic factors to limit any subsequent increase in HIVDR. If population-levels of PDR to NNRTI are elevated, countries should convene a structured decision-making process to review the data and refer to WHO’s Guidelines on the public health response to pretreatment HIV drug resistance for appropriate actions given the country context (10) (Fig.3).

Strategic objective 2: Monitoring and surveillance

Obtain quality data on HIVDR from periodic surveys, while expanding the coverage and quality of routine viral load and HIVDR testing to inform continuous HIVDR surveillance; monitor quality of service delivery, and collect and analyse data recorded as part of routine patient care for the purpose of evaluating programme performance to prevent HIVDR.

Global and national policy decisions on ART and HIV service delivery need to be informed by reliable national data on HIVDR prevalence and trends. HIV treatment scale-up should be accompanied by measures to monitor the quality of ART delivery and surveillance of HIVDR, as recommended by WHO (22) and partners, including the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) (23) and the United States President’s Emergency Plan for AIDS Relief (PEPFAR) (24). Dissemination of results within countries and to WHO will allow a coordinated response to be implemented.

Monitoring the quality of HIV treatment service delivery at ART clinics

Delivery of HIV care at ART clinics should be routinely assessed using existing monitoring and evaluation systems and internationally agreed indicators: WHO’s strategic information guidelines for HIV in the health sector (25), Site improvement through monitoring system (26), and WHO’s guidelines on person-centred HIV patient monitoring and case surveillance (27).

Monitoring the quality of HIV service delivery through the assessment of early warning indicators (EWI) of HIVDR as part of a comprehensive approach to HIV programme monitoring, in addition to other quality-of-care indicators, should be performed annually using routinely collected data available from patient medical and pharmacy records. EWI (Box 2) are strongly associated with, and highly predictive of, HIVDR (28). Monitoring of EWI at clinics providing ART enables LMIC to measure and respond to factors associated with emergence of HIVDR. Where routine data collection is challenging or data are of suboptimal quality, enhanced supervision and additional resources may be required to support this process.

Box 2: Early warning indicators of HIVDR and quality of care

- On-time pill pick-up
- Retention on ART at 12 months
- Drug stock-out
- Viral load suppression
- Viral load testing completion
- Appropriate switch to second-line ART
Monitoring resistance

Periodic nationally representative surveys are the gold standard to inform the prevalence of HIVDR, and survey results should be used to guide national programmes on optimal population-level ARV regimen selection. PDR survey findings provide evidence to support a country’s choice of recommended regimens for first-line ART, PrEP and post-exposure prophylaxis (PEP) (Boxes 3 and 4). Likewise, nationally representative data on ADR guide selection of second- and third-line ART regimens, monitor switch practices, and provide information about viral load suppression among the population surveyed. HIVDR data from newly diagnosed infants provide evidence to support selection of first-line ART and can inform on composition of subsequent regimens.

As HIVDR testing is not routinely offered to all individuals starting ART in most LMIC, programme data cannot currently be used to estimate levels of PDR. Countries may be able to use routine programme data to make statements about viral load suppression and ADR as the use of routine viral load testing expands, the quality of programme data improves, and HIVDR testing becomes more regularly available in LMIC. For example, if individual HIVDR testing becomes routinely available and offered to all patients failing second-line regimens, routine programme HIVDR data could be used to inform continuous surveillance and make population-level recommendations for third-line ART regimens.

Box 3: Monitoring HIV drug resistance in all populations

No surveillance efforts are currently in place to specifically monitor HIVDR in key populations, adolescents, or pregnant and breastfeeding women. Research on HIVDR in these populations can inform the need to develop and implement survey methods that specifically assess HIVDR in these groups. Pooled multi-country HIVDR survey data will be able to generate disaggregated HIVDR information by age group (e.g. adolescents, young adults), gender, and other characteristics if recorded. As countries work to strengthen the coverage and quality of routine viral load and HIVDR programme data, it is expected that disaggregation of HIVDR data for people on ART will be feasible.

Box 4: Considerations for monitoring HIV drug resistance in programmes implementing PrEP

- Incident HIV can occur despite adherence to PrEP when individuals are exposed to emtricitabine-resistant virus, TDF-resistant virus, or both (29). Continued surveillance of mutations that may affect the efficacy of ARV drugs used to prevent HIV is needed.
- If PrEP is administered to individuals who are not aware of their status, HIVDR can rapidly emerge. Monitoring the threat of PrEP-associated HIVDR in populations accessing PrEP is warranted, particularly in LMIC settings, where HIV testing services may be suboptimal or stock-out of HIV diagnostic reagents can occur.

Web Annex 2 presents the scale-up plan for HIVDR surveillance, providing estimated costs of monitoring HIVDR at a country level. It lists recommended HIVDR surveillance activities for 2017–2021 for the UNAIDS Fast-Track countries.

Strategic objective 3: Research and innovation

Encourage relevant and innovative research, leading to interventions that will have the greatest public health impact on minimizing HIVDR; fill existing knowledge gaps on the risk of HIVDR for newer ARV drugs and the impact of service delivery interventions to increase viral load suppression and contain HIVDR.

A collaborative research approach will facilitate sharing of evidence and support evidence-based policy decisions. HIVDR research priorities can be implemented only if adequate funding support is available. Implementation science research can inform innovative service delivery models, including approaches for adherence support in different populations and settings, and improving treatment retention. The outputs from the Conference on Drug Optimization (CADO) (30) and the Paediatric Conference on ARV Drug Optimization (PADO) (31) can guide clinical science research for the identification of new ARV drugs, and the development of innovative formulations to support adherence. Validating the clinical impact of in vitro drug resistance detection on HIV subtypes predominating in the African region will become increasingly important, as first-line ART regimens change. Assessing resistance emerging from new ARV drugs and reporting promptly is critical. Point-of-care resistance testing can support effective strategies to minimize unnecessary switches to second- and third-line ART. Mathematical
modelling and cost-effectiveness analysis are useful to inform decision-making on the impact of interventions to prevent and respond to HIVDR. All populations should be represented in HIVDR research, with a focus on assessing prevalence and determinants of HIVDR in adolescents, pregnant and breastfeeding women, and key populations.

Strategic objective 4: Laboratory capacity

Strengthen laboratory capacity and quality to support and expand use of viral load monitoring, and build capacity to monitor HIVDR in low- and middle-income countries.

Within countries, general laboratory capacity needs to be assessed, and opportunities identified, for the integration of HIVDR activities into the national laboratory strategy and budget. Laboratory systems need to be strengthened to ensure they can provide essential laboratory services, including for the effective diagnosis, monitoring and management of HIV infection, common coinfections such as tuberculosis, other comorbidities and drug toxicity. Within that context laboratory capacity should be expanded and strengthened to perform HIVDR testing in individuals failing second-line ART regimens (and potentially other groups of individuals in the future); to conduct resistance testing to newer drug classes, including integrase inhibitors; and to use field-friendly specimens such as dried blood spots (DBS).

All countries and partners need to ensure availability of high-quality viral load testing, including prompt reporting and use of results, and the use of point-of-care viral load testing should be expanded. WHO HIVResNet Laboratory Network collaboration enables support for in-country HIVDR testing, and HIVDR surveillance implementation in countries with limited laboratory capacity. The efficiency of testing for HIVDR should be improved, interpretation of resistance mutations simplified, and opportunities to synergize and integrate functions across AMR and tuberculosis resistance laboratories identified.

Strategic objective 5: Governance and enabling mechanisms

Ensure that governance and enabling mechanisms (advocacy, country ownership, coordinated action and sustainable funding) are in place to support action on HIVDR.

Management of HIVDR is the responsibility of the global community, within the wider context of health policies, strategies and resourcing of health care. Endorsement of the commitment to support the Global Action Plan on AMR reflects the global consensus on the importance of a coordinated effort to tackle AMR at a political level. National HIVDR strategies and plans should be integrated within (or linked to) broader national AMR strategies and plans.

ARV drug stewardship seeks to achieve optimal clinical outcomes for individuals receiving ARV drugs, minimize drug toxicity and adverse events, and limit the selection of drug-resistant virus. Responsible ARV drug stewardship requires the engagement of every stakeholder to be aware of, and to implement, existing global and national recommendations for monitoring HIVDR. Responsible stewards prevent and respond to HIVDR appropriately, and optimize programme functioning in ways to prevent it.

Countries should ensure that national HIVDR strategy includes formation of a functional national HIVDR working group, chaired by the national ART programme. This working group should be charged with the planning and execution of routine HIVDR surveys; programmatic assessments of quality-of-care indicators associated with HIVDR; prevention and response to HIVDR; the strengthening of laboratory capacity and data management; and the use and dissemination of HIVDR survey data and programmatic information for the public good.

Action among all partners, including people living with HIV and communities, needs to be taken to increase awareness of the burden and impact of HIVDR. Communication strategies should reach all audiences and be consistent across global and national partners. Synergy between the AMR and HIVDR Global Action Plans opens the possibility for collective work to raise awareness and build country capacity to respond, conduct research, identify sustainable funding, and promote common health system platforms to address HIVDR and other AMR.

Countries are encouraged to identify mechanisms for sustainable funding, with HIVDR integrated into national HIV plans and budgets. Donors should engage with countries to maintain the required funding levels to enable appropriate monitoring, prevention and response to HIVDR. Sustained efforts after 2017 will be critical to minimize HIVDR and ensure the 2020 targets for viral load suppression in people living with HIV on ART are met.
An effective HIVDR response requires a long-term multi-partner effort, working at different levels across a range of sectors. Countries are responsible for strengthening surveillance and developing and implementing national strategies to prevent, monitor and respond to AMR, including HIVDR. Political willingness is required to guarantee regular national or external funding allocation, and is essential in view of competing health priorities. External support may be required; therefore, inter-country and regional coordination is critical to the success of HIVDR prevention and response.

Global and country non-state partners play a pivotal role in building capacity and supporting countries in the planning and implementation of their national HIVDR strategy. Partners, including nongovernmental organizations, are vital enablers who catalyse country-driven activities and support governments to ensure timely interpretation and use of findings. The pharmaceutical and diagnostic industries have a collective responsibility to develop effective low-cost drugs, diagnostics and technologies for the treatment and monitoring of HIV.

People living with HIV, community organizations and civil society have a critical role in advocacy, policy development and resource mobilization, which can contribute greatly to strengthening HIVDR prevention, monitoring and response. Communities and people living with HIV can advocate for access to uninterrupted treatment, quality provision of HIV care and appropriate monitoring, including viral load testing. They can also encourage routine HIVDR surveillance and identification and implementation of locally generated, sustainable solutions to prevent HIVDR.

Researchers are required in both public and private sectors for the development of more robust, safer and better-tolerated ARV drugs; ARV formulations that facilitate adherence to treatment; and diagnostics to improve HIVDR monitoring. Researchers are invited to address unanswered questions on the clinical impact of mutations and the burden of HIVDR in subpopulations using ARV drugs for treatment or prevention. Operational research can inform better service delivery models to improve ARV adherence and treatment outcomes.

Bilateral and multilateral development agencies and donors play a pivotal role in advocating for and raising awareness on the importance of HIVDR prevention, monitoring and response. Funds to address the HIV epidemic, including the development and implementation of national HIVDR strategies, should be made available in a responsible, effective and sustainable manner.

WHO provides strategic leadership on the development of norms and standards for HIVDR prevention and monitoring, and articulates evidence-based policies to promote an effective HIVDR response. WHO has a global convening role to engage partners on research priorities on HIVDR, to coordinate a platform to support development and implementation of national HIVDR strategies, and to promote the integration of HIVDR into national HIV, tuberculosis, AMR and broader health programmes.
PART 4: THE FRAMEWORK FOR ACTION ON HIVDR

The framework sets out the strategic objectives with suggested actions for members of the global community. The framework needs to be adapted at the regional and national levels and actions should be prioritized, in collaboration with relevant partners. The framework will form the basis to monitor implementation of the Global Action Plan on HIVDR.

### Strategic objective 1: Prevention and response

<table>
<thead>
<tr>
<th>Countries</th>
<th>Global and national partners</th>
<th>Community and people living with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strengthen patient, clinic and programme factors associated with and predictive of resistance, and foster environments that enable clinic accountability.</td>
<td>• Support countries in strengthening the use of routine viral load testing (and HIVDR testing, when applicable); improving adherence counselling and retention; and improving ARV drug supply chains to prevent stock-outs.</td>
<td>• Advocate the need for quality ART service delivery to prevent HIVDR emergence.</td>
</tr>
<tr>
<td>• Regularly review and update national policies, guidelines and protocols on the use of ARVs (including for ART, PrEP and PEP), laboratories and HIV service delivery, based on WHO guidelines.</td>
<td>• Support human resource and institutional capacity-building efforts to improve the quality of HIV programmes and services.</td>
<td>• Advocate the need for prompt correction of programmatic gaps, when identified though EWI and other quality indicators, and the timely use of viral load results and HIVDR surveillance findings to effectively respond to HIVDR.</td>
</tr>
<tr>
<td>• Adopt service delivery models within a “treat all” strategy to ensure uninterrupted ARV drug supply, and maximize retention in care and adherence to treatment, particularly in vulnerable groups such as adolescents, pregnant and breastfeeding women, and key populations.</td>
<td>• Participate in country-led dialogues to review and triangulate all sources of data, in order to characterize and support the response required to address HIVDR.</td>
<td>• Promote and provide services for improving ART and PrEP adherence and retention in care.</td>
</tr>
<tr>
<td>• Monitor and ensure quality of PrEP services and programmes to prevent HIVDR emergence.</td>
<td>• Support local initiatives to characterize good practices and scale up effective and sustainable interventions.</td>
<td>• Create demand for viral load testing and HIVDR testing (where applicable) among people living with HIV, families and nongovernmental organizations, and ensure clinicians and programmes respond to this demand.</td>
</tr>
<tr>
<td>• Reinforce literacy of health-care workers and laboratory staff on how to interpret and use viral load results.</td>
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<tr>
<td>• Implement actions to improve quality of ART service delivery systems to prevent HIVDR emergence (Table 2).</td>
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<tr>
<td>• If the national PDR prevalence of NNRTIs is $\geq 10%$, act following WHO’s Guidelines on the public health response to pretreatment HIV drug resistance.</td>
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<tr>
<td>• If suboptimal population levels of viral load suppression are detected:</td>
<td>• If suboptimal population levels of viral load suppression are detected:</td>
<td></td>
</tr>
<tr>
<td>○ Implement a national PDR survey to ascertain if PDR levels are a possible explanation for low levels of viral load suppression, and if ADR is being transmitted at a significant level.</td>
<td>○ Review EWI and other quality indicators to ascertain possible reasons for low levels of viral load suppression and HIVDR emergence (e.g. ARV drug supply management, adherence, use of pre-qualified ARV drugs, or other barriers).</td>
<td></td>
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<tr>
<td>○ Review levels of routine programmatic viral load testing coverage; monitor timeliness and appropriate use of viral load results to switch individuals to second-line ART if indicated; assess whether the frequency of switch from first- to second-line ART is less than expected.</td>
<td>○ Review levels of routine programmatic viral load testing coverage; monitor timeliness and appropriate use of viral load results to switch individuals to second-line ART if indicated; assess whether the frequency of switch from first- to second-line ART is less than expected.</td>
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</tr>
<tr>
<td>○ If population-levels of PDR in ART naive infants are elevated, implement WHO recommendations to initiate children less than 3 years of age on PI-based ART (presuming this is not already standard practice in the country).</td>
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</table>
Researchers

- Generate evidence regarding which public health interventions have the greatest impact in preventing and responding to HIVDR, to be used for national and global decision-making, including in the areas of treatment adherence, retention in care and PrEP.
- Develop mathematical models that assist in-country analysis and adaptation of the response to HIVDR.

Bilateral and multilateral donors

- Ensure adequate resources are allocated to support the national strategy to prevent and respond to HIVDR.

WHO

- Ensure normative guidance on the use of ARV drugs for prevention and treatment are regularly updated and disseminated, and incorporate emerging evidence on resistance to new drug classes.
- Monitor implementation of recommendations for the public health response to HIVDR.

Table 2 displays, in more detail, concrete actions countries and partners can take as part of the prevention and response strategic objective to address quality gaps in HIV programmes. If implemented, these actions can prompt site- and national-level action to mitigate factors associated with HIVDR. These actions should be part of the national HIV strategy and linked to the broader HIVDR, multidrug resistance tuberculosis and AMR action plans.

Table 2: Public health actions to prevent HIV drug resistance and respond to suboptimal performance quality-of-care indicators (6)

<table>
<thead>
<tr>
<th>Area:</th>
<th>HIVDR prevention actions for adults, adolescents and children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribing practices</strong></td>
<td>• Development and regular update of evidence-based care and treatment guidelines for adults and children, founded upon scientific evidence, public health principles and international recommendations</td>
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<td></td>
<td>• Guidelines dissemination and training of providers in appropriate triple-drug prescribing practices based on national and/or international treatment guidelines</td>
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<td></td>
<td>• Maintaining a continuous drug supply at clinic level for adult and paediatric populations to prevent the need to substitute, switch, or dispense mono- or dual-therapy due to drug shortages or stock-outs; see “Drug stock-outs (supply chain management)”</td>
</tr>
<tr>
<td></td>
<td>• Regular update of ARV drugs included in the national essential medicine list: inclusion of new ARV drugs and exclusion of obsolete ones in line with international recommendations</td>
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<td></td>
<td>• Procurement of WHO quality-assured ARV drugs, or drugs registered by other national or international regulatory agencies</td>
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<tr>
<td><strong>Loss to follow-up</strong></td>
<td>• Defaulter tracing to re-engage individuals into care and to characterize the contribution of deaths and silent transfers</td>
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<tr>
<td></td>
<td>o Preventing losses due to transfer of care without knowledge of the original clinic (i.e. silent transfers) requires:</td>
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<td></td>
<td>• improved processes to report and record transfers, defaulter tracing, and use of national unique patient identifiers</td>
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<td></td>
<td>• improved processes to track adolescents as they move from paediatric care into adult ART services</td>
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<td></td>
<td>• improved processes to track and monitor pregnant and breastfeeding women living with HIV as they transfer between PMTCT services and general adult ART care</td>
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<td></td>
<td>o Preventing losses due to unascertained deaths requires:</td>
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<td></td>
<td>• clinical care improvements to minimize mortality</td>
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<td></td>
<td>• strengthened ascertainment of deaths (e.g. engaging families to report deaths, linking ART records to death registries)</td>
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<tr>
<td></td>
<td>o Preventing losses due to disengagement from care requires:</td>
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<td></td>
<td>• strengthened and better resourced defaulter tracing mechanisms</td>
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<td></td>
<td>• initiation of patient tracing as close to the date of last missed clinic or pharmacy appointment as possible</td>
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<td></td>
<td>• close support of adolescents as they transition from paediatric to adult ART programmes</td>
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<td></td>
<td>• Strengthened community outreach and counselling, SMS appointment reminders, alternative clinic appointment times (e.g. night or weekend hours), decentralization of ART delivery, and alternative models of care, such as home-based care</td>
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<tr>
<td></td>
<td>• Provision of more than a one-month supply of ART to decrease the frequency of clinic visits may support engagement in care and reduce burden on dispensing systems</td>
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<table>
<thead>
<tr>
<th>Retention</th>
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<tbody>
<tr>
<td>• Recommendations as per loss to follow-up</td>
</tr>
<tr>
<td>• Improving facility service provision (e.g. reduce wait times, improve staff attitudes, eliminate or reduce patient costs)</td>
</tr>
<tr>
<td>• Defaulter tracing to re-engage patients who have defaulted back into care</td>
</tr>
<tr>
<td>• Reduction of HIV-associated stigma and discrimination for people living with HIV and key populations among communities and health-care providers</td>
</tr>
<tr>
<td>• Extra care for high-risk people*</td>
</tr>
<tr>
<td>• Provision of community support for people living with HIVc d e</td>
</tr>
<tr>
<td>○ Community-level interventions include adherence clubs and use of non-clinical or lay patient advocates and peer support partners to encourage adherence and provide psychological support</td>
</tr>
<tr>
<td>○ Family-based care that allows parents and children to be seen at the same time and place to minimize time and costs required for clinic visits</td>
</tr>
<tr>
<td>○ Supporting disclosure among couples and for paediatric and adolescent patients</td>
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<tr>
<th>On-time pill pick-up</th>
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<tr>
<td>• Adherence support f</td>
</tr>
<tr>
<td>○ This includes peer counselling, SMS services, reminder devices, cognitive behavioural therapy, behavioural skills, fixed-dose combinations and once-daily regimens</td>
</tr>
<tr>
<td>• Decentralization of refill visits and ART services</td>
</tr>
<tr>
<td>• Reduction of HIV-associated stigma</td>
</tr>
<tr>
<td>• Provision of more than a one-month supply of ARV drugs</td>
</tr>
<tr>
<td>• Use of objective measures of adherence to counsel patients</td>
</tr>
<tr>
<td>• Electronic or paper-based pharmacy registers that allow rapid detection of missed ARV pick-ups and the opportunity for defaulter tracing</td>
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</tbody>
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<table>
<thead>
<tr>
<th>On-time appointment keeping</th>
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<tbody>
<tr>
<td>• Recommendations as per retention and on-time pill pick-up</td>
</tr>
<tr>
<td>• Electronic or paper-based appointment scheduling</td>
</tr>
<tr>
<td>• SMS or telephone call reminders</td>
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<table>
<thead>
<tr>
<th>Drug stock-outs (supply chain management)</th>
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</thead>
<tbody>
<tr>
<td>• Strengthening of drug forecasting, procurement, and supply information and distribution systemsg</td>
</tr>
<tr>
<td>• Global and regional planning prior to and during change of preferred ARV regimens</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Viral load suppression</th>
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<tbody>
<tr>
<td>• Interventions to improve adherence linked to improved virological suppression</td>
</tr>
<tr>
<td>○ This includes peer counsellors, support groups, SMS and reminder devices, behavioural skills training, medication adherence training, and use of fixed-dose combinations, child-friendly formulations, and once-daily regimens</td>
</tr>
<tr>
<td>○ Enhanced and tailored adherence support for populations at higher risk of virological failure (i.e. children, adolescents, young adults, pregnant and breastfeeding women)</td>
</tr>
<tr>
<td>• Routine viral load monitoring as per national guidelines with timely and appropriate clinical response to high viral loads in all patient populations</td>
</tr>
<tr>
<td>• Implementation of a process to ensure prompt switch to second-line ART when indicated (e.g. decentralization of switch committees, health-care worker training on second-line regimens)</td>
</tr>
<tr>
<td>• Viral load completion</td>
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<thead>
<tr>
<th>Viral load completion</th>
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<tbody>
<tr>
<td>• Addressing logistical challenges associated with specimen transport, equipment breakdown, personnel shortages and weak laboratory information management systems</td>
</tr>
<tr>
<td>• Expanding access to viral load sample collection methodologies that are child-friendly (e.g. DBS)</td>
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<tr>
<td>• Demanding support from clinicians and people living with HIV to improve viral load literacy among patients and caregivers</td>
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## Strategic objective 2: Monitoring and surveillance

<table>
<thead>
<tr>
<th>Countries</th>
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<tbody>
<tr>
<td>• Ensure HIVDR monitoring is coordinated by the national AIDS programme and linked to the national AMR and multidrug resistance tuberculosis plans.</td>
</tr>
<tr>
<td>• To inform nation and global policies, regularly generate nationally representative HIVDR estimates following a standardized approach and validated methods (Web Annex 2).</td>
</tr>
<tr>
<td>• Promptly disseminate HIVDR survey results in country and to WHO for timely public health assessment.</td>
</tr>
<tr>
<td>• Monitor the quality of service delivery through the collection of EWI of HIVDR and other indicators through available monitoring and evaluation systems.</td>
</tr>
<tr>
<td>• Assess whether routinely available viral load and HIVDR data are of adequate quality, completeness and coverage to inform national HIVDR estimates across age groups (children, adolescents, young adults), subpopulations (pregnant and breastfeeding women) or key populations.</td>
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<table>
<thead>
<tr>
<th>Global and national partners</th>
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<tbody>
<tr>
<td>• Support countries in routine implementation of HIVDR surveillance using standardized methods.</td>
</tr>
<tr>
<td>• Leverage existing capacity at the programme level where feasible, and build institutional capacity to implement effective HIVDR monitoring and surveillance.</td>
</tr>
<tr>
<td>• Ensure HIVDR surveys and programme monitoring (including EWI) are funded as a core component of the ART programme, and that ministries of health are leading the monitoring of HIVDR.</td>
</tr>
<tr>
<td>• Eliminate barriers to efficient HIVDR data sharing between national programmes, WHO and partners.</td>
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<thead>
<tr>
<th>Community and people living with HIV</th>
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<tbody>
<tr>
<td>• Advocate for the routine implementation of HIVDR monitoring, for regular monitoring of EWI and other quality-of-care indicators, and for regular generation of HIVDR national estimates.</td>
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<thead>
<tr>
<th>Bilateral and multilateral donors</th>
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<tbody>
<tr>
<td>• Ensure HIVDR surveys and monitoring of indicators associated with HIVDR are regularly funded and implemented according to agreed standards.</td>
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<tr>
<th>WHO</th>
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<tbody>
<tr>
<td>• Ensure that HIVDR surveillance and monitoring is strategically and programmatically linked to broader AMR and tuberculosis resistance surveillance and monitoring.</td>
</tr>
<tr>
<td>• Develop guidelines for HIVDR surveillance (for periodic survey and to generate national estimates using routine programme data), and periodically assess the need to update based on new evidence and lessons learned from implementation.</td>
</tr>
<tr>
<td>• Set the standard and develop a framework to assess the use of routine viral load and HIVDR programme data, for the purposes of informing national HIVDR prevalence and trends.</td>
</tr>
<tr>
<td>• Facilitate surveillance of mutations that may impact the efficacy of PrEP in populations using ARV drugs to prevent HIV transmission.</td>
</tr>
<tr>
<td>• Develop methods to assess the prevalence and patterns of resistance in individuals failing second-line ART.</td>
</tr>
<tr>
<td>• Strengthen national and global repositories of HIVDR surveillance data to support national and high-level global health recommendations; provide technical assistance to strengthen quality data storage and management.</td>
</tr>
<tr>
<td>• Regularly report global and regional levels of HIVDR and trends.</td>
</tr>
<tr>
<td>• Support countries to regularly monitor EWI of HIVDR using available monitoring and evaluation systems (where feasible), and to conduct HIVDR surveillance.</td>
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</table>
### Strategic objective 3: Research and innovation

| Countries | • Identify research questions of public health importance for the local context, and help promote evidence-based interventions aimed at improving programme performance to prevent HIVDR.  
• Collate all relevant HIVDR-related research information with public health relevance for the country in a national repository owned by the national AIDS programme. |
| Community and people living with HIV | • Advocate for adequate investments in HIVDR research and innovation.  
• Work with national programmes and research institutions to ensure research meets ethical standards and incorporates community perspectives. |
| Bilateral and multilateral donors | • Prioritize funding support for research questions with public health importance and impact for the national programme.  
• Ensure adequate investment in the research and development of HIV prevention tools, including vaccines and diagnostics, in addition to new ARV drugs. |
| Researchers | • Conduct implementation science research, including cost-effectiveness studies, to identify service delivery approaches that will most effectively prevent HIVDR.  
• Develop simple, affordable public health-oriented tests that combine viral load with HIVDR testing in a variety of different specimen types (e.g. blood spots and liquid) for near or at the point-of-care testing.  
• Develop simple, affordable public health-oriented approaches for high-throughput resistance testing and algorithms for the interpretation of HIVDR test results.  
• Assess HIVDR in vulnerable groups, such as pregnant and breastfeeding women, children and adolescents, and key populations.  
• Assess the prevalence and patterns of resistance in individuals failing second-line ART to support an improved switching algorithm.  
• Define the clinical impact of drug-resistance mutations and how to optimally interpret genotypic data, particularly for low-abundant resistant variants and mutations emerging from new ARV drugs, including integrase inhibitors.  
• Conduct research on the effect of long-acting injectable ART on HIVDR.  
• Develop a mathematical model to inform decision-making on interventions to prevent and respond to HIVDR, at the global and local level.  
• Assess pockets of HIVDR being transmitted within well-defined geographic areas or populations, and identify suitable targeted prevention strategies. |
| WHO | • Convene a research prioritization process in collaboration with research institutions and expert networks.  
• Drive a global discussion on shared visions for a priority research agenda for HIVDR.  
• Facilitate the research agenda related to the application of next generation sequencing for HIVDR testing; establish clinically relevant thresholds for reporting the presence of low-abundance resistant variants; and establish quality assurance guidance for next generation sequencing. |
Strategic objective 4: **Laboratory capacity**

| **Countries** | • Integrate HIVDR testing into broader national AMR and laboratory strategies and plans.  
  • Strengthen country laboratory services and quality assurance for viral load testing, including prompt reporting of results for clinical care.  
  • Strengthen country laboratory services for HIVDR testing, using DBS and HIVDR testing of the integrase coding region.  
  • Designate a national laboratory with HIVDR testing capacity and submit an application for membership in the WHO Laboratory Network.  
  • Expand coverage, quality and use of viral load and HIVDR testing (i.e. individuals failing second-line ART); expand use of point-of-care viral load testing. |
| **Global and national partners** | • Incorporate HIVDR laboratory strengthening into laboratory capacity-building efforts within the Global Health Security Agenda.  
  • Support countries to develop national capacity for quality-assured viral load testing; commit to greater investment for developing and expanding point-of-care technologies for measurement of viral load when available.  
  • Support HIVDR testing for the purpose of HIVDR surveillance in countries with no resources or capacity. |
| **Community and people living with HIV** | • Advocate for the expansion of quality viral load testing for all individuals countrywide, and for the use of HIVDR testing in individuals failing second-line ART, when possible. |
| **Bilateral and multilateral donors** | • Allocate adequate resources to expand viral load testing to all people in need.  
  • Allocate resources to support membership in the WHO Laboratory Network, for at least one designated laboratory in each country to support surveillance. |
| **WHO** | • Identify opportunities for the efficient integration of HIVDR into broader national AMR and laboratory strengthening strategies and plans, including the use of shared health systems and laboratory platforms.  
  • Encourage countries to designate a laboratory for HIVDR testing, build capacity and apply for membership in the WHO Laboratory Network.  
  • Expand HIVDR surveillance to include the integrase-coding region.  
  • Provide technical assistance to countries to generate quality-assured viral load and HIVDR test results and to scale up HIVDR testing using DBS. |
Strategic objective 5: Governance and enabling mechanisms

Ensure that governance and enabling mechanisms (advocacy, country ownership, coordinated action and sustainable funding) are in place to support action on HIVDR.

### Advocacy and communication

| Countries | • Ensure decision-makers are aware of the potential impact of HIVDR on global targets and HIV programme sustainability.  
• Engage partners, including civil society, to implement country-level communication strategies to improve understanding and awareness of the risk of HIVDR emergence at all levels.  
• Ensure country-level communication synergies are related to WHO’s Global Action Plan on AMR, Global Health Sector Strategy on HIV and Consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection, as well as the Global Health Security Agenda.  
• Strengthen literacy on the risk of HIVDR emergence among individuals and health-care workers. |
|---|---|
| Global and national partners | • Build HIVDR language into all relevant technical material, guidance documents and tools to be used in routine communications with supported countries.  
• Advocate for a central role of HIVDR surveillance, prevention and response within the national AIDS programme. |
| Community and people living with HIV | • Advocate through the national AIDS programme on the need to combat HIVDR.  
• Build community engagement and literacy for preventing and responding to HIVDR. |
| WHO | • Support countries to develop the business case for HIVDR and to link it to the AMR country action plan.  
• Effectively communicate the importance of combating HIVDR with different audiences, to increase HIVDR awareness and commitment.  
• Improve partner and donor awareness of WHO recommendations to monitor and respond to HIVDR. |

### Sustainable funding

| Countries | • Identify and allocate national resources to fund HIVDR activities as a core component of ART programmes.  
• Include costing of all elements of HIVDR prevention, monitoring and response in national HIV strategic plans, including local government funding commitments, PEPFAR cooperative agreements, and applications for Global Fund grants. |
|---|---|
| Global and national partners | • Mobilize sustainable financing to support strategies to prevent, respond to and monitor HIVDR at global, national and local levels.  
• Ensure adequate resources are allocated for HIVDR national strategies from the country’s HIV budget, Global Fund, PEPFAR country operating plans, or other funding sources.  
• Ensure adequate funding to support research, product development and innovation on HIVDR (including work related to diagnostics, new ARV drugs and vaccine development). |
| WHO | • Identify opportunities with WHO HIVResNet and other stakeholders to leverage funding to support and coordinate the global prevention, monitoring and response to HIVDR. |
### Coordination, integration, alignment and country ownership

#### Countries
- Strengthen country ownership and coordination through the development of a five-year national HIVDR strategy, with milestones and a funding plan. Integrate this strategy into the national HIV plan and link it to the AMR plan.
- Leverage synergies with national AMR, tuberculosis, malaria and hepatitis programmes.

#### Global and national partners
- Support a central role of the national AIDS programme in the development of a national strategy to monitor, prevent and respond to HIVDR.
- Support alignment with recommendations from WHO on HIVDR prevention, monitoring and response.
- Support implementation of all elements of the Global Action Plan on HIVDR, including providing resources and sharing data for global reports.

#### WHO
- Assist Fast-Track countries to implement country-level action to monitor, prevent and respond to HIVDR, harnessing national support.
- Promote and foster alignment with the ministry of health and key implementing partners for coordinated technical support.
- Ensure continuous dialogue between academia, country programmes, policy-makers and donors on HIVDR.
- Host a global repository of HIVDR data; monitor progress in implementation of the Global Action Plan by countries and organizations; and assess financial support received for various elements of the plan. Disseminate information through regular global reports.
PART 5: IMPLEMENTATION, MONITORING AND REPORTING

Working with partners, WHO will take overall responsibility for coordinating the Global Action Plan; for monitoring and reporting on the progress of its implementation; and for convening partners around collaborative actions. It is estimated that the total cost of coordination, technical support and capacity-building for the 35 Fast-Track countries by WHO headquarters and regional offices will be approximately US$ 25 million for the five-year period – an estimated 0.03% of the total investment needed for the HIV response between 2016 and 2021.

Monitoring and evaluation

Monitoring and evaluation of the Global Action Plan is required for global coordination, to identify and respond to barriers to progress, and to inform action. Monitoring and evaluation is also required for accountability and reporting back to the global health community, including the governing bodies of WHO on behalf of Member States, the Global Fund, implementing partners, donors and other stakeholders. The monitoring and evaluation framework (Web Annex 1) will evaluate the process of implementation of the Global Action Plan on HIVDR by countries and stakeholders, and assess the outcomes resulting from implementation of the Global Action Plan. To the extent possible, the suggested indicators leverage previously established indicators and existing global reporting processes, and will be extracted through WHO’s surveys. Country-level data sources include the Global AIDS Monitoring survey, the National Commitments and Policy Instrument, the AIDS Medicines and Diagnostics Service, the Global Price Reporting Mechanism, and routine country HIVDR surveys and annual programme quality assessment reports. When relevant, targets are derived from existing EWI of HIVDR targets. Information from WHO and other stakeholder reports will supplement country-level information to enable reporting on governance and HIVDR-related research priorities.

Technical documents supporting the strategic objectives of the Global Action Plan on HIVDR

- Guidelines on the public health response to elevated levels of pretreatment HIV drug resistance 2017 http://
REFERENCES


For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv