Combating HIV drug resistance, a little known but growing threat

DRAFT ZERO FOR CONSULTATION
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Global threat of HIV drug resistance and impact of no action

The emergence of HIV drug resistance (HIVDR) poses a significant threat to ending the AIDS epidemic as the number of people initiating antiretroviral therapy (ART) increases. Recently, several low- and middle- income countries (LMIC) have reported levels of HIVDR at or above 10% amongst antiretroviral (ARV) naive patients starting ART and up to 37% among individuals re-starting ART with prior exposure to ARVs (1). These levels are concerning and where needed should be confirmed using appropriate national representative surveys. If levels of pre-treatment HIV drug resistance (PDR) are over 10% in sub-Saharan Africa, it is predicted that an excess of 420 000 people will die in the next 5 years and costs of ART delivery will increase by nearly US$ 3 billion (2).

Individuals with infections caused by drug-resistant pathogens are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources than individuals with the same infections caused by susceptible microbes. Similarly, HIVDR is associated with poor virological outcomes (3), increased mortality (4,5) and reduced durability and effectiveness of current first-line ARV regimens (6).

Available data show that approximately 10-15% of individuals starting ART fail therapy at 12 months, equating to about 320 000 patients only in 2015. If PDR reaches 15%, an additional 96 000 individuals annually are predicted not to respond to first-line ART due to pre-treatment resistance and will unnecessarily take ineffective drugs. (45) This will necessitate a switch to costlier second-line regimens, resulting in an increased annual cost for drug procurement of US$ 19.2 million. This dramatic rise in cost is particularly concerning at a time when we need to use all available resources to expand access to ARVs.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) warns that after significant reductions, declines in new HIV infections among adults have stalled, failing to decline for at least 5 years and are even rising in some regions (7). If not addressed, the increase in HIVDR is predicted to result in 300 000 new HIV infections by 2021 (2) and to significantly fuel the AIDS epidemic over the next 15 years.

Global commitment to end the AIDS epidemic and combat antimicrobial resistance

By the end of 2015, 17 million people were accessing ART, less than half of those living with HIV (8). UN Member States have committed to achieving ambitious targets for individuals receiving ART by 2030. In 2015, UNAIDS set global targets (9), including “90-90-90” by 2020 (90% of all people living with HIV will know their HIV status; 90% of all people with diagnosed HIV infection will receive ART and 90% of all people accessing ART will have viral suppression). While the “Treat All” approach combined with the scale-up of pre-exposure prophylaxis (PrEP) will undoubtedly lead to a decrease in AIDS mortality and HIV incidence, a further increase in HIVDR is expected. HIVDR leads to a suboptimal response to ART and poses a serious barrier to achieving the last “90” target (3).

Ending AIDS is not the only goal that UN Member States have committed to. The global community has recognized that combatting antimicrobial resistance (AMR) requires action across all government sectors and society (10). Addressing HIVDR is an important part of WHO’s commitment to AMR, which threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. The increase in HIVDR, rising prevalence of Multi-Drug Resistant Tuberculosis (MDR-TB) and emergence of P.falciparum multdrug resistance pose substantial threats to ending the epidemics of HIV/AIDS, TB and malaria. Globally, 700 000 die every year from drug resistant pathogens (11).

Continued momentum is required in order to reach global targets for HIV in the next 5 years and make substantial progress towards achieving the Sustainable Development Goals (SDG)/12) by 2030. The 2016 Political Declaration on HIV and AIDS to accelerate the fight against HIV demonstrates UN Member States’ commitment to ending the AIDS epidemic by 2030 (13). The World Health Organization (WHO) Global Health Sector Strategy on HIV 2016–2021 (14), endorsed at the World Health Assembly in May 2016, outlines the global vision, goals and targets for interventions on HIV prevention, treatment and care and human rights to achieve this.

Opportunities to prevent, monitor and respond to HIVDR

The majority of countries scaling up HIV treatment are still experiencing programmatic challenges that facilitate the emergence and transmission of HIVDR (15). While virus-related factors leading to resistance emergence cannot be controlled, countries and partners can play an important role to minimize HIVDR by addressing patient- and programme-related factors.
WHO recommends that every National AIDS Programme should have a robust HIVDR surveillance and monitoring strategy (16), which is relatively inexpensive (approximately US$ 200 000 per year) and feasible to implement. HIVDR surveillance in individuals about to initiate ART and among those on ART provides valuable population-level information to guide first-, second- and third-line ART regimen selection and should be implemented every 3 years. The WHO HIVDR strategy also recommends annual monitoring of early warning indicators\(^1\) (EWI) of HIVDR, which are ART programme and clinic factors associated with the emergence of preventable HIVDR or with successful population-level viral load suppression. EWI provide evidence of situations favouring HIVDR emergence for all people receiving ART and can assist decision-makers to identify clinics or programmatic areas deserving more attention and support.

Implementation of WHO recommendations to initiate ART for all individuals living with HIV and PrEP to those at substantial risk will propel the global community toward the elimination of AIDS as a public health threat (17). Commitment to end AIDS, combat AMR and provide high-quality treatment and care to all people living with HIV are ideal catalysts to generate the attention needed to monitor and respond to the emerging threat of HIVDR.

### Global Action Plan on HIVDR: a call to action

Collaborative effort to monitor and address HIVDR needs to be strengthened on a global scale. To protect our investments on HIV/AIDS all stakeholders should act responsibly and promptly to ensure that HIVDR does not undermine the attainment of the global targets on health and HIV and that the most effective treatment is provided to all people living with HIV (PLHIV), including key populations, pregnant women, children and adolescents.

The Global Action Plan on HIVDR details five strategic objectives to address resistance to HIV under the broader principals of the Global Action Plan on AMR (10). A framework has been developed following extensive consultation to outline the key actions for partners to use available evidence, take preventive action by ensuring timely and sustained quality of ART service delivery (including scaled-up and accessible viral load testing) and respond effectively and with urgency to increasing threats of drug resistance.

Several reports suggest that HIVDR may have reached levels in LMIC that threatens to reverse a decade of benefits to morbidity and mortality from HIV. With this action plan, the goal of ensuring effective treatment for all can be supported and efforts to end the AIDS epidemic with a public health approach will be sustained. The time to act is now. We have been complacent for too long. All global and national partners are accountable if HIVDR is not appropriately monitored and addressed.

\(^1\) On time pill pick-up; retention on ART at 12 months; drug stock outs; viral load suppression; and viral load testing completion.
HIV drug resistance does not undermine the attainment of the global targets on health and HIV. The most effective treatment is provided to all people living with HIV, including key populations, pregnant women, children and adolescents.

By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

1. Surveillance
- Plan & implement surveillance of HIVDR & monitor service delivery quality using agreed standardized methods, based on normative guidance & tools for countries.

2. Research & strengthened programme data
- Strengthen programme data and encourage relevant and innovative research leading to greatest impact; fill the gaps in knowledge on risk of HIV drug resistance for newer molecules and impact of service delivery interventions on viral load suppression and HIVDR.

3. Response
- Use all available evidence in a timely manner to inform ART programme and public health actions.

4. Laboratory capacity
- Strengthen laboratory capacity & quality to ensure the availability of a comprehensive global laboratory network that supports viral load and resistance testing in low- & middle-income countries.

5. Enabling mechanisms
- Ensure that enabling mechanisms (advocacy, country ownership, coordinated action & sustainable funding) are in place to support action on HIVDR.
TARGETS OF GLOBAL ACTION PLAN ON HIVDR

- developing and implementing HIVDR surveillance using recommended standard methods
- assessing the quality of ART service delivery at clinic and programme level
- implementing viral load testing and achieving >70% viral load testing coverage
- increasing rate of ART regimen switches among people failing ART
- expanding laboratory capacity and using WHO designated laboratories for HIVDR testing
- using HIVDR data to inform national ART guidance and programme response
- incorporating multi-sectoral approach in HIVDR strategy

EXPECTED OUTCOMES IN 2021

Routine surveillance activities performed in all fast-track countries
Routine monitoring of clinic and programme level quality of care indicators in all fast-track countries
All fast-track countries use reliable data to inform ART guidelines
Rates of switches to second and third line increased
No further increase of new infections with HIVDR
Part 1: The emerging threat of HIVDR

The global burden of HIVDR

Despite huge advances in prevention and treatment of HIV, countries continue to experience programmatic challenges that facilitate the emergence and transmission of HIVDR. In the first 8 years after ART roll-out (2004 to 2010), HIVDR has increased at an estimated rate of 29% and 14% per year in eastern and southern Africa respectively (18), with PDR reaching 7% globally in 2010 (19). This increase has been driven primarily by raised levels of resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) in Africa (18,19). More recently, higher levels of HIVDR have been observed among people naive to ARVs in several LMIC, including Angola (16%), Argentina (13%), Botswana (10%), Cuba (22%), Mexico (15%), Papua New Guinea (16%) and South Africa (14%)(1, 20-25). Worryingly, even higher levels of resistance are evident among individuals restarting ART after treatment interruption or with prior exposure to ARVs to prevent HIV mother-to-child-transmission (PMTCT), with 37% of those carrying resistant virus before treatment re-initiation (19).

Definitions of HIVDR

HIVDR is caused by a change (mutation) in the virus’s genetic structure and affects the ability of a particular drug or combination of ARV drugs to block the replication of HIV. All current ARVs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of resistant virus.

- **Transmitted HIVDR (TDR)** occurs when a previously uninfected ARV-naive person is infected with a drug-resistant virus. Globally, most TDR is derived from people whose ART fails and who subsequently transmit resistant virus to previously uninfected people.
- **Acquired HIVDR (ADR)** occurs when drug resistance mutations develop in the presence of ARVs. It may emerge because of suboptimal adherence, treatment interruptions, inadequate plasma drug concentrations or the use of suboptimal drugs or drug combinations (28).
- **Pre-treatment HIVDR (PDR)** refers to resistance detected in individuals starting ART and can be either transmitted or acquired due to previous ARV drug exposure(s), for example women who have received ARVs for PMTCT or people who have previously had ART and who reinitiate therapy after defaulting from care.

UNAIDS warns that after significant reductions, declines in new HIV infections among adults have stalled, failing to decline for at least 5 years and are even rising in some regions. Levels of PDR over 10% in sub-Saharan African fast track countries are predicted to result in 300 000 new HIV infections by 2021, contributing to the epidemic and threatening global efforts to end AIDS as a public health threat by 2030 (SDG 3.3). It is therefore imperative that the global HIV community take action to ensure that we remain vigilant to the evolving threat of HIVDR and develop a coordinated health sector response. The urgency for action is growing: as of the end of 2015, 17 million people were accessing ART (8). WHO recommendations on earlier initiation of ART (17) equates to 21 million more people who still are yet to initiate HIV treatment and 37 million who will need to remain on treatment for life.

Successful 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 that will contribute towards achieving the SDGs. Sustained success to achieve the UNAIDS targets will be dependent on functional health systems and effective and well-tolerated HIV treatment.
To tackle the epidemic, a greater investment in HIV programmes in LMIC is needed to avoid an estimated excess of 420,000 AIDS deaths and nearly US$ 3 billion additional ART costs over the next 5 years due to levels of PDR over 10% (2). The increased financial cost in addition to the human cost attributable to HIVDR in the context of scarcity of resources is particularly concerning. It is estimated that 7% of overall programme costs are attributable to HIVDR (in settings with PDR over 10%)(2). Costs of second-line regimens in LMIC are, on average, 150% higher than first-line regimens (US$ 120 mean cost per patient/year compared to US$ 330) (27). Options beyond second-line are even more costly: the lowest possible price for a third-line regimen is around US$ 2000 per patient/year, almost 18 times more than the lowest price for first-line regimens. If PDR reaches 15% globally, it is estimated that an additional 96,000 individuals will require second-line regimens, resulting in an annual extra cost of US$ 19.2 million only for second-line drug procurement.

**Antimicrobial stewardship** refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials. By endorsing the Global Action Plan on AMR (10), the global community has recognized that combating AMR requires action across all sectors and society. Responsible **antiretroviral stewardship** to contribute to the response to HIVDR requires the engagement of everyone. Without immediate collective and sustained global action at all levels, the hard-won gains in HIV-related morbidity and mortality witnessed over the last decade will be reversed and the ability to provide effective and safe ART to all PLHIV greatly jeopardized.

**A call for action**

The WHO Global Action Plan on HIVDR is a 5-year plan (2017–2021) aligned with the WHO Global Action Plan on AMR, as part of the global effort to address AMR. The Action Plan supports the commitment of the UN 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 antimicrobial resistance among people living with HIV". The aims of the Global Action Plan on HIVDR are to ensure that:

- HIV drug resistance does not undermine the attainment of the global targets on health and HIV; and
- the most effective treatment is provided to all people living with HIV, including key populations,\(^3\) pregnant women, children and adolescents.

This Plan outlines the key roles and actions for Member States, global and national partners and the WHO Secretariat over the next 5 years, structured around five strategic objectives (Fig. 1). The broad principles of the WHO Global Action Plan on AMR (whole society engagement including a one-health approach, prevention first, access, sustainability and incremental targets for implementation) are supported by the Global Action Plan on HIVDR.

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\(^3\) WHO defines key populations as: men who have sex with men; people who inject drugs; people in prisons and other closed settings; sex workers; and transgender people. [http://www.who.int/hiv/pub/guidelines/keypopulations/en/](http://www.who.int/hiv/pub/guidelines/keypopulations/en/)
Fig. 1. Strategic objectives of the Global Action Plan on HIVDR 2017–2021

Global commitment to these actions is required to ensure the long-term outcomes and success of HIV programming envisioned in the WHO Global Health Sector Strategy for HIV 2016–2021 (Strategic direction 2 Interventions for impact and 3 Delivery for equity) (14).

The Global Action Plan is supported by the following technical documents on national strategies for surveillance and monitoring of HIVDR:

2. HIV patient monitoring system guides for guidance on EWI (in development 2016).

and the following technical reports:

Guiding principles of the Global Action Plan

The Global Action Plan leverages the following principles and approaches:

**A public health approach**

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**

A coordinated and integrated approach to HIVDR allows for improved resource mobilization, greater sharing of information and enhances research into innovative approaches to tackling HIVDR. WHO’s global HIVDR strategy is supported by WHO HIVResNet, an advisory body of experts and partners committed to ARV stewardship through surveillance and response to HIVDR and the building of laboratory capacity. However, the collaboration at global and national levels and between key partners (Member States, non-governmental organizations, communities, civil society organizations, UN funds, programmes and agencies and international implementing partners) need to be strengthened to ensure increased awareness, advocacy and political and programmatic commitment to tackling HIVDR. WHO provides strategic leadership and a platform to support implementation and monitoring of the global response to HIVDR. PLHIV, health workers and communities should be empowered and involved in all activities related to the monitoring and response of HIVDR. Funders and national and international organizations need to take major responsibility to support this effort.

**Country ownership**

Member States have the responsibility to monitor and respond to HIV, including HIVDR, and to assure that high-quality public health care is provided to their citizens. A national HIVDR strategy with funding allocation and milestones should be developed and integrated into both the national HIV strategic plan and the national action plan on AMR. HIVDR data should be analysed and routinely used at national and local levels to inform HIV treatment programme quality improvements and improve the effectiveness of clinical care of PLHIV.

**Focus on high-impact countries**

The Global Action Plan is focused on 35 UNAIDS fast-track countries (29) that account for 90% of new HIV infections. These countries should conduct the full package of surveillance activities described in the WHO HIVDR Strategy during the 5-year time frame of the Global Action Plan (16,30). While focused attention will be given to monitor progress in implementation among the fast-track countries, all countries should “know their HIVDR epidemics” by implementing essential surveillance elements and responding appropriately.

**Sustainable investment**

Investing in HIVDR surveillance and response is not only a moral responsibility but is a cost-saving intervention that must be supported by major funders of the global response to HIV. All countries should have a fully funded national plan that includes an assessment of resource needs to conduct HIVDR surveillance activities, scale-up country surveys and conduct EWI monitoring. Resources should be allocated towards combinations of interventions that will achieve the greatest impact.

**Standardized methods**

Programmatic and policy responses to HIVDR need to be based on best available evidence. To enable appropriate interpretation of results and comparison of national and global HIVDR trends, quality data should be leveraged in accordance with consistent standards and robust survey methodologies should be employed. WHO has developed a comprehensive package of essential surveys that should be routinely implemented (16). Routine programmatic data can be used to inform national levels of HIVDR in countries with optimal coverage and quality of VL testing and data system. As ART programmes evolve and new evidence becomes available from implementation, survey guidance will be revised accordingly.
Strategic objectives

The Global Action Plan on HIVDR has five strategic objectives and each objective has specific recommendations and actions assigned to key stakeholders.

Fig. 2. Strategic objectives of the Global Action Plan on HIVDR

Objective 1: Surveillance

Plan and implement surveillance of HIVDR and monitoring of quality of service delivery using agreed standardized methods, based on normative guidance and tools for countries.

Action needs to be taken immediately to ensure existing normative guidance is used to develop national HIVDR strategies and that these align with both national plans for HIV and AMR. All actions should be supported by clear rationales of their benefit and cost effectiveness. Commitment from all partners will be required to ensure implementation of surveillance while improving coverage and quality of routine laboratory and programmatic data.

Objective 2: Research and strengthened programme data

Strengthen programme data and encourage relevant and innovative research leading to greatest impact; fill the gaps in knowledge on risk of HIVDR for newer molecules and impact of service delivery
interventions on viral load suppression and HIVDR.

Priorities for research need to be identified, with a focus on the long-term impact of HIVDR on patient outcomes and the use of innovative diagnostics to guide evidence-based practice. Clinical and implementation science research should be supported by funders and implementing partners. Modelling will be useful to determine cost-effectiveness of public health responses to HIVDR. Quality of programme routine data on viral load and HIVDR testing, where available, should be improved to inform national decision-making.

Objective 3: Response

Use all available evidence in a timely manner to inform ART programme and public health actions.

HIV policy decisions on ART and service delivery need to be based on reliable national data of levels and trends of HIVDR. Countries will need to be supported to respond in a timely fashion to findings on EWI and surveys of PDR and ADR. Decision frameworks for the use of HIVDR survey data and programmatic indicators at site, district or national levels will improve patient outcomes.

Objective 4: Laboratory capacity

Strengthen laboratory capacity and quality to ensure the availability of a comprehensive global laboratory network that supports viral load and resistance testing in low- and middle-income countries.

All countries and partners need to ensure availability and high quality of viral load testing, including prompt reporting and use of results. Laboratory capacity in LMIC must be expanded and strengthened to perform HIVDR testing, including use of dried blood spots (DBS) and testing for resistance to newer drug classes, such as integrase inhibitors. Existing WHO HIVResNet laboratories are equipped to support in-country resistance testing and serve as reference laboratories to conduct HIVDR testing for other countries.

Objective 5: Enabling mechanisms

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

All partners should work collectively to support the implementation of the Global Action Plan by 2021. Action needs to be taken immediately to ensure that awareness of the burden and impact of HIVDR is increased among all partners, including PLHIV and communities. Communication strategies should reach all audiences and be consistent across global and national partners. Countries must identify mechanisms for sustainable funding and donors need to engage with countries to maintain required funding levels. WHO HIVResNet will continue to provide coordinated technical input with the WHO Secretariat facilitating a platform for implementation and monitoring of the Global Action Plan Framework (Part 3).

Drivers of HIVDR

Factors contributing to HIVDR can be grouped into four categories:

Patient-specific factors: Adherence to ART is an essential component of individual and programmatic treatment success. Poor adherence is a predictor of virological failure, emergence of HIVDR, disease progression and death. Sustained scale-up of ART depends on the ability of programmes to deliver care in a way that minimizes treatment interruptions and maximizes adherence. Individual factors associated with poor adherence include untreated depression, active substance abuse, poor insight into disease and treatment, being an adolescent or young adult, a higher pill burden, more frequent dosing and forgetfulness (31). Children face particular challenges, related to drug formulations and palatability and dependency on caregivers who may themselves fall ill. Stigma may prevent PLHIV from revealing their status to others and serve as a barrier to HIV treatment adherence (32). Conversely, disclosure of HIV infection status has been reported as being protective against virological failure (33).

Programmatic factors: Long-term HIV care requires robust and integrated systems to support adherence and trace individuals with unknown treatment outcomes. ART programme factors that relate to HIVDR include: demand for services which outstrip available capacity; ARV stock-outs leading to treatment interruptions; limited human resources and infrastructure; fragile drug procurement and supply management systems; high cost for (and lack of) routine viral load monitoring; difficulties sustaining high-quality service while decentralizing care; and weak monitoring and evaluation systems assessing quality of care and treatment outcomes.
Regimen and drug-specific factors: A recognized limitation of NNRTI-based regimens is their lower genetic barrier to resistance compared with regimens using boosted protease inhibitors (bPI), despite similar rates of virological suppression. Suboptimal regimens and inappropriate prescribing practices can further increase the risk of selecting for drug resistant virus. Interactions between drugs (for example rifampicin and nevirapine) can favour emergence of HIVDR by reducing the concentration of ARVs to sub-therapeutic levels. Populations with previous exposure to ARVs are also more likely to carry PDR, leading to more rapid virological failure and further acquisition of HIVDR. Complex regimens with a high pill burden also reduce adherence and the use of fixed-dose combinations can improve adherence, facilitate rational prescribing and streamline drug procurement.

Virus-related factors: HIVDR selection and mutation patterns may differ across HIV subtypes. For example, after exposure to sd-NVP, more HIVDR is observed in HIV-1 subtype D as compared to subtype A (34). Subtype C has a lower genetic barrier to resistance and more readily selects the K65R mutation as compared to subtype B (35). Additionally, pre-existing polymorphism and replication capacity may influence the emergence and clinical impact of resistance.

While virus-related factors leading to resistance emergence cannot be controlled, countries and partners can play an important role to minimize HIVDR by addressing patient and programme-related factors.

Surveillance of HIVDR
To minimize the emergence and spread of HIVDR, WHO recommends HIV treatment scale-up be accompanied by measures to monitor and improve the quality of ART delivery and surveillance of HIVDR (15,17).

WHO HIVDR surveillance guidance (15) focuses on four assessment activities that will provide countries with evidence to inform the optimization of patient- and population-level treatment outcomes:

- Monitoring of clinic-level EWI of HIVDR
- Surveys of pre-treatment HIV drug resistance (PDR) in populations initiating ART
- Surveys of acquired HIV drug resistance (ADR) in populations receiving ART
- Surveys of HIVDR among infants less than 18 months old

EWI
EWI definitions and targets follow international standards (36) and WHO recommends that countries monitor them on an annual basis (15) as part of the routine programme monitoring and evaluation activities. While HIVDR testing remains complex and not affordable for routine patient care in most countries, the monitoring of patient and clinic factors associated with the emergence of preventable HIVDR is comparatively inexpensive.

Recommended EWI of HIVDR are:

- on-time pill pick-up;
- retention on ART at 12 months;
- drug stock-outs;
- viral load suppression; and
- viral load testing completion.

EWI should be monitored at all ART clinics and results used to identify best practices and identification of locally appropriate and sustainable solutions to address gaps in ART service delivery that can lead to emergence of preventable HIVDR. Score-carding (or stratified performance strata) is used, thus facilitating identification of areas of greatest need and allocation of resources (15).
Surveys of pre-treatment and acquired drug resistance

WHO recommends priority survey activities to be conducted every 3 years in populations starting ART to estimate the prevalence of PDR (Table 1). Previous exposure to ARVs should be assessed at the time of ART initiation and resistance prevalence calculated among (i) populations starting ART regardless of ARV prior exposure, (ii) populations reporting no previous exposure to ART and (iii) populations reporting prior exposure to ARVs.

Surveys of ADR inform the choice of second- and third-line regimens as well as inform on the proportion of population failing at 12 and 48 months, who should be switched to second-line regimens because of carrying resistant virus. The ADR survey is designed to yield nationally representative point prevalence estimates of (a) programme-level viral load suppression and (b) the prevalence of HIVDR in populations receiving ART for 12 (±3) months and populations receiving ART for at least 48 months (Table 1).

It is advised to conduct PDR and ADR surveys concomitantly, to reduce cost and optimize the logistics.

Table 1. Recommended high-priority HIVDR surveys

<table>
<thead>
<tr>
<th>Type of survey</th>
<th>Population of interest</th>
<th>Outcome measure</th>
<th>Programmatic relevance</th>
<th>Recommended periodicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDR</td>
<td>Individuals initiating ART</td>
<td>Nationally representative estimate of HIVDR among individuals about to start ART</td>
<td>Presence of resistance prior to ART initiation can compromise both the therapeutic and prevention benefits of first-line ART. Results inform the choice of drugs to be included in first-line treatment, as well as pre- and post-exposure prophylaxis.</td>
<td>Priority element. To be repeated every 3 years.</td>
</tr>
<tr>
<td>ADR</td>
<td>Individuals receiving ART for (a) 12 (+/-3) months and (b) at least 48 months</td>
<td>Nationally representative estimates of viral load suppression and levels/patterns of HIVDR in individuals who have been on ART for 12 (+/-3) months and/or ≥ 48 months.</td>
<td>Viral load suppression is a strong indicator of regimen and programme performance. ADR may compromise the effectiveness of second- and third-line ART, as well as pre- and post-exposure prophylaxis. Adult and paediatric ADR surveys should be conducted separately.</td>
<td>Priority element. To be repeated every 3 years.</td>
</tr>
</tbody>
</table>

While WHO’s recommendations include HIVDR testing to tailor third-line regimen only among patients failing darunavir-based second-line ART, some countries offer HIVDR testing to individuals initiating or failing first- or second-line ART, irrespective of the regimen. WHO is developing guidance for countries on the appropriate use of viral load and HIVDR routinely collected data to inform public health decision-making.

Due to greater operational complexity, WHO no longer recommends the routine implementation of surveys of transmitted HIVDR among recently infected populations. However, in limited circumstances, where results are likely to directly influence a planned public health intervention, implementation of these surveys may be warranted.

Surveillance of HIVDR among treatment-naive infants less than 18 months old

Surveys to assess the prevalence of HIVDR among treatment-naive infants younger than 18 months, newly diagnosed with HIV using early infant diagnosis (EID), are relevant in settings where many infants are exposed to or acquire HIV infection. The survey will provide results that inform the choice of first- and second-line paediatric ARV regimens.
Challenges of surveillance implementation and use of data

Global HIVDR surveillance began in 2004 with the first surveys conducted in two countries, Mexico and South Africa. Between 2004 and 2012, 282 HIVDR surveys were conducted in 38 countries with implementation peaking in 2010 (46 surveys in 12 countries). From 2012 onwards there has been a steady decline in the number of HIVDR surveys implemented annually with only 54 in 22 countries between 2013 and 2015 (37).

WHO surveillance guidance (16) was updated in 2014 to recommend survey methods yielding nationally representative estimates of HIVDR. Between 2014 and July 2016, 10 PDR and 4 ADR surveys have been implemented, but results disseminated from 4 surveys only. To date, 25 additional surveys (14 PDR, 11 ADR) are planned for 2016/2017 using the new WHO survey’s recommended methods.

Many countries and implementing partners in countries with a high HIV burden have yet to incorporate HIVDR-related activities into national HIV strategic plans, leading to a lack of reliable drug resistance surveillance data for many countries. Policy and programme decision-making must be based on reliable data; however, they often have to rely on limited data from relatively small studies, designed with other objectives, or from data generated from readily available specimens or from a convenient sample, which are unlikely to be representative of the ART programme in a specific country. In addition, limited data are available on HIVDR in certain important populations such as key populations, children, adolescents and women who have taken ARVs for PMTCT on more than one occasion. Limited data also exist on the proportion of individuals with prior ARV exposure re-initiating ART after interruption; this group is most at risk of carrying resistant virus and have poor response to ART (38). Furthermore, where relevant data does exist, timely dissemination within national and global stakeholders is not prioritized and appropriate action is not always taken.

Countries through regional consultations have identified a number of barriers to surveillance implementation and country ownership:

- Insufficient awareness of the need for monitoring and responding to HIVDR at various levels within Ministry of Health and of the implication of the threat of HIVDR threat to the National AIDS Programme.
- HIVDR is perceived as a research activity, led by researchers, laboratory experts, and international partners, limiting timely information sharing, national ownership and use of data.
- Implementing partners’ scientific and ethical review processes are often lengthy and burdensome and are an identified barrier to survey implementation.
- There is inadequate awareness of funding opportunities to support HIVDR work.
- Conflict with other competing national public health priorities.
- Inadequate partner and donor awareness and engagement.
- Inadequate laboratory capacity for HIVDR testing.
- National regulations limiting the ability to ship specimens for HIVDR testing outside the country.
- Insufficient human resources with high turnover of staff.

WHO will continue to work with partners to support countries in addressing these challenges and to ensure that monitoring, surveillance and scaling-up of viral load testing support increased efforts to address the risks of increased HIVDR and reduce the threats to achieving national and global HIV goals.

Responding to HIVDR

Findings from EWI monitoring and HIVDR surveys should be used to respond to HIVDR and prevent further transmission.

EWI findings form the basis of recommendations for action, either at the clinic level or, if many clinics do not achieve desired targets, at the National AIDS Programme level. Action should be preceded by a period of investigation at national and clinic levels, to identify causes for suboptimal performance and their solutions. Investigations may include qualitative interviews of patients and providers at high-functioning and low-functioning clinics, and case series or case control studies to assess for determinants of poor performance.
General actions may include: increased training and resources for specific aspects of care; strengthening of record-keeping systems; provision of targeted support for adherence; changes in service delivery models and reduction of barriers to continuous access to care; development of novel supply chain management and drug procurement techniques; and building of laboratory infrastructure.

PDR survey results provide evidence to support the choice of nationally recommended regimens for first-line ART, PrEP and post-exposure prophylaxis (PEP).

A potential weakness of the current preferred first-line ARV regimen for adolescents and adults is the NNRTI Efavirenz (EFV), for which HIV can develop resistance through a single mutation change. Survey results can be used to inform national responses when substantial levels of resistance to NNRTI are detected in populations initiating ART.

WHO will issue technical recommendation to guide countries in making appropriate public health actions that address the issue of HIVDR within the public health approach.

The level of pre-treatment NNRTI resistance triggering public health action is a country decision based on availability of resources and infrastructures; levels of 10%-15% resistance are a reasonable threshold, based on trade off considerations around equity, human right, feasibility and practices in the Global North. PDR prevalence should be analysed separately among those with and without prior exposure to ARVs, to identify if actions should be targeted to only one of the two groups (all ART starters or subpopulation of individuals starting ART with previous exposure).

Results from surveys of ADR should be used to monitor successful switch practices in countries. Switch rate to second-line has been historically very low and suboptimal in most LMIC. While only approximately 4–5% of individuals are on second-line ART, 25% of people fail first-line ART and 70% of those carry resistance mutations, thus necessitating switching to second-line. Countries should use the proportion of patients failing with NNRTI resistance to gauge the appropriateness of their switching rate and practice. Furthermore, ADR surveys generate nationally representative VL suppression estimates among people on ART for 12 (± 3 ) months and ≥ 48 months; in countries with suboptimal VL testing coverage, these VL suppression data can be used to measure country performance against the last 90 UNAIDS target (90% viral load suppression among patients on ART).

For children, the first-line regimen contains a protease inhibitor (PI) as the preferred drug to match the two-NRTI backbone. Lopinavir/r was selected in 2013 as the preferred ARV, over nevirapine (NVP) due to concerns for increased NNRTI resistance among infants exposed to NVP in utero or through breastfeeding. However, despite these recommendations, just over half (370 400 of 661 550) of children on first-line ART were receiving NVP-based first-line regimens. Surveys of HIVDR in infants younger than 18 months old inform the proportion of children carrying NNRTI-resistant virus and provide convincing evidence to accelerate implementation of WHO guidance in countries where children are still initiated on NNRTI-based ART. This survey is most useful when implemented prior to national updates of recommended paediatric ART guidelines. Also, by estimating the level of resistance to NNRTI, results will help guide usefulness of these ARVs as a component of second- and third-line regimens.

As of 2016 for several countries, these survey results (NVP resistance levels in excess of 50%) were the impetus to initiate all children younger than 3 years old with a PI-based regime, representing an example of a recommended first-line ARV regimen changing due to increased HIV resistance to a first-line drug.
Part 2: Collective strategy against HIVDR

Shared responsibility on HIVDR

The World Health Assembly adoption of the Global Action Plan on AMR (10) reflects the global consensus of the importance for a coordinated effort to tackle AMR at a political level. Synergy between the AMR and HIVDR action plans opens possibilities for shared work to raise awareness and build capacities of governments to respond, conduct research and identify sustainable funding. HIVDR surveillance, monitoring and response should be country-driven, with inter-country, regional and global coordination.

Antimicrobial stewardship seeks to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections and limit the selection of antimicrobial resistant strains (41).

Antiretroviral stewardship seeks to achieve optimal clinical outcomes for patients receiving ARVs, minimize their toxicity and adverse events, and limit the selection of drug resistant HIV. Responsible ARV stewardship requires the engagement of every stakeholder to be aware of and to implement existing global and national recommendations for monitoring levels of HIVDR and to respond appropriately. Greater awareness, commitment and targeted action are required at all levels to meet the growing challenges of HIVDR.

Member States must recognize their shared responsibility for ensuring the long-term effectiveness of available ARVs and take full responsibility for assessing the level of HIVDR within their borders and prepare and implement an appropriate management strategy. A national HIVDR strategy with funding allocation and milestones should be developed and integrated into both the national HIV strategic plan and the national action plan on AMR.

Senior government officials play a critical role as political willingness is required to guarantee successful implementation of the HIVDR plan and is essential in view of multiple competing priorities. External support may be required; therefore, inter-country and regional coordination is critical to the success of HIVDR prevention strategies, both for information sharing and planning. Support for regional coordination will be important to ensure such cooperation.

National Strategy for HIVDR surveillance, monitoring and response

1. Fostering country ownership through:
   a. formation of national HIVDR working groups to coordinate activities and align in-country stakeholders
   b. development and integration of a 5-year national HIVDR plan into national HIV strategic planning leasing with AMR national plan;
   c. identification and allocation of resources; and
   d. integration of surveillance activities into routine programme activities.

2. HIVDR assessments and response:
   a. use of standardized HIVDR surveillance methods, definition, tools and targets;
   b. annual monitoring of EWI of HIVDR; and
   c. appropriate and timely programme response to in-country levels of HIVDR and close identified gaps in service delivery.
3. Leveraging of enablers:
   a. use of WHO-designated laboratory for HIVDR testing;
   b. appropriate HIVDR data management with the goal of using all available information to minimize the emergence and transmission of drug-resistant HIV;
   c. sustained advocacy though PLHIV and community’s involvement highlighting the importance of HIVDR among national decision-makers; and
   d. raise awareness and sensitize patients and health workers about the risk of HIVDR emergence through use of community voices.

4. Timely national and global dissemination of information for programmatic action and ART guideline development.

Implementation partners and non-governmental organizations play an important role in building capacity and supporting countries in the planning and implementation of their national strategy for HIVDR. Partners and NGOs are vital enablers who catalyse country-driven activities and must hold governments responsible for timely interpretation and use of findings.

Community organizations and civil society must become heavily engaged in approaches to prevent and manage HIVDR and demand identification and implementation of locally generated and sustainable solutions to problems which drive HIVDR, such as poor retention, inadequate access to and use of viral load monitoring and stock-outs of ARVs. Communities and PLHIV need to advocate for routine surveillance of HIVDR and hold governments and donors responsible that fail to do so and to institute corrective actions to mitigate HIVDR.

WHO’s Consolidated guidelines for the use of antiretroviral drugs presents new recommendations that provide an enabling environment for community engagement in the delivery of ART, ranging from differentiated care models to community-led ARV delivery approaches. The UNAIDS paper Stronger Together outlines the many areas in which community-based service delivery is vital for the success of HIV programmes, including advocacy, participation in accountability, delivery of health and other services, and research and financing (42). Médecins sans Frontières (MSF) also outlines implementation approaches for a number of community ART delivery models in the report Closer to Home (43).

Health system and community treatment programmes need to review their training modules in order to inform PLHIV, communities, care givers and health workers about the risks of HIVDR and ways to prevent it becoming a serious problem at individual and public health levels. Education of prescribers and patients is also needed on the importance of viral load monitoring and prompt action when levels become detectable, indicating treatment failure.

Bilateral and multilateral donors. Enacting principles of ARV stewardship, the investment in HIV treatment must be protected. It is the responsibility of funding institutions to ensure that the funds are spent in a responsible, effective and sustainable manner and that levels of HIVDR are routinely monitored and appropriate actions are taken to minimize it when and where necessary.

WHO is the leading technical agency on HIV/AIDS, tasked to set the standards in normative guidance on HIVDR surveillance, monitoring and response and provide technical assistance to Member States. The WHO HIVResNet advise on the control and surveillance of HIVDR, in addition to developing HIVDR laboratory networks at global, regional and national levels, and developing a global HIVDR data repository. WHO has a global leadership function to engage partners, articulate evidence-based policy and build sustainable institutional capacity.
Financial and human costs of HIVDR

The cost of the Global Action Plan on HIVDR

The overall cost of implementing the Global Action Plan on HIVDR is based on implementing HIVDR strategies and building capacity within fast-track countries, as well as global and regional costs for technical support and research activities.

The cost of monitoring HIVDR and collaborative global response to rising levels should be compared with the additional cost that would be incurred if no HIVDR monitoring and pre-emptive action were taken. To estimate the effects of HIVDR resistance on financial costs, a ‘scenario-based’ model built on simple assumptions has been developed, not to estimate the exact cost of the actions required globally but to provide orders of magnitude and illustrations of the impact of HIVDR on ART programmes. Further modelling will be needed to refine the analyses outlined in the Global Action Plan.

This section addresses the following questions:

- What might be the projected costs of monitoring HIVDR and implementing pre-emptive measures to delay resistance? (cost of the GAP)
- What might be the cost implications of waiting until HIVDR to first-line ART increase to >10%? (cost of no action or global burden’s cost)

Cost of implementing HIVDR surveillance and monitoring activities

As discussed in Part 2, all countries scaling up ARV should monitor HIVDR resistance regularly for appropriate decision-making. At a minimum, they should: (i) develop a 5-year national HIVDR surveillance and monitoring plan; (ii) build national capacity for HIVDR surveillance; (iii) conduct routine HIVDR surveys (PDR, ADR) and EWI monitoring; and (iv) disseminate results in a timely manner for prompt action. Although some countries already monitor resistance through research studies, implementing the surveys using WHO’s recommended methodology is critical even if it entails additional costs.

Table 3 indicates the expected total cost of monitoring HIVDR at country level. It assumes that the main recommendations of the Global Action Plan are followed, that PDR and ADR surveys are monitored every 3 years, that EWI are monitored annually and that survey in children <18 months are monitored every 5 years. It also assumes that all 35 fast-track countries will implement HIVDR surveillance and EWI monitoring as recommended in the scale up plan (Annex 4).

Annual HIVDR surveillance and monitoring costs on average, less than US$ 248 000 per country (a total of US$ 1 240 million over a 5-year period). The minimum surveillance package (PDR, ADR, EWI) costs even less, an average of US$ 220 000 per country per year. The cost of monitoring resistance is a small fraction of the investment of the ART programme. The minimum HIVDR surveillance package costs US$ 0.55 per person on ART per year in the 35 fast-track countries.4

Table 3: Indicative costs of surveillance and monitoring of HIVDR

<table>
<thead>
<tr>
<th>Budget/survey (US$ K)</th>
<th>PDR &amp; ADR combined</th>
<th>Early Warning Indicators</th>
<th>&lt;18 months survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol development &amp; training</td>
<td>25</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Survey coordination</td>
<td>107</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Site support visits</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td>56.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping</td>
<td>94.35</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Other laboratory cost</td>
<td>21.2</td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Technical support</td>
<td>22.8</td>
<td></td>
<td>22.8</td>
</tr>
<tr>
<td>Data analysis and interpretation, quality assurance, report production and distribution</td>
<td>25</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>373</strong></td>
<td><strong>50</strong></td>
<td><strong>139.5</strong></td>
</tr>
</tbody>
</table>

4 US$ 7.700 million (= 220 000 × 35)/13 957 769 people on ART in the 35 fast-track countries. 5 ADR includes two time points: patients on ART for 12 months (460 specimens) and patients on ART for 48+ months (560 specimens). It assumes: 30 ART clinics; 1350 specimens tested; resistance testing at US$ 150; viral load testing at US$ 60. 6 EWI implementation costs should be integrated to HIV M&E budget as WHO advises countries to integrate the collection of these indicators routinely as part of the global M&E health sector plans. EWI cost reflects the needed funds for existing data verification/validation. 7 Sample size = 490 specimens.
Overall cost of implementing the Global Action Plan on HIVDR

The total annual costs amount to approximately US$ 15 million and just above US$ 75 million for the 5-year period (Table 4). This estimate is a ‘fully loaded’ annual cost at its peak, if all countries and partners were able to implement all GAP recommendations on HIVDR: HIVDR monitoring, capacity building and advocacy, laboratory quality assurance and data management.

It should be noted that this ‘peak cost’ represents only a limited fraction of the cost needed to ensure optimal quality of an ART programme and make programmatic improvements to prevent and respond to HIVDR (data system strengthening, prevention of drug stock out, optimal retention in care and adherence support, strategy to minimize loss to follow-up and treatment interruptions, scale-up of viral load testing and timely identification and switch to second-line of patients failing ART). In addition, cost associated with the introduction of newer first-line regimens, cost for increased use of second-line regimens, building laboratories for HIVDR testing in LMIC and to implement a global research agenda for the next 5 years are not included in the GAP cost.

The full cost of implementing the Global Action Plan only represents approximately 0.03% of the investment needed in the HIV response between 2016 and 2021 (44,45).

Table 4. Overall costs of implementing the Global Action Plan on HIVDR

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Budget (US$ K)</td>
<td>2017</td>
<td>2018</td>
</tr>
<tr>
<td>Surveillance and Monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance (PDR &amp; ADR 12&amp;48+)</td>
<td>373</td>
<td>–</td>
</tr>
<tr>
<td>&lt;18 months</td>
<td>146</td>
<td>–</td>
</tr>
<tr>
<td>EWI</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>National coordination and data management</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Global coordination</td>
<td>Coordination, advocacy, reporting and global database</td>
<td></td>
</tr>
<tr>
<td>WHO HQ</td>
<td>3000</td>
<td>3000</td>
</tr>
<tr>
<td>WHO Regions</td>
<td>3000</td>
<td>3000</td>
</tr>
<tr>
<td>Laboratory (QA)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>15 274</td>
<td>76 370</td>
</tr>
</tbody>
</table>
Costs of inaction

If levels of HIVDR are allowed to grow substantially, the global target of 90% of people on ART with viral suppression by 2020 and 95% by 2030 will never be achieved. Complacency and continued inaction at the national and global level will lead to attenuation of the potential full health benefits of ART. The economic impact of HIVDR and the cost of inaction could be devastating for many countries.

To tackle the epidemic by 2030, a great investment in HIV programmes in LMIC is needed; this investment would be much higher if HIVDR is not addressed and prevented, and newer drugs are not immediately made available at affordable prices. An analysis of the financial and human impact of HIVDR across sub-Saharan Africa estimates that if levels of PDR are over 10%, in the next 5 years HIVDR is predicted to be responsible for 424,937 additional AIDS deaths, over 302,000 new infections, and will result in costs of ART delivery of nearly US$ 3 billion (2) (Table 2).

Table 2. Projected impact of pre-treatment HIVDR >10% on AIDS deaths, new infections and ART costs in sub-Saharan Africa between the present and 2021.

<table>
<thead>
<tr>
<th></th>
<th>AIDS deaths</th>
<th>New infections</th>
<th>ART costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-Track scenario</td>
<td>2,711,785</td>
<td>3,225,740</td>
<td>US$ 37,468 million</td>
</tr>
<tr>
<td>% attributable to HIVDR</td>
<td>15.67%</td>
<td>9.39%</td>
<td>7.96%</td>
</tr>
<tr>
<td>Attributed to HIVDR</td>
<td>424,937</td>
<td>302,897</td>
<td>US$ 2,982 million</td>
</tr>
</tbody>
</table>

Currently, approximately 10% of people starting ART fail therapy at 12 months (45), equating to 320,000 individuals annually at the global level. If pre-treatment HIVDR reaches 15%, an additional 96,000 individuals annually are predicted not to respond to first-line ART and will unnecessarily take ineffective drugs. This will necessitate a switch to costlier second-line regimens, resulting in an increased annual cost for drug procurement of US$ 19.2 million.

Projections of cost for no action on HIVDR beyond 2021 are even more concerning. In a country with 10 million adults and level of PDR over 10%, HIVDR is estimated to cost ART programmes and funders US$ 20 million annually, meaning that by 2030 an excess of US$ 300 million will be diverted to treating people with HIVDR virus rather than prevention and efforts aimed at increasing access to ART. For more populous countries, the burden will be even greater. Cost of inaction far outweighs the cost of taking action as recommended in this global action plan.

With levels of PDR over 10%, in the next 15 years HIVDR is predicted to be responsible for 872,577 additional AIDS deaths, over 485,000 new HIV infections, and will result in costs of ART delivery of US$ 6.7 billion (2).

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9 Using the Spectrum Goals model, by applying the impact of drug resistance as estimated using the HIV Synthesis model. Estimating current level of PDR > 10%, applying the average level of impact projected between the present and 2030 (2). Estimates based on adults only. Higher levels of drug resistance are seen in children due to use of drugs aiming to prevent acquisition and to higher levels of resistance acquisition on ART.
Part 3: The Framework for action on HIVDR

Management of HIVDR is a shared responsibility for the entire global community within the wider context of health policies, strategies and resourcing of health care. The framework sets out each strategic objective followed by recommended actions for each member of the global community. The framework needs to be adapted at the regional and national level and actions should be prioritized, in collaboration with relevant partners. Partners have specific contributions to the framework dependent on their mandate, capacities and interests.

The Framework will form the basis for the monitoring framework for the Global Action Plan on HIVDR (Annex 3).

Objective 1: SURVEILLANCE. Plan and implement surveillance of HIVDR and monitoring quality of service delivery using agreed standardized methods, based on normative guidance and tools for countries.

<table>
<thead>
<tr>
<th>Countries’ action</th>
<th>Global and national partners’ action</th>
<th>WHO’s action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Develop a 5-year national HIVDR strategy and integrate it into the national HIV strategic plan, with milestones and a funding plan.</td>
<td>• Eliminate barriers to data sharing and streamline data sharing between countries, partners and donors.</td>
<td>• Periodically review recommended survey methods based on new evidence and lessons learned from implementation.</td>
</tr>
<tr>
<td>• Routinely implement the WHO HIVDR Surveillance Strategy as part of the ART scale-up plan, using WHO’s recommended standard methods.</td>
<td>• Streamline partners’ scientific and ethical review process to facilitate and encourage survey implementation in supported countries.</td>
<td>• Develop a streamlined and integrated indicator reporting process supported by operational guidance that enables responsible collection of data and encourages its use.</td>
</tr>
<tr>
<td>• Monitor quality programme indicators and use them proactively at clinic and programme level to make adjustments where needed to minimize HIVDR.</td>
<td>• Ensure that funded HIVDR surveys are implemented using consistent and standardized methods and provide technical assistance as needed.</td>
<td>• Develop surveillance methods to assess the population level burden of HIVDR potentially generated by PrEP scale-up interventions.</td>
</tr>
<tr>
<td>• Treat HIVDR data as a “public health good” and ensure timely dissemination of survey results, in-country and externally, to inform national and global ART guidelines.</td>
<td>• Build local and national capacity for high-quality data management; leverage existing capacity where feasible and build institutional rather than personal capacity.</td>
<td>• Develop global repository of HIVDR surveillance data to support national and high-level global health recommendations.</td>
</tr>
<tr>
<td>• Support countries in the development of national 5-year HIVDR strategies, HIVDR surveillance implementation, analysis and interpretation.</td>
<td>• Support countries in the development of national 5-year HIVDR strategies, HIVDR surveillance implementation, analysis and interpretation.</td>
<td>• Provide technical assistance in data storage and management.</td>
</tr>
<tr>
<td>• Publish regular updates on levels and trends of HIVDR.</td>
<td></td>
<td>• Support countries in the development of national 5-year HIVDR strategies, HIVDR surveillance implementation, analysis and interpretation.</td>
</tr>
</tbody>
</table>
### Objective 2: RESEARCH AND STRENGTHENED PROGRAMME DATA

Strengthen programme data and encourage relevant and innovative research leading to greatest impact; fill the gaps in knowledge on risk of HIVDR for newer molecules and impact of service delivery interventions on viral load suppression and HIVDR.

| Countries’ action | • Ensure the completeness and quality of routine viral load laboratory data (and HIVDR where applicable).  
• Identify specific programmatic interventions aimed at improving programme performance to prevent HIVDR that best fit the local context.  
• Assess impact of these interventions on HIVDR and viral load suppression  
• Collate all relevant HIVDR-related research information with public health relevance for the country in a national repository owned by the National AIDS Programme. |
|---|---|
| Global and national partners’ action | • Support countries in strengthening application and use of routine viral load testing (and HIVDR testing when applicable).  
• Prioritize support for research questions with public health importance and impact, including assessing impact of service delivery interventions on viral load suppression and HIVDR.  
• Invest in basic science research to answer new and evolving questions in HIVDR, including the clinical impact of HIVDR present at low-abundance and new diagnostics, such as cheap point of care tests to detect HIVDR.  
• Promptly share research data conducted in countries that have public health relevance. |
| WHO’s action | • Drive global discussion on shared vision for priority research questions.  
• Ensure surveillance approaches keep up as new ARV drugs become available.  
• Set the standard on use of routine laboratory data generated in the course of patient care for the purpose of informing ART guidelines and ART programme decision-making. |
| Research community’s action | • Monitor risk of resistance where dolutegravir is scaled up in large treatment programmes.  
• Conduct implementation science research to identify service delivery approaches that will most effectively minimize HIVDR in key populations, including adolescents, pregnant women and children; measure the impact of proposed interventions.  
• Conduct ad hoc HIVDR surveys/studies among pregnant women, adolescents, children and other key populations; as well as ad hoc surveys to assess differences across subnational areas.  
• Develop innovative user-friendly approaches for HIVDR testing, interpretation and reporting.  
• Conduct operational research to identify the barriers providers face when applying the treatment algorithm (appropriate switching) and develop recommendations and tools to improve provider practices related to switching.  
• Develop mathematical models to determine which public health/programme actions are optimal at different levels of HIVDR, given varying levels of human and economic resources.  
• Develop affordable, user-friendly approaches near or at the point-of-care resistance testing.  
• Develop simple public health-oriented genotype reporting.  
• Research the effect on HIVDR of long-acting injectable ART. |
**Objective 3: RESPONSE.** Use all available evidence in a timely manner to inform ART programme and public health actions.

<table>
<thead>
<tr>
<th>Countries’ action</th>
<th>Global and national partners’ action</th>
<th>WHO’s action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use HIVDR survey results supplemented by other available data to inform revision of national ART guidelines.</td>
<td>• Encourage and support country ownership and appropriate responses to HIVDR survey and EWI data, augmented by other available information.</td>
<td>• Develop a decision framework for country actions to prevent and respond to HIVDR based on surveillance and quality programme indicators data.</td>
</tr>
<tr>
<td>• Develop and implement national strategies to tackle HIVDR and integrate them into HIV national strategic plans and routine M&amp;E.</td>
<td>• Facilitate and support programmatic actions in response to HIVDR survey results and findings from quality programme indicators.</td>
<td>• Develop a policy document that enables prioritization by countries of those patients most in need of an HIVDR genotypic test (applicable in countries with existing drug resistance testing capacity and/or countries planning to introduce it).</td>
</tr>
<tr>
<td>• Guarantee availability and use of viral load testing to ensure that patients failing therapy are identified and promptly switched from first- to second- and second- to third-line therapies.</td>
<td>• Hold donors and governments responsible for their engagement to assess and respond to HIVDR.</td>
<td>• Support local initiatives to characterize best practices and their scale-up.</td>
</tr>
<tr>
<td>• Create and foster environments that enable clinic accountability.</td>
<td>• Use findings from quality programme indicators in a timely way; develop ways of improving ART service delivery systems and patient adherence to ART.</td>
<td>• WHO’s action</td>
</tr>
</tbody>
</table>

**Objective 4: LABORATORY CAPACITY.** Strengthen laboratory capacity and quality to ensure the availability of a comprehensive global laboratory network that supports viral load and resistance testing in low- and middle-income countries.

<table>
<thead>
<tr>
<th>Countries’ action</th>
<th>Global and national partners’ action</th>
<th>WHO’s action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Establish and/or strengthen country laboratory services and quality for viral load testing, including prompt reporting of results for clinical care.</td>
<td>• Incorporate HIVDR laboratory strengthening into laboratory capacity-building efforts within the Global Health Security Agenda.</td>
<td>• Expand and strengthen the WHO HIVResNet laboratory network, assuring high-quality analysis of samples collected as part of the WHO HIVDR Surveillance Strategy.</td>
</tr>
<tr>
<td>• Establish and/or strengthen capacity on genotyping using dried blood spots and testing for resistance of new molecules.</td>
<td>• Continue to develop national capacity for quality assured viral load testing and resistance testing.</td>
<td>• Provide framework to generate quality assured viral load and HIVDR testing results for HIVDR surveillance and progressively expand to cover testing for clinical care.</td>
</tr>
<tr>
<td></td>
<td>• Support countries in the utilization, when available and approved, of innovative user-friendly approaches for HIVDR testing, interpretation and reporting.</td>
<td>• Integrate integrase inhibitor drug resistance testing into the WHO HIVDR Surveillance Strategy.</td>
</tr>
</tbody>
</table>
Objective 5: ENABLING MECHANISMS. Ensure that enabling mechanisms (advocacy, country ownership, coordinated action and sustainable funding) are in place to support action on HIVDR.

<table>
<thead>
<tr>
<th>Advocacy and Communication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries’ action</strong></td>
<td></td>
</tr>
<tr>
<td>• Strengthen country ownership and coordination through functional national HIVDR working groups, concrete implementation plans accompanied by funding strategies.</td>
<td></td>
</tr>
<tr>
<td>• Engage stakeholders, including civil society, for implementing country-level communication strategies to improve understanding and awareness on HIVDR.</td>
<td></td>
</tr>
<tr>
<td>• Ensure country-level communication synergies related to AMR, Health Sector Strategy, consolidated ART Guidelines and Global Health Security Agenda.</td>
<td></td>
</tr>
<tr>
<td>• Build community engagement for preventing and responding to HIVDR, including patient and health worker literacy on HIVDR and its importance for viral suppression.</td>
<td></td>
</tr>
<tr>
<td><strong>Global and national partners’ action</strong></td>
<td></td>
</tr>
<tr>
<td>• Build HIVDR language into guidance documents and tools shared with countries; use it in routine communications with supported countries.</td>
<td></td>
</tr>
<tr>
<td>• Advocate for a central role of HIVDR surveillance and response within the national AIDS programmes.</td>
<td></td>
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<td>• Actively encourage countries to implement surveys as part of their ART scale-up plan, use their data and share them in a timely manner.</td>
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<td>• Ensure HIVDR strategy is included in all relevant technical material.</td>
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<td><strong>WHO’s action</strong></td>
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<tr>
<td>• Develop a communication and advocacy strategy, including targeted messages to different audiences to increase HIVDR awareness and commitment for national programme managers, stakeholders and funders, civil society and general public.</td>
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<th>Sustainable funding</th>
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<tr>
<td><strong>Countries’ action</strong></td>
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<tr>
<td>• Budget for activities on surveillance of and response to HIVDR in Global Fund concept notes and PEPFAR country operational plans.</td>
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<td>• Ensure that HIVDR surveys are funded by the national budget as a routine part of ART scale-up, in the absence of external support.</td>
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<td>• Seek alternative sources of internal and external funding.</td>
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<td><strong>Global and national partners’ action</strong></td>
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<tr>
<td>• Mobilize sustainable financing of a range of HIVDR activities at global, national and local levels.</td>
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<td>• Identify mechanisms to guarantee that HIVDR surveillance and response is funded as a mandatory component of any country’s ART scale-up plan (for example include HIVDR surveillance in the Risk Mitigation Register of the Global Fund; include HIVDR surveillance in the Treatment and Care portfolio of PEPFAR).</td>
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<td>• Identify innovative ways to support countries’ implementation of HIVDR surveys (for example some of the laboratories with WHO HIVResNet laboratory network offer free-of-charge specimen testing for HIVDR).</td>
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<td><strong>WHO’s action</strong></td>
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<tr>
<td>• Work with fast-track countries to garner support for implementation of country-level HIVDR prevention, surveillance and response.</td>
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<tr>
<td>• Seek for opportunities within WHO HIVResNet and other stakeholders to leverage funding to support survey implementation and global coordination.</td>
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### Coordination, Integration, Alignment and Country Ownership

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<th>Countries’ action</th>
<th>Global and national partners’ action</th>
<th>WHO’s action</th>
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| • Establish or strengthen national HIVDR working groups to improve country ownership, partner coordination and timely use of HIVDR data.  
• Ensure the inclusion of HIVDR into national HIV national strategic plans.  
• Ensure EWIs are integrated into M&E framework and HIVDR surveys are integrated into routinely funded activities within ART programmes. | • Ensure and adopt cohesive and aligned recommendations on HIVDR assessment and response.  
• Support implementation of the Global Action Plan for HIVDR, including providing resources and sharing data for global reports.  
• Encourage and support country ownership to ensure appropriate response to HIVDR survey and EWI data. | • Seek active support from the WHO HIVResNet Steering Group as a technical advisory group and as a donor collaboration forum.  
• Promote and foster alignment with key implementing partners.  
• Support countries in developing and implementing national HIVDR strategies.  
• Ensure partner alignment for coordinated technical support.  
• Monitor development and implementation of HIVDR strategies by Member States.  
• Publish biennial global reports, including an assessment of countries and organizations with plans and progress on implementation and financial support received for various elements of the GAP. |

### Scale up plan of HIVDR surveillance

To effectively monitor and prevent HIVDR, doing more of the same is simply not enough. HIVDR surveillance and a coordinated response must be a greater priority for all National AIDS Programmes. While all Member States are expected to implement the essential elements of the WHO HIVDR surveillance strategy, this scale-up plan specifically focuses on the 35 UNAIDS fast-track countries. Efforts to scale up the response to HIVDR in these countries need to be coherent and delivered with support from all relevant partners. Annex 4 summarizes the HIVDR surveillance activities fast-track countries are recommended to implement between 2017 and 2021.
Annexes

Annex 1: Consultative process

A consultative process to inform the Global Action Plan on HIVDR started in October 2015. To date, this has involved one-to-one and group consultations with key partners:

- WHO/HIVResNet and ART drug optimization think tank (Boston, February 2016).
- In February 2016, a series of individual consultations was also held with the Public Health Agency of Canada and Global Affairs Canada, Botswana Harvard Partnership, the Clinton Health Access Initiative, the Elizabeth Glaser Pediatric AIDS Foundation, the African Society for Laboratory Medicine and International Centre for AIDS Care and Treatment Program (ICAP).
- WHO regional guidelines consultations in Africa with key staff from ministries of health and other stakeholders from 35 countries: 18 anglophone countries (Johannesburg, April 2016), 12 francophone (Douala, May) and 5 lusophone countries (Maputo, June 2016).
- Regional online consultation in the Americas (14 countries) (July 2016).
- US Centers for Disease Control and Prevention (Atlanta, May 2016).

In addition, inputs from the expert meeting on the global research agenda for HIVDR, held by the National Institute of Allergy and Infectious Diseases (Rockville, May 2016), will be included in the Global Action Plan.

In early 2016, a two-page summary of the Global Action Plan was produced in English, French and Portuguese. This listed the five strategic objectives and formed a basis for discussion and development. (http://www.who.int/entity/hiv/drugresistance/hivdr-action-plan-2016-2021/en/ outlines the process and provides links, including to an ongoing technical survey that was launched in February 2016.)

The regional consultations in Africa and the Americas provided an opportunity to engage directly with national staff that works directly on HIVDR issues. They provided detailed responses on the situation in their country as well as recommendations for the Plan.

The consultation process is iterative and the inputs received so far have fed into this consultative draft of the Global Action Plan. For example, the definition and scope of the strategic objectives has evolved and these will be refined further as more feedback is received.

An online multi-stakeholder survey will also be conducted to engage members of the wider HIV community, including representatives of PLHIV and civil society organizations. The inputs received from the International AIDS Society Conference in Durban, particularly the Satellite session on Combatting HIV Drug Resistance: WHO Early Warning Indicators Report and the Global Action Plan on HIVDR (July 2016), will start the next stage of further refining and improving the strategic objectives and framework for action.

Some key activities planned include:

- WHO regional consultation in Western Pacific and South-East Asia (Bangkok, August 2016);
- online consultation on the zero draft of the GAP: 18 July–15 September 2016;
- online consultations with community and civil society; and
- WHO/HIVResNet Steering group meetings (Durban, July 2016; Geneva, October 2016).

The launch of the final version of the Global Action Plan on HIVDR is planned for the beginning of 2017.
Annex 2: List of resources


WHO HIVDR; http://www.who.int/hiv/topics/drugresistance/en/.


<to be updated during consultation process>
Annex 3: Abbreviations and acronyms

- ADR: Acquired drug resistance
- AIDS: Acquired immune deficiency syndrome
- AMR: Antimicrobial resistance
- ART: Antiretroviral therapy
- ARV(s): Antiretroviral drugs
- CROI: Conference on Retroviruses and Opportunistic Infections
- DRV: Darunavir
- DTG: Dolutegravir
- EFV: Efavirenz
- EID: Early infant diagnosis of HIV
- EWI: Early Warning Indicator
- GAP: Global Action Plan
- GHSS: Global Health Sector Strategies
- HIV: Human immunodeficiency virus
- HIVDR: HIV drug resistance
- IAS: International AIDS Society
- ICAP: International Center for AIDS Care and Treatment Programs
- LMIC: Low- and middle-income countries
- NNRTI: Non-nucleoside reverse transcriptase inhibitor
- NRTI: Nucleoside reverse transcriptase inhibitor
- PDR: Pre-treatment drug resistance
- PEPFAR: President’s Emergency Programme for AIDS Relief (US)
- PI: Protease inhibitor
- PLHIV: People living with HIV
- PMTCT: Prevention of mother-to-child transmission of HIV
- PrEP: Pre-exposure prophylaxis
- RAL: Raltegravir
- ROP: Regional Operational Plan
- SDG: Sustainable Development Goals
- TDR: Transmitted drug resistance
- UN: United Nations
- UNAIDS: Joint United Nations Programme on HIV/AIDS
- VL: Viral load
- WHO: World Health Organization
Zero Draft of the Global Action Plan on HIVDR - for consultation

Annex 4: Scale-up plan of recommended HIVDR Surveillance for the 35 UNAIDS fast-track priority countries (2017–2021)

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**Source:** PEPFAR website: http://www.pepfar.gov/countries/bilateral/.
**Annex 5: Monitoring framework**

The global monitoring framework, will track the implementation of the action plan through monitoring and reporting in 2021.

<table>
<thead>
<tr>
<th>HIVDR strategic objectives</th>
<th>Timeline for action</th>
<th>Indicator</th>
<th>Targets</th>
<th>Method of verification</th>
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<tr>
<td><strong>1. Surveillance</strong></td>
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<tr>
<td>National HIVDR strategy</td>
<td>Develop national HIVDR working group</td>
<td>Integrate HIVDR strategy into national strategic HIV plan</td>
<td>Number of Member States with national HIVDR strategy</td>
<td>100% of fast-track countries with HIVDR strategy</td>
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<tr>
<td>Surveillance strategy</td>
<td>Review concept notes for HIVDR surveillance activities</td>
<td>Plan nationally representative priority surveillance activities</td>
<td>Total number of Member States conducting and reporting on: Surveillance of PDR (1 in 3 years) Surveillance of ADR (1 in 3 years) Surveillance of infants less than 18 months</td>
<td>100% fast-track countries conducting PDR and ADR surveys according to scale-up plan</td>
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<tr>
<td>Monitor quality indicators</td>
<td>Identify if EWI data routinely available at clinic level</td>
<td>Plan and implement EWI monitoring as part of routine M&amp;E</td>
<td>Conduct annual monitoring of EWI</td>
<td>100% of fast-track countries conducting annual EWI reporting</td>
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<td>Global repository of HIVDR surveillance</td>
<td>Functioning global repository of HIVDR</td>
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<td><strong>2. Research and strengthened programme data</strong></td>
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<tr>
<td>Research</td>
<td>Define priorities for research and identify key areas for investment</td>
<td>Plan and conduct clinical science research</td>
<td>Annual WHO HIVResNet meetings</td>
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<td>Programmatic data</td>
<td>VL scale-up plan developed</td>
<td>VL scale-up plan implemented</td>
<td>Annual WHO HIVResNet meetings</td>
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<td>3. Response</td>
<td>Viral load</td>
<td>Secured funding for viral load scale-up</td>
<td>Implement scale-up of viral load testing</td>
<td>Number of Member States implementing quality viral load testing</td>
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<td>Appropriate switch</td>
<td>Review and streamline second-third-line switching procedures</td>
<td>Expedite ART regimen switch following ART Guidelines, coupled with enhanced forecasting and procurement of second-line ARVs</td>
<td>Number of Member States achieving an increase in the switch rate</td>
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<td>Decision framework</td>
<td>Use normative guidance on HIVDR surveillance methods, definitions, tools and targets to develop HIVDR response strategy</td>
<td>Use survey results to inform programmatic actions to address levels of HIVDR</td>
<td>Delivery of ART programme to minimize transmission and emergence of HIVDR</td>
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<td>Policy on HIVDR testing</td>
<td>Develop and publish policy document on HIVDR</td>
<td>Policy document on HIVDR</td>
<td>WHO</td>
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<td>4. Laboratory capacity</td>
<td>Laboratory network</td>
<td>Identify national laboratories eligible to apply for WHO designation</td>
<td>Use WHO designated laboratories for HIVDR testing and start to build laboratory capacity at national level - expand capacity of DBS testing. All WHO ResNet laboratories accredited for HIVDR testing on DBS</td>
<td>Number of Member States using WHO designated laboratories for HIVDR testing and starting to build national laboratory capacity for HIVDR testing. 100% WHO ResNet labs accredited for DBS</td>
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<td></td>
<td>Working groups</td>
<td>Develop national HIVDR working group</td>
<td>Ensure HIVDR group engagement in strategy development and implementation</td>
<td>Number of Member States that refer to multisectoral approach in HIVDR strategy, plans and programmes</td>
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<td>5. Enabling mechanisms</td>
<td>Advocacy</td>
<td>Engage stakeholders to improve understanding and awareness of HIVDR</td>
<td>Continue to communicate importance of HIVDR</td>
<td>All routine communications on ART to include HIVDR</td>
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<td></td>
<td>Funding</td>
<td>Identify and allocate resources for HIVDR</td>
<td>Commit funds for HIVDR surveillance and monitoring</td>
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</table>
References


27 Global Price Reporting Mechanism GPRM WHO; http://apps.who.int/hiv/amds/price/hdd/.


37 Stanford University HIV Drug resistance database; http://hivdb.stanford.edu/.


40 WHO antiretroviral survey 2015.


