WHO HIV drug resistance network steering group meeting report, June 2021

ISBN 978-92-4-003854-7 (electronic version)
ISBN 978-92-4-003855-4 (print version)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules/).


Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

This publication contains the report of the HIVResNet steering group meeting and does not necessarily represent the decisions or policies of WHO.

Layout by ACW, London
CONTENTS

Acknowledgements........................................................................................................iv
Abbreviations................................................................................................................iv
Background....................................................................................................................v
Session 1: Welcome and introduction of new Steering Group members..........................1
Session 2: Looking back: what was done in 2020.............................................................3
Session 3: Looking ahead: what is planned for 2021.......................................................4
Annex 1. Meeting agenda.................................................................................................11
Annex 2. List of participants..........................................................................................12
ACKNOWLEDGEMENTS

This report was written by Seth Inzaule (WHO consultant) with contributions from Neil Parkin (Data First Consulting, Inc., WHO consultant), Amalia Giron (WHO consultant) and Michael R. Jordan (WHO consultant). Michael R. Jordan (WHO consultant, Levy Center for Integrated Management of Antimicrobial Resistance, Tufts University) coordinated the development of the report under the overall coordination of Marco Vitoria (Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, WHO). We are extremely grateful for the participation and contribution of the presenters, Steering Group members and the chairs.

ABBREVIATIONS

3TC  lamivudine
ABC  abacavir
ART  antiretroviral therapy
CADO  Clinical Adult working group for Drug Optimization
DTG  dolutegravir
FTC  emtricitabine
HIVResNet  HIV drug resistance network
NNRTI  non-nucleoside reverse-transcriptase inhibitor
NRTI  nucleoside reverse-transcriptase inhibitor
PADO  Paediatric working group on Drug Optimization
PI  protease inhibitor
PrEP  pre-exposure prophylaxis
TAF  tenofovir alafenamide
TDF  tenofovir disoproxil fumarate
ZDV  zidovudine
BACKGROUND

The WHO HIV drug resistance network (HIVResNet) is a group composed of international experts, researchers, laboratorians, organizations, partners, stakeholders, and civil society members. HIVResNet has an important advisory role and implementation function in global efforts to prevent, monitor and respond to HIV drug resistance. Established in 2004 by a partnership between WHO and the International AIDS Society, WHO HIVResNet supports the monitoring and prevention of HIV drug resistance, the optimization of HIV drug resistance testing, the monitoring of the quality of antiretroviral therapy (ART) delivery for preventing HIV drug resistance and the development of policies related to optimal first- and second-line ART.

Governance of WHO HIVResNet is provided by its Steering Group, which also serves as the main advisory body to WHO on HIV drug resistance. The Steering Group advises WHO on strategies to tackle HIV drug resistance that are consistent with WHO’s mandate; in addition, Steering Group members chair thematic working groups of the Global Action Plan on HIV drug resistance and support WHO in implementing and reporting on elements of the Global Action Plan. In addition, Steering Group members support WHO in setting the agenda and content development of the annual WHO HIVResNet meeting.

The Steering Group met virtually on 9 June 2021. Annex 1 provides the meeting agenda and Annex 2 the list of participants. Steering Group members reviewed the activities conducted by the Secretariat in 2020 and provided guidance and direction on activities planned for 2021. Specifically, the Steering Group reviewed and provided technical considerations to the planned content of WHO’s 2021 HIV drug resistance report, a proposal to develop a target product profile for HIV drug resistance testing to support individual patient management in low- and middle-income countries, a proposed joint WHO HIVResNet, Clinical Adult working group for Drug Optimization (CADO), and Paediatric working group on Drug Optimization (PADO) meeting and strategic direction on updating the 2017–2021 five-year Global Action Plan on HIV drug resistance.
SESSION 1: WELCOME AND INTRODUCTION OF NEW STEERING GROUP MEMBERS

Presentation 1: Review of HIVResNet Steering Group membership, roles and responsibilities and summary of the 2019 HIVResNet Think Tank discussions

Presenter: Silvia Bertagnolio, WHO

Summary of key points

- **Changes in the steering group composition.** Having completed a three-year term, three members have left the steering group. They are Tobias F. Rinke de Wit (Netherlands), Anne-Genevieve Marcelin (France) and Charles Holmes (USA).

- **Four new members accepted to serve in the Steering Group.** Jacqueline Wambui (Kenya), Eleanor Namusoke-Magongo (Uganda), Rossanna A. Ditangco (Philippines) and Susan Eshleman (USA).

- **Changes in the Secretariat.** Silvia Bertagnolio has left the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes at WHO and will join WHO’s Division of Antimicrobial Resistance as unit head for control and response strategies.

- **Review of HIVResNet Steering Group governance, roles, and responsibilities.** WHO HIVResNet is a body of international experts, researchers, laboratorians, organizations, partners, stakeholders, and civil society members with an advisory and implementation role to prevent, monitor and respond to HIV drug resistance. WHO HIVResNet is governed by a Steering Group, with WHO serving as Secretariat. The Steering Group is the main advisory body to WHO on HIV drug resistance activities. WHO HIVResNet activities are mainly carried out through five technical working groups structured around the five strategic objectives of the Global Action Plan on HIV drug resistance. The five thematic areas are: (1) prevention and response; (2) monitoring and surveillance; (3) research and innovation; (4) laboratory capacity; and (5) governance and enabling mechanisms. Members of the five working groups are drawn from the larger HIVResNet, and each working group has defined terms of reference and is chaired by one or more Steering Group members. The Working Group for Prevention and Response to HIV Drug Resistance is integrated into the Working Group on HIV Clinical Services of the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes since the groups are united in their shared goal of improving the quality of HIV care service delivery.

- **Review of 2019 WHO HIVResNet Think Tank meeting.** Key highlights from the ResNet Think Tank meeting held in Johannesburg were reviewed and include the impact of HIV drug resistance on HIV treatment strategies and the use of HIV drug resistance testing to optimize individual patient management within the public health ART approach.

- **Impact of HIV drug resistance on HIV treatment strategies**
  - Tenofovir disoproxil fumarate (TDF) is WHO’s recommended nucleoside reverse-transcriptase inhibitor (NRTI) backbone in first-line ART and zidovudine (ZDV) is the recommended NRTI backbone in second-line ART. In WHO’s 2019 global report on HIV drug resistance, most surveys showed that treatment fails for up to 60% of people receiving long-term ART without TDF resistance; however, among those with TDF resistance, 25% have resistance to both ZDV and TDF. In addition, studies suggest that NRTI resistance may have minimal impact on successful suppression of viral loads among people taking protease inhibitor (PI)-based regimens. Likewise, TDF has less toxicity and is better tolerated than ZDV. The Steering...
Group therefore discussed the possibility of maintaining TDF for people transitioning from non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based first-line ART to dolutegravir (DTG)- or PI-based second-line ART. This topic was extensively discussed during the 2019 WHO HIVResNet meeting, and the evidence available at that time was reviewed. During the 2019 meeting, 60% of participants indicated that there is sufficient evidence to warrant retaining TDF when transitioning to DTG-based second-line ART, and 65% indicated that there is ample evidence to support the retention of TDF when switching to a PI-based second-line regimen. During the 2021 HIVResNet Steering Group meeting, it was noted that data from the Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) trial support the 2019 Think Tank HIVResNet preferences. However, the general consensus was that more evidence is necessary before changing ART guidelines.

Data from WHO surveys of infants presented to the WHO HIVResNet meeting in 2019 showed a high prevalence of dual resistance to abacavir (ABC) and lamivudine (3TC) and emtricitabine (FTC) among treatment-naive infants living with HIV younger than 18 months of age. In addition, an extensive review of data from published studies was also discussed. Based on the evidence presented in 2019, 77% of the meeting participants supported replacing ABC in first-line ART, with 90% favouring tenofovir alafenamide (TAF); 57% suggested replacing ABC use in second-line ART, with 94% showing a preference for TAF. It was noted, however, that TAF is still not recommended for children weighing less than 25 kg.

Use of HIV drug resistance testing to optimize individual patient management within the public health ART approach

During the 2019 WHO HIVResNet meeting, the potential for using HIV drug resistance testing to optimize individual patient management in low- and middle-income settings was discussed. Specific scenarios for which HIV drug resistance testing could be used for individual patient management discussed in the meeting included the following.

87% of participants suggested a need for drug resistance testing among people for whom DTG-based first-line ART is failing, 94% suggested using it for in people for whom PI-based ART is failing, 100% suggested drug resistance testing for children for whom treatment is failing, and 93% supported using it for pregnant women for whom treatment is failing regardless of the type of regimen or line of treatment.

The Steering Group noted that several low- and middle-income countries currently perform drug resistance testing for clinical management of patients. WHO’s plan to develop a target product profile to support optimal drug resistance testing was discussed. 81% of the participants agreed on the need to develop a target product profile for a drug resistance test to support testing for individual patient management.

74% of participants favoured the development of a simplified drug resistance testing report for use by clinicians.

The use of drug resistance testing for people with low-level viraemia <1000 copies/mL was recommended by only 50%.

The 2019 WHO HIVResNet meeting participants also reviewed the activities the Secretariat and the working groups of the Global Action Plan on HIV drug resistance had planned for 2020. WHO HIVResNet meeting participants gave priority to the top four Secretariat activities as follows.

- Support the generation of HIV drug resistance evidence and its use to inform treatment guidelines.
- Develop and support HIV drug resistance surveillance and guidance methods.
- Support the sustainability of HIV drug resistance–related activities at both the WHO and country levels.
- Publish periodic reports on the HIV drug resistance status globally.
SESSION 2: LOOKING BACK: WHAT WAS DONE IN 2020

PRESENTATION 1: Review of the WHO Secretariat accomplishments in 2020

Presenter: Silvia Bertagnolio, WHO

- In 2020, WHO developed or updated the following guidance documents:
  - **WHO HIVResNet HIV drug resistance laboratory operational framework.** It provides:
    » an updated list of responsibilities of network laboratories;
    » consideration for incorporating next-generation sequencing methods;
    » assay validation recommendations; and
    » updates to the standard operating procedures for post-testing quality assurance of HIV sequences related to genotyping of the integrase gene or using next-generation sequencing.
  - **Manual for HIV drug resistance testing using dried blood spot specimens.** Updates include:
    » emphasis on best practices for dried blood spot preparation, storage, and shipment as well as selection of appropriate controls; and
    » procedure for dried blood spot genotyping using the ThermoFisher genotyping kit.
  - **HIV drug resistance surveillance in countries scaling up pre-exposure prophylaxis.** This technical guidance describes the methods and implementation considerations to monitor the prevalence of HIV drug resistance among pre-exposure prophylaxis (PrEP) users diagnosed with HIV through a cross-sectional survey. The outcomes of the survey will be used to inform the selection of maximally effective first-line combination ART for PrEP users who acquire HIV.
  - Alignment of HIV drug resistance early warning indicator definitions with **WHO’s 2020 strategic information guidelines**, including the addition of the following three new indicators:
    » total attrition from ART (replaces the indicator retention on ART after 12 months);
    » people living with HIV who have suppressed viral load (replaces the indicator viral load suppression 12 months after ART initiation); and
    » appropriate second viral load test.
  - WHO provided an update on the progress in technical support provided to countries in 2020:
    » review of national HIV drug resistance strategy (four countries);
    » implementation of HIV drug resistance surveys (20 countries);
    » development of national funding proposals or peer review of Global Fund to Fight AIDS, Tuberculosis and Malaria funding request (20 countries); and
    » development of technical briefs in collaboration with the Global Fund and the United States President’s Emergency Plan for AIDS Relief (PEPFAR) to guide countries in preparing funding applications for HIV drug resistance priority activities.
  - HIV treatment clinical guidance: HIV drug resistance data played an important role in the development of WHO’s 2021 updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation, and monitoring. Specifically, data that contributed to guidance development included:
    » switching to second-line ART after a single viral load of >1000 copies/mL for people receiving an NNRTI-based first-line regimen, with the rationale partly based on the high levels of NNRTI resistance ranging from 50% to 90% observed among people with viral non-suppression during a viral load test in WHO acquired drug resistance surveys and in peer-reviewed literature; and
    » switching to second-line ART after enhanced adherence counselling among people receiving NNRTI-based ART with persistent low-level viraemia of between 50 and 1000 copies/mL, with the rationale for this guideline partly being the emergence of drug-resistant virus among people with low-level viremia.
  - WHO supported 10 countries with the analysis of HIV drug resistance survey data and writing country-specific HIV drug resistance reports that included implications for ART programmes and public health policy.

- Progress has been made in implementing HIV drug resistance surveys, with 15 surveys currently ongoing in nine countries. Seventeen countries plan to conduct surveys in 2021–2022.
- Expansion of the WHO HIVResNet laboratory network: the network has expanded from 31 laboratories in 2019 to 34 laboratories in 2021. Eighteen laboratories
are designated as national laboratories, 10 as regional laboratories and six as specialized laboratories. Fifteen of the 34 laboratories have been approved to use dried blood spots as a specimen type for HIV drug resistance testing. At present, only eight laboratories have validated assays for genotyping the integrase region of the HIV-1 pol gene.

- HIV drug resistance advocacy: The Secretariat conducted activities to advocate for the importance of HIV drug resistance prevention and monitoring, including:
  - developing advocacy and educational materials and participating in the 2020 World Antimicrobial Awareness Week;
  - updating the WHO webpage on HIV drug resistance, including new infographics and maps;
  - contributing to the 2020 Global Antimicrobial Resistance and Use Surveillance System report; and
  - publishing a systematic review and meta-analysis on the impact of pretreatment drug resistance among people initiating NNRTI-based treatment in the *Journal of Infectious Diseases*.

---

**SESSION 3: LOOKING AHEAD: WHAT IS PLANNED FOR 2021**

**Presentation 1: Planned work plan for WHO in 2021**

**Presenter:** Silvia Bertagnolio, WHO

**Activities planned for 2021 include:**

- Development of normative guidance on HIV drug resistance
  - **Publication of the laboratory-based acquired HIV drug resistance survey method.** This new acquired HIV drug resistance survey method leverages remnant viral load specimens from adults and children and adolescents with viral load \( \geq 1000 \) copies/mL. This method is suitable for implementation in countries that have viral load testing coverage \( \geq 60\% \) and has several advantages over the traditional clinic-based methods in terms of logistics, costs and offering a large sample size to support assessment of acquired HIV drug resistance across various subpopulations, including people receiving DTG-based regimens.

- **Publication of updated clinic-based acquired HIV drug resistance survey method.** This updated clinic-based acquired HIV drug resistance method provides precise estimates for viral load suppression and HIV drug resistance outcomes for people receiving DTG-based regimens. Like the viral load laboratory-based acquired HIV drug resistance survey method, it is designed to be conducted among adults and among children and adolescents simultaneously.

- Updating tools to support the collection and analysis of early warning indicators of HIV drug resistance. Once updated, these tools will support the collection of data and analysis at the clinic level of quality-of-care indicators associated with and predictive of HIV drug resistance. The tools will be updated to align with WHO’s updated strategic information guidance and will include three new indicators: total attrition from ART, people living with HIV who have suppressed viral loads and appropriate second viral load test. In addition, all definitions will be aligned with WHO’s most recent strategic information guidance.

- **Publication of the updated HIV drug resistance strategy.** The updated strategy describes new and revised survey methods described previously.

- Planned systematic reviews and meta-analyses to assess the impact of NRTI resistance on DTG-based ART to inform guidance on TLD transition and ART sequencing.

- Capacity building and country support: support countries with the following:
  - developing and implementing national action plans to prevent, monitor and respond to HIV drug resistance;
  - strengthening HIV drug resistance surveillance in low- and middle-income countries by providing specialized technical assistance for implementing HIV drug resistance surveys;
• debriefing health ministries on national HIV drug resistance survey results, including policy implications; and

• training health ministry personnel on updated WHO-recommended HIV drug resistance survey methods and guidance.

• Dissemination of HIV drug resistance data

○ Publication of planned 2021 global HIV drug resistance report.


○ Disseminate HIV drug resistance data and guidance through global webinars and possibly in peer-reviewed articles.

• WHO HIVResNet laboratory network: support laboratories in the network by:

  ○ managing applications from laboratories seeking new designations, conducting audits of 5–10 laboratories during 2021–2023 and providing continual support on proficiency testing for all the network laboratories; and

  ○ supporting network laboratories with validation of integrase assays.

• HIV drug resistance database: update the HIV drug resistance database to further support countries with the quality assurance and report generation, with emphasis on the new acquired HIV drug resistance survey methods and automated report generation, with linkage of final quality-assured and approved results to WHO’s Country Intelligence Database.

• Support development of ARV drug policy guidelines and treatment strategies: WHO proposes to host a series of virtual joint meetings with WHO HIVResNet, the Clinical Adult working group for Drug Optimization (CADO) and the Paediatric working group for Drug Optimization (PADO) in September and October 2021. During the meetings, WHO HIVResNet is anticipated to provide guidance on treatment optimization strategies from a resistance standpoint.

• Future direction of individual-level genotyping for patient management: With some countries already performing individual-level HIV drug resistance testing and with a need for evidence-based guidance around individual HIV drug resistance testing for clinical management, WHO plans:

  ○ to conduct a survey with HIV programme managers in low- and middle-income countries to estimate the number of HIV drug resistance genotype tests being performed annually for clinical management and to determine the number of countries with national policies recommending using drug resistance testing for individual patient management;

  ○ to conduct a formal market assessment for potential use of drug resistance testing in collaboration with other stakeholders; and

  ○ to develop a draft target product profile for an HIV drug resistance test initially focusing on sub-Saharan Africa.

**Summary of overall remarks and discussions**

• As a follow-up to the 2019 WHO HIVResNet meeting, preliminary data from the NADIA trial show a minimal effect of NRTI resistance on viral suppression among people taking the fixed-dose combination of TDF, 3TC and DTG, thus supporting keeping TDF when switching to DTG-based second-line ART. Nevertheless, more data and additional analyses are required to effectively inform future ART guidance. Several studies including DRAFT, ARTIST and ACTG 5381 are designed to address this question and are ongoing.

• Regarding individual-level HIV drug resistance testing, it was noted that logistics challenges, especially the long turnaround-time experienced in countries using drug resistance testing for managing people receiving PI-based regimens, should be considered when determining an optimal drug resistance test for use in low- and middle-income countries.

**Presentation 2: 2021 HIV drug resistance report plan**

**Presenter:** Amalia Giron, WHO

**Summary of the planned 2021 HIV drug resistance report**

The planned 2021 HIV drug resistance report includes the following.

• Country-level survey data: summaries will include the results from surveys of pretreatment HIV drug resistance among infants younger than 18 months and among adults, acquired drug resistance surveys and surveys for HIV drug resistance among PrEP users diagnosed with HIV. Tentatively, the new report will include 63 surveys from 31 countries.

• Pooled analyses are planned and include:

  ○ Pretreatment HIV drug resistance among adults

  » Global and regional pretreatment HIV drug resistance prevalence estimates disaggregated by drug, drug class, sex, previous ARV drug exposure and CD4 cell count

  » Pretreatment HIV drug resistance prevalence by drug and HIV-1 subtype

  » Prevalence of integrase inhibitor drug resistance mutations among integrase inhibitor–naive adults, with results reported in aggregate and stratified by HIV-1 subtypes

  » Prevalence of NNRTI pretreatment HIV drug resistance, which may affect newer ARV drugs such as dapivirine, doravirine or rilpivirine.

  ○ Pretreatment HIV drug resistance among infants

  » Prevalence of pretreatment HIV drug resistance by WHO region, disaggregated by ARV drug class and by NRTI drug: ABC, ZDV, TDF + TAF and FTC + 3TC

  » The prevalence of pretreatment HIV drug resistance by ARV drug and HIV-1 subtype
» Assessing for associations between the observed prevalence of NRTI resistance among infants and the regimen for preventing mother-to-child transmission of HIV taken by mothers with the survey year used as a proxy for this regimen

» Comparing the prevalence of viral suppression and acquired HIV drug resistance in the following subgroups:
  - people receiving NNRTI-based ART versus people receiving DTG-based ART;
  - people receiving NNRTI-based first-line ART versus people receiving PI-based second-line ART;
  - children and adolescents versus adults;
  - people receiving ART for 12 months versus people receiving ART for 48 or more months;
  - people receiving LPV/r-based second-line ART versus people on ATV/r-based second-line ART;
  - NRTI resistance prevalence among people for whom first-line ART regimens are failing:
    - prevalence of TDF among people for whom ZDV-based first-line ART is failing; and
    - prevalence of ZDV resistance among people for whom TDF-based first-line ART is failing.

» HIV drug resistance among PrEP users diagnosed with HIV
  - Prevalence of NRTI resistance among PrEP users diagnosed with HIV: available WHO survey data will be supplemented by the results from the Global Evaluation of Microbicide Sensitivity (GEMS) study.

» Progress and gaps in implementing the Global Action Plan on HIV drug resistance

Summary of overall remarks and discussions

- Although the content of the planned 2021 HIV drug resistance report is comprehensive, some aspects necessitate cautious interpretation.

- Resistance to DTG-based regimens is probably underreported since it is being scaled up on an ongoing basis. The sampling depth and the limited time during which people are likely to have been on DTG-based regimens will probably be inadequate to yield precise population-level prevalence estimates of DTG resistance. Moreover, only a few laboratories in the network (8 of 34) have been designated for genotyping of the integrase gene. This limited capacity may reduce testing capacity or the quality of the genotypes if sequencing is to be performed exclusively in WHO-designated laboratories. Nevertheless, the need to understand DTG efficacy under routine programmatic settings is important, emphasizing the need to increase capacity within WHO HIVResNet to genotype the integrase region of HIV-1.

- Caution is required when predicting resistance to newer ARV drugs, especially those for which data on resistance are insufficient (dapivirine and doravirine).

- The potential for using data implemented following non-WHO methods was addressed. It was agreed that data from national surveys such as the Population-based HIV Impact Assessments could be used. In addition, future considerations to standardize ways to analyse aggregate HIV drug resistance genotypic data from individual-level drug resistance testing performed for clinical purposes in low- and middle-income countries were discussed. Notably, standardized approaches for analysing drug resistance test results obtained for routine clinical management may yield programmatically relevant data.

- The need to understand the contribution of PrEP use to the prevalence and patterns of drug resistance observed in pretreatment drug resistance surveys was highlighted as was the need for survey methods to obtain information on resistance from new ARV drugs being used for PrEP such as the long-acting injectable cabotegravir. The HPTN 083 and HPTN 084 trials showed that the efficacy of long-acting cabotegravir is superior to TDF + FTC for HIV PrEP and may likely be approved for routine use. The risk of emergence of resistance during breakthrough infections among people receiving long-acting cabotegravir was of concern because the mutations causing cabotegravir resistance are likely to cause resistance to DTG as well. Moreover, it was noted that there are still considerable challenges in timely detection of HIV infections among people who become infected while receiving long-acting cabotegravir, thus increasing the risk of resistance developing.

Presentation 3: Target product profiles for HIV drug resistance testing

Presenter: Neil Parkin, WHO consultant

Summary of key points

- Background
  - The need for a target product profile on HIVDR was established in previous discussions with WHO HIVResNet in 2019. A target product profile describes the targets for various test characteristics (often “minimal” and “optimal”) that should be met to fulfil a defined need.

- HIV drug resistance testing for individual patient management is being performed in many low- and middle-income countries; however, to date, WHO has not developed standards on using individual patient drug resistance testing. Countries have requested that WHO provide guidance for using drug resistance testing for routine patient management, thus underscoring the need for developing norms and standards around individual HIV drug resistance testing for patient management.

- Overview of current HIV drug resistance testing landscape: the most common drug resistance tests are sequencing-based assays.
  - Sequencing assay methods
    - Sanger-based sequencing
Most common technology
· Existing infrastructure and know-how
· Kits and (mostly) home-brew due to costs

Next-generation sequencing
· This sequencing technology is increasingly being adopted in some places

Available sequencing assays include the kit-based ThermoFisher/CDC HIV-1 genotyping kit (Sanger), the ABL DeepChek HIV kit (Sanger and NGS) the Vela Sentosa SQ HIV kit (NGS) and many laboratory-developed tests

Point mutation assays
· Test for limited number of specific mutations in a viral sequence associated with drug resistance
· Pre-existing knowledge of which drug resistance mutations to target is required. Mutations and mutation patterns associated with DTG resistance remain to be fully defined.
· Simpler, less expensive than full sequencing
· Potential for decentralized or point-of-care implementation
· Potential for reduced cost
· Available potential mutation assays include the Aldatu PANDAA qDX assay, the University of Washington OLA simple assays, Discidium and the Insilixa solid-phase melting curve analysis

Regulatory oversight differs based on the intended use of a drug resistance test: for example, for surveillance or for patient management. Oversight is also different if the assay used is a commercial kit or if it is an assay developed in the testing laboratory (in-house assay).

Surveillance
· In-house assays, developed by genotyping laboratories themselves, may require extensive validation
· Kit-based assays may either be used for research only or may require higher approvals such as ISO 134585

Patient management
· Assays developed in-house may require approvals from local clinical regulatory agencies
· Commercial kits require higher approvals such as CE-IVD, FDA 510 (k) and WHO prequalification

WHO has developed guidance for developing target product profiles, which involves a nine-step process: (1) determining the need for a target product profile; (2) developing a one-page document for planning clearance; (3) determining the audience outside WHO; (4) constituting a scientific target product profile development group; (5) producing version 0.1 of the target product profile; (6) posting version 0.1 for 28-day online public consultation; (7) discussing comments with the target product profile development group and producing version 1.0; (8) posting version 1.0 on the website; and (9) uploading metadata to the WHO directory.

Potential use cases for HIV drug resistance genotyping in low- and middle-income countries
· Use cases can broadly be grouped into two groups: for surveillance and for patient management. In addition, the type of patient (such as adult, child or pregnant woman) may need to be considered.
· For patient management, the key purposes are to inform the optimization of the ART regimen and to inform the need to switch from one regimen to another.
· Potential use cases for patient management include:
  » HIV drug resistance testing before ART initiation
    · To support selection of EFV-, DTG- or PI/r-based ART
      · Patients seroconverting while taking PrEP containing either reverse-transcriptase inhibitors or integrase strand transfer inhibitors
      · Patient re-entering care after treatment interruption
  » After failure of EFV-based ART
    · To inform whether to switch to a different regimen or continue EFV-based ART
  » After failure of DTG-based ART
    · To inform whether to switch to a different regimen or continue the current DTG-based regimen
    · To inform treatment optimization with respect to the choice of NRTIs used in combination with DTG
  » After PI/r-based ART fails to suppress viral loads
    · To inform whether to switch to a different regimen or to continue the current regimen
    · To inform treatment optimization with respect to the choice of NRTIs used in combination with PI/r
• Assay characteristics for consideration (draft list for discussion)
  » Sensitivity for amplification (minimum viral load needed for a reliable and reproducible result)
  » Sensitivity for detection of drug-resistance mutations present at low abundance (input copy number dependent)
  » Specimen type(s)
  » Region(s) covered (PR, RT, IN)
  » HIV-1 subtype coverage
  » Cost
  » Throughput (tests per week)
  » Reagent stability, storage requirements, etc.
  » Equipment requirements
  » Time to results
  » Operator training
  » Biosafety
  » Data capture and transfer

• Next steps
  □ Complete the market survey
  □ Determine the audience
  □ Form a target product profile working group or scientific development group
  □ Define and set priorities for use cases
  □ Develop draft target product profile(s)
  □ Circulate for comment (HIVResNet meeting Oct 2021)
  □ Adapt, consolidate, and form consensus

Summary of discussions
• Although target product profile development is clearly needed, WHO should consider the following.
  □ Defining and setting priorities for use cases for drug resistance testing are critical. For example, it was suggested that rather than having a target product profile that covers all possible use cases, it would be good to first set priorities for the use cases and develop a target product profile that is tailor-made for the priority use cases. However, it was noted that target product profile development must be forward-looking and anticipate scenarios likely to be realized in the near future.
  □ Implementation constraints for drug resistance tests include turnaround time, which needs to be minimal for results to be clinically actionable.
  □ Developing a target product profile for ARV drug-level tests, which can be used to screen people who need a drug resistance test.

• The need for better public health messaging around resistance was also highlighted, since the current messaging by clinicians creates unwarranted fear among patients. Although the challenge posed by resistance in improving treatment outcomes ought to be communicated to patients, it was suggested that this be done in a friendlier way, since patients are bound to be on treatment for life under the current available ART landscape.

Presentation 4: 2021 HIVResNet meeting plan

Presenter: Silvia Bertagnolio, WHO

• WHO has various working groups supporting different aspects of HIV care and treatment, including CADO, PADO and HIVResNet. Historically these groups have met separately; however, to promote cross-fertilization of ideas and synergy, meetings will be held jointly in 2021 with HIVResNet, providing relevant inputs to the CADO and PADO meetings as they pertain to HIV drug resistance. The joint meeting structure will:
  □ enhance bridging between groups;
  □ ensure alignment of guiding principles;
  □ leverage the expertise of each group to optimize overall outcomes; and
  □ lead to the development of a shared vision.

• WHO is planning five sessions of virtual meetings between 22 September and 12 October 2021 as follows:

□ Session 1: Separate WHO HIVResNet meeting
  » The WHO HIVResNet meeting will review the content of WHO’s 2021 HIV drug resistance report and focus on developing use cases for individual patient management.

□ Session 2: CADO and PADO meeting with WHO HIVResNet input
  » These sessions will focus on ARV drug sequencing approaches, new treatment strategies and ARV drugs currently in development. During this session, a representative or small group from WHO HIVResNet will report to CADO and PADO on possible drug resistance test use cases as defined by HIVResNet. The goal will be to receive additional input into these possible use cases from CADO and PADO.

□ Session 3: CADO and PADO separate dive-in on key topics with the support of WHO HIVResNet
  » CADO will focus topics such as dual ARV drug regimens, and PADO will focus on neonatal regimens as well as ARV drugs in development and future HIV treatment innovation strategies. HIVResNet will contribute to the PADO and CADO discussions by providing input and guidance from a drug resistance standpoint.
Session 4: separate WHO HIVResNet day to further define a target product profile for HIVDR tests

WHO HIVResNet will meet separately to further develop and discuss the target product profile for HIV drug resistance tests for low- and middle-income countries. Discussions will include reviewing the current landscape of drug resistance testing and reviewing the results from WHO’s survey assessing current HIV drug resistance testing for clinical care in low- and middle-income countries.

Session 5: joint session with WHO HIVResNet, PADO and CADO to combine the pieces

The goal of the final session will be to reach consensus on the specific PADO and CADO objectives and the draft outline target product profile for HIV drug resistance tests.

Summary of discussions

- The Steering Group made the following suggestions regarding the joint WHO HIVResNet and CADO and PADO sessions:
  - Include discussions on target product profile for ARV drug-level tests and leverage the expertise of pharmacologists from PADO and CADO. At the minimum, an expert can provide an overview of currently available ARV drug-level test, feasibility, and future directions. It was noted that various groups are working on rapid tests, including saliva- and urine-based point-of-care ARV drug tests, with promising results; these can be reviewed at the meeting by a pharmacological expert as part of the landscaping exercise.
  - Focusing on an algorithm for a drug resistance test that also includes an ARV drug level test coupled with clear priority use cases would provide needed guidance to countries on scenarios in which drug resistance testing for patient management would be most useful.

Presentation 5: Extension of the Global Action Plan on HIV drug resistance

Presenter: Silvia Bertagnolio, WHO

- The five-year Global Action Plan on HIV drug resistance developed in 2017 will end in 2021; however, HIV drug resistance emergence and transmission remains a global challenge, and the Global Action Plan therefore needs to be expanded. Ongoing opportunities addressed by the objectives of the current Global Action Plan on HIV drug resistance include the following.
  - Prevention and response
    - Several countries in eastern Europe and Asia continue to use NNRTI-based ART. Adoption of DTG-based ART is ongoing but at a slower than anticipated rate.
  - Surveillance and monitoring
    - As widespread uptake of DTG-based regimens is in its infancy, it remains necessary to expand the uptake of HIV drug resistance surveys, with specific focus on the HIV-1 integrase region to obtain sufficient data on DTG resistance among people taking ART with viral non-suppression to guide national and global ART policy-making.
    - At present, there has been low uptake of surveillance of HIV drug resistance surveys among people seroconverting with HIV while receiving PrEP.
  - Research and innovation
    - Many research questions are yet to be addressed (see priority list in the Global Action Plan).
    - Viral load testing coverage remains suboptimal in some countries.
  - Laboratory capacity
    - The capacity to genotype the HIV-1 integrase gene remains limited within WHO HIVResNet.
  - Governance and enabling mechanisms
    - All elements of the Global Action Plan on HIV drug resistance should be reflected in national HIV action plans, and elements of the Global Action Plan on HIV drug resistance should be implemented as a comprehensive package to prevent, monitor, and respond to the emergence and transmission of drug-resistant HIV. Most countries, however, have yet to adopt the Global Action Plan into their national HIV action plan.
    - There is a need to educate the broader community of stakeholders, including people living with HIV, clinicians, providers, health-care workers, and the broader community, about HIV drug resistance in simple lay terms to support prevention, monitoring and response to drug-resistant HIV.
  - Potential ways in which the Global Action Plan on HIV drug resistance 2017–2021 can be revised and extended in the future include:
    - developing and adopting a completely new Global Action Plan on HIV drug resistance after thoroughly reviewing the existing Global Action Plan and landscaping needs and stakeholder input.
    - identifying areas of the existing Global Action Plan on HIV drug resistance that require updating, with an eye toward integrating into WHO’s broader antimicrobial resistance framework. This could be accomplished by embedding the Global Action Plan on HIV drug resistance into the Global Action Plan on Antimicrobial Resistance.
Create a living document with regular revisions or updates that are made when necessary. In this way, the Global Action Plan on HIV drug resistance would not be time bound.

Summary of discussions

There was agreement that the Global Action Plan on HIV drug resistance remains highly relevant. Suggestions for its revision included incorporating it into other WHO strategies, in particular the global health sector strategies on HIV, viral hepatitis, and sexually transmitted infections for 2022–2030, which recently received approval from the World Health Assembly, and linking it to the Global Action Plan on Antimicrobial Resistance. Overall, the need for integrating the Global Action Plan on HIV drug resistance, either with the responses to diseases supported by the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes (hepatitis or sexually transmitted infections) or across departments with linkage to WHO’s Antimicrobial Resistance Action Plan is important for its sustainability. Regardless of how the Global Action Plan on HIV drug resistance is integrated, first steps include identifying elements of the current Global Action Plan that require revision and to perform landscaping to characterize the extent to which the current Global Action Plan has been implemented and whether it still meets the expected aspirations. Possible future directions of the Global Action Plan on HIV drug resistance may be discussed at the 2021 WHO HIVResNet meeting.
## ANNEX 1. MEETING AGENDA

### WHO HIVResNet Steering Group Meeting

**9 June 2021**

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Welcome and updates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17:30–17:45</strong></td>
<td>Welcome and meeting objectives</td>
</tr>
<tr>
<td></td>
<td>Introductions of new Steering Group members</td>
</tr>
<tr>
<td></td>
<td>Silvia Bertagnolio and Marco Vitoria</td>
</tr>
<tr>
<td><strong>17:45–18:00</strong></td>
<td>Summary of 2019 HIVResNet Think Tank</td>
</tr>
<tr>
<td></td>
<td>Silvia Bertagnolio</td>
</tr>
<tr>
<td><strong>18:00–18:30</strong></td>
<td>2020 highlights and plan for 2021</td>
</tr>
<tr>
<td></td>
<td>Silvia Bertagnolio</td>
</tr>
<tr>
<td><strong>18:30–18:40</strong></td>
<td>Quick Q&amp;A for clarifications</td>
</tr>
<tr>
<td></td>
<td>Chair: Irene Mukui</td>
</tr>
</tbody>
</table>

### Session 2

#### Zooming in on key areas

| **18:40–18:50**         | 2021 HIV drug resistance report plan                          |
|                         | Amalia Giron                                                  |
| **18:50–19:00**         | Discussion                                                    |
|                         | Chair: Irene Mukui                                             |
| **19:00–19:10**         | Target product profile for HIV drug resistance test           |
|                         | Neil Parkin                                                   |
| **19:10–19:20**         | Discussion                                                    |
|                         | Chair: John Mellors                                           |
| **19:20–19:30**         | 2021 HIVResNet meeting plan                                   |
|                         | Silvia Bertagnolio                                             |
| **19:30–19:40**         | Discussion                                                    |
|                         | Chair: John Mellors                                           |
|                         | Silvia Bertagnolio                                             |
| **19:50–20:10**         | Discussion                                                    |
|                         | Chair: Irene Mukui                                             |

### Session 3

#### Looking ahead

| **20:10–20:30**         | Questions for the Steering Group                              |
|                         | Chair: John Mellors                                           |
|                         | Wrap-up, announcements and closing remarks                     |
|                         | Silvia Bertagnolio                                             |
ANNEX 2. LIST OF PARTICIPANTS

John W. Mellors
University of Pittsburgh Medical Center
Pittsburgh, PA, USA

Irene Mukui
Drugs for Neglected Diseases Initiative (DNDI)
Nairobi, Kenya

Santiago Avila
Centre for Research in Infectious Diseases
Mexico City, Mexico

Andrew Phillips
University College London
London, United Kingdom

Roger Paredes
Irsi Caixa
Barcelona, Spain

Jonathan M. Schapiro
National Hemophilia Center
Sheba Medical Center
Ramat Gan, Israel

Gillian Hunt
National Institute of Communicable Diseases
Johannesburg, South Africa

Mohamed Chakroun
Fattouma Bourguiba Teaching Hospital
Monastir, Tunisia

Alash’le Abimiku
Institute of Human Virology
University of Maryland School of Medicine
Baltimore, MD, USA

Martin Choo
Asia Pacific Council of AIDS Service Organizations
Bangkok, Thailand

Alexandra Calmy
Geneva University Hospital
Geneva, Switzerland

Yunus Moosa
University of KwaZulu-Natal
Durban, South Africa

Paul Sandstrom
National HIV and Retrovirology Laboratories
Public Health Agency of Canada
Ottawa, ON, Canada

Jacqueline Wambui
African Community Advisory Board Treatment Access Partnership
Lusaka, Zambia

Susan Eshleman
HIV Prevention Trials Network (HPTN) Laboratory Center
Baltimore, MD, USA

Eleanor Namusoke-Magongo
Ministry of Health
AIDS Control Program
Kampala, Uganda

Rossana A. Ditangco
AIDS Research Group
Department of Health Research
Institute for Tropical Medicine
Manila, Philippines

Natalia N. Ladnaia
AIDS Prevention and Control Research Unit
Central Research Institute of Epidemiology
Federal Service on Customers’ Rights Protection and Human Well-Being Surveillance
Moscow, Russian Federation

WHO

Headquarters
Silvia Bertagnolio
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Marco Vitoria
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Meg Doherty
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Consultants
Amalia Giron
Consultant, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Seth Inzaule
Consultant, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Michael Jordan
Tufts University School of Medicine
Boston, MA, USA
Consultant, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

Neil Parkin
Data First Consulting
Consultant, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
Regional and country offices

Shakiwa Fausta Mosha
WHO Regional Office for Africa

Fatim Cham Jallow
WHO Regional Office for Africa

Bridget Mugisa Akora
WHO Regional Office for the Eastern Mediterranean

Nicole Simone Seguy
WHO Regional Office for Europe

Elena Vovc
WHO Regional Office for Europe

Jones Sandra
PAHO/WHO – Subregional Program Coordination, Caribbean