CONTENTS

Acknowledgements ........................................................................... iv
Background .................................................................................... iv

Session 1: HIVResNet update .......................................................... 1
Presentation 1: New WHO operating model and programme of work: opportunities and risks
for HIV drug resistance .................................................................. 1
Presentation 2: HIV drug resistance @ WHO: what’s on the agenda? ...................................................... 2

Session 2: Technical sessions on NRTI backbone optimization .... 10
Discussant 1: Abacavir (ABC)/XTC (3TC or FTC) resistance among infants younger than 18 months
diagnosed with HIV: results from a WHO global report ................. 10
Discussant 2 and 3: Clinical implications of ABC resistance among infants starting first-line antiretroviral therapy ...... 11
Discussant 4: NRTI resistance: implications for antiretroviral therapy for children in Uganda and Cameroon ...... 12
Discussant 5: TDF resistance among adults for whom EFV-based first-line antiretroviral therapy is failing .......... 13
Discussant 6: Optimal NRTI backbone for people for whom TDF + XTC + EFV is failing and switching to
DTG-based antiretroviral therapy .................................................. 14
Discussant 7: Optimal NRTI backbone for individuals for whom TLD is failing and switching to PIs ............... 15

Session 3: Future scoping: innovations to improve HIV drug resistance surveillance and ability to
provide better quality and person-centred HIV care? ................. 16
Presentation 1: Results from a survey on the use of HIV drug resistance testing in Africa ......................... 16
Presentation 2: HIV drug resistance testing options: technology landscapes, costs, gaps and opportunities .... 17
Presentation 3: Cost–effectiveness of HIV drug resistance testing among people for whom first- and
second-line antiretroviral therapy has failed .................................. 19
Presentation 4: Challenges with resistance testing in DBS and plasma specimens from people with
low-level viraemia ......................................................................... 20

Session 4: Looking forward – priorities for WHO HIVResNet and partners ............. 22
Annex 1. Additional results from participant questionnaire ............... 26
Annex 2. Meeting agenda ................................................................. 30
Annex 3. List of participants ............................................................ 32
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BACKGROUND

The WHO HIV drug resistance network (WHO HIVResNet) is a large 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. Established in 2004 by a partnership between WHO and the International AIDS Society, the WHO HIVResNet supports activities to monitor and control the emergence of HIV drug resistance, optimize the use of HIV drug resistance testing, monitor the quality of antiretroviral therapy delivery for the purpose of preventing HIV drug resistance and support policies related to optimal first-, second- and subsequent-line antiretroviral therapy selection.

HIVResNet and its five working groups support the Global Action Plan on HIV drug resistance. The goal of the Global Action Plan is to articulate synergistic actions required to prevent HIV drug resistance from undermining global targets on health and HIV and to provide the most effective treatment to all people living with HIV. The Global Action Plan has five strategic objectives:

• prevention and response;
• monitoring and surveillance;
• research and innovation;
• laboratory capacity; and
• governance and enabling mechanisms.

This meeting took place on 19 October 2019 in Johannesburg, South Africa, immediately after the XXVIII International Workshop on HIV Drug Resistance and Treatment Strategies (http://www.hivresistance2019.co.za), thus capitalizing on the presence of HIVResNet members, key opinion leaders and other WHO advisers. Annexes 1–3 provide additional results from participant questionnaires, the meeting agenda and the list of invited participants.

The meeting began with a review of recent changes in WHO’s operational model and updates from the chairs of the five HIV drug resistance Global Action Plan working groups. This overview was followed by three thematically divided technical sessions. The meeting concluded with a think tank session in which priorities for WHO to focus on over the next five years were discussed.
Presentation 1: New WHO operating model and programme of work: opportunities and risks for HIV drug resistance

Presenter: Meg Doherty, WHO

Summary of key points

- The Thirteenth General Programme of Work is WHO’s new five-year strategy. It is designed to focus WHO’s work on impact at the country level. Specifically, the Thirteenth General Programme of Work aligns all work with the Sustainable Development Goals to improve the health of all people in all countries and establishes a clear mission to promote health, keep the world safe and serve vulnerable people.

- The Thirteenth General Programme of Work outlines three strategic priorities attached to ambitious goals:
  - Advancing universal health coverage
    - Delivery of essential health services
    - Financial protection
    - Access to essential health products
  - Addressing health emergencies
    - Prepare
    - Prevent
    - Detect and respond
  - Promoting healthier populations
    - Determinants of health
    - Risk factors to health
    - Channels to address health determinants and risks

- The new WHO goal is the Triple Billion targets: 1 billion more people to benefit from universal health coverage, 1 billion more people better protected from health emergencies and 1 billion more people enjoying better health and well-being. These ambitious targets must be met over the next five years to be on track for delivering the Sustainable Development Goal targets by 2030.

- To achieve the goals, WHO’s work will span a spectrum from supporting mature health systems with policy dialogue to strengthen systems for the future to support service delivery and filling gaps in emergencies in more fragile health systems. WHO will focus global public goods on impact, and work streams will be tailored to provide what countries need to significantly improve the health of their people.

- There are three key strategic shifts in the way WHO will work. They can be summarized by “working smarter to increase country level impact”. All WHO staff members will be empowered to connect their work to the three strategic priorities and articulate how their work feeds into, and is measured by, achieving the Triple Billion targets. The three key strategic priorities are:
  - Step up leadership
  - Drive impact in every country
  - Focus global public goods on impact

- A key function of WHO is developing normative guidelines. In 2019, WHO published updated HIV care and treatment guidelines.

  - Important knowledge gaps exist:
    - Gaps in knowledge regarding the best third-line and optimal antiretroviral drug sequencing in the age of dolutegravir (DTG) recommended for first- and second-line treatment
    - Gaps in knowledge regarding the recycling of tenofovir disoproxil fumarate (TDF) in TDF + lamivudine (3TC) + DTG (TLD) after TDF + 3TC + efavirenz (TLE) use and in second-line treatment. This knowledge gap can be informed by research and implementation data focused on HIV drug resistance.

- Future directions of WHO work

  - Impact at the country level is paramount with priorities and global goods focused on country needs
  - The Department of global HIV, Hepatitis, and STIs Programmes offers opportunities for:
    - Integrating communicable and noncommunicable diseases
    - Sharing resources and laboratory networks
    - Working across the three levels of WHO (country, region and headquarters)
  - Overall disease-specific funding is reduced, including for HIV activities

- The 2019 WHO HIVResNet Meeting focuses on helping WHO to give priority to activities that drive impact at the country level and consider opportunities for fundraising.
Objective of the meeting:
Identification of high-priority activities for the HIV drug resistance work stream over the next five years is a key outcome of this meeting. Priorities should support the three strategic priorities of the WHO thirteenth General Programme of Work listed above and have high impact at the country level.

Presentation 2: HIV drug resistance @WHO: what’s on the agenda?
Presenter: Silvia Bertagnolio, WHO

Summary of key points

- The five-year Global Action Plan on HIV drug resistance raises awareness of the need to prevent, monitor and respond to HIV drug resistance and provides a framework of action for all stakeholders to ensure that HIV drug resistance does not threaten the achievement of the global targets to end AIDS as a public health threat.

- Successful implementation of the Global Action Plan is a shared responsibility of countries and global and country stakeholders, including non-state partners, people living with HIV, community organizations, researchers and bilateral and multilateral donors. Each stakeholder has a role to play and actionable responsibilities.

- To support implementation of the Global Action Plan, WHO has created five working groups around each of the five strategic objectives of the Global Action Plan:
  1. Prevention and response
  2. Monitoring and surveillance
  3. Research and innovation
  4. Laboratory capacity
  5. Governance and enabling mechanisms, including awareness and advocacy

- Group 1 leverages the existing WHO working group on quality of care and integrated HIV drug resistance prevention in the broader WHO quality of care agenda.

- Groups 2 and 4 directly support WHO’s normative guidance development as well as data quality assurance and the WHO HIVResNet laboratory coordination.

- Groups 3 and 5 support the Global Action Plan in areas where WHO has no or limited capacity.

- HIV drug resistance surveillance is a core of WHO’s agenda. The objective of surveillance is to monitor levels and trends of HIV drug resistance over time with the purpose of informing national and global treatment policies.

- WHO provides the following support to countries implementing surveys:
  - Develop guidance on HIV drug resistance surveillance
  - Support country capacity in adapting and implementing generic surveillance guidance into operational country protocols
  - Build the capacity of countries in data management and quality assurance of epidemiological and sequence data (WHO HIV drug resistance database)
  - Support countries in data interpretation, use of data in the country context and dissemination within stakeholders
  - Global reporting (the high-level findings of WHO’s HIV drug resistance report 2019 were summarized). The data reported included the results of surveys of pretreatment HIV drug resistance among adults initiating antiretroviral therapy, surveys of acquired HIV drug resistance among adults with unsuppressed viral loads, pretreatment HIV drug resistance among infants newly diagnosed with HIV and the monitoring of quality of care indicators, especially important in optimizing population-level viral load suppression and HIV drug resistance prevention, since countries are globally shifting to using DTG in first-line antiretroviral therapy.

- WHO does not fund surveys: most are supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (funded 24 countries in 2015 and 34 countries in 2018–2020) and some by PEPFAR and by national governments.

- Current WHO HIVResNet laboratory capacity was reviewed. As of October 2019, 30 laboratories were designated for HIV drug resistance testing for surveillance purposes. WHO manages the following laboratory-related activities:
  - Laboratory normative guidance for drug resistance testing (operational framework)
    - Describes how WHO strives for high quality, standardized drug resistance test results
    - Specimen-handling recommendations
    - Sequence quality assurance procedures
    - Recommendations for validating integrase in-house genotyping (sensitivity and reproducibility)
  - Support the implementation of recommended quality control approaches for sequence data
    - Sequence quality assurance tools and training (webinars)
    - Quality control of web tool design and testing to include integrase
  - Periodic review of network laboratory performance
    - To ensure continued compliance with HIVResNet designation criteria

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  - Support the implementation of recommended quality control approaches for sequence data
    - Sequence quality assurance tools and training (webinars)
    - Quality control of web tool design and testing to include integrase
  - Periodic review of network laboratory performance
    - To ensure continued compliance with HIVResNet designation criteria
Align HIV drug resistance laboratory capacity with survey activities in countries (such as managing the process of designating new laboratories)
  » Identify national HIV drug resistance laboratory needs; support and manage new laboratory designation where needed
  » Respond to new applications
Perform quality assurance of sequences and interpret HIV drug resistance survey data
  » Standardized evaluation to enable between-country comparisons
  » Consistent and centralized data management

The WHO HIVResNet global research agenda as defined in the 2017 WHO HIVResNet meeting report was reviewed. Progress in all tier 1 and tier 2 research agenda items was being made except for two items. Research progress can be viewed in the 2018 Global Action Plan progress report.

Over the past year, there has been increased country ownership of HIV drug resistance work; 46% of WHO HIV focus countries have included HIV drug resistance in national HIV plans, and the Global Fund has increased its support from 24 countries in 2015 to 34 countries during 2018–2020. PEPFAR also is support 12 countries. WHO and partners provide continual technical support, and Working Group 5 of the Global Action Plan planned increased community engagement in 2020.

WHO is inviting stakeholders in the private and industry sector to provide unrestricted funding to support the implementation of the GAP; this can be achieved through a pool funding mechanism aimed to increase resources and opportunities to support WHO key activities on HIVDR.

Summary of discussion

WHO’s five-year Global Action Plan on HIV drug resistance is centred around five main themes, each of which has a functional working group to support deliverables related to each of these work streams. The Global Fund has increased its funding of HIV drug resistance surveys in countries, and the HIV drug resistance laboratory network has expanded to include 30 designated laboratories, 18 of which are designated for genotyping of the integrase region of HIV-1. Future funding for HIV drug resistance work at WHO was discussed: the private sector is invited to provide financial contributions to the newly established WHO pool fund to implement and monitor the Global Action Plan for HIV drug resistance. Funds will be pooled and used according to the Global Action Plan monitoring needs and priorities (including monitoring HIV drug resistance emergence in countries, report writing and dissemination). WHO will reserve the right to refuse any contribution that does not meet the priorities or requirements for the Global Action Plan activities. Contributions will not be directly used to develop WHO guidelines.

Presentations 3–8: WHO Global Action Plan on HIV drug resistance — working group presentations

Working Group 1: Prevention and response

**Presenter:** Charles Holmes, Georgetown University, Co-Chair, Working Group 1

**Summary of key points:**

- **Working Group 1 – objectives**
  - To regularly convene experts in HIV quality, HIV drug resistance prevention, donors, multilateral partners, civil society and implementers to discuss priorities, share best practices and generate new products to focus country and global attention on preventing HIV drug resistance.

- **Work plan and focus areas**
  - Creation of a resource library of HIV-specific quality of care operational tools, guidance documents and country experiences to be hosted on an online platform (possibly the WHO Global Learning Laboratory for Quality Universal Health Coverage) to support human resource and institutional capacity-building
  - Dissemination of best practices around quality of HIV care approaches through journal supplements and sessions at meetings and conferences
  - Identify strategies to improve the suboptimal quality of care to prevent and respond to HIV drug resistance, for use in national and global decision-making
  - Written contribution to the WHO Global Action Plan progress report

- **Accomplishments in 2019**
  - Monthly working group calls (led by WHO and working group chair) – expert presentations, discussions to shape group output, sharing of partner tools and updates and updates on donor quality strategies
  - Development of the WHO technical brief on quality of HIV services, generating buy-in from broad stakeholder groups and launch at the 10th International AIDS Society Conference on HIV Science in 2019 in Mexico City.
  - Initial development of the WHO Global Learning Laboratory module for HIV quality of care, including stakeholder consultations
10th International AIDS Society Conference on HIV Science: quality of care satellite session: addressing the quality gap within HIV programmes: improving clinical outcomes and preventing HIV drug resistance

- Planned activities 2020–2021 (Table 1)

**Working Group 2 – Monitoring and surveillance**

**Presenter:** Michael Jordan, Levy Center for Integrated Management of Antimicrobial Resistance, Tufts University, Co-Chair, Working Group 2

**Summary of key points**

- **Working Group 2 – objectives**
  - Support WHO in developing normative guidance on HIV drug resistance surveillance by reviewing, commenting on and discussing draft guidance documents

**Table 1. Planned activities 2020–2021, Working Group 1**

<table>
<thead>
<tr>
<th>Activities and products</th>
<th>Purpose</th>
<th>Expected country impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Global Learning Laboratory for Quality Universal Health Coverage</td>
<td>Provide a platform for WHO Member States to share national approaches to improving the quality of HIV services, to disseminate global best practices through webinars and documents and stimulate new collaborations</td>
<td>Improved HIV programme retention, adherence and suppression of viral loads</td>
</tr>
<tr>
<td>Advocate with countries for use of WHO Global Learning Laboratory</td>
<td>Improve capacity at the country level to adopt and implement national quality frameworks, strategies and programmes</td>
<td>Improved HIV programme retention, adherence and suppression of viral loads</td>
</tr>
<tr>
<td>Review of national progress on Global AIDS Monitoring HIV services quality indicators and dialogue with select countries</td>
<td>To stimulate greater attention to HIV quality indicators and promote country-level actions to improve recommendations for improvements of quality of care in countries</td>
<td>Improved HIV programme retention, adherence and suppression of viral loads</td>
</tr>
<tr>
<td>WHO quality of HIV services pre-meeting at the Institute for Healthcare Improvement Quality forum in Johannesburg, 6–10 May 2019</td>
<td>To promote cross-learning between the HIV quality agenda and broader health services quality efforts and methods</td>
<td>Increased awareness of the links between HIV and broader health services</td>
</tr>
<tr>
<td>Discussion and commentary regarding patient and provider perspectives on the quality of care</td>
<td>Promote the measurement of patient and provider experience to improve person-centredness and HIV programme outcomes</td>
<td>More responsive health system and programme impact</td>
</tr>
<tr>
<td>Quality scoping call for 2021 WHO guidelines and contribute to the antiretroviral drug guidelines chapter on service delivery and quality section</td>
<td>Update WHO consolidated antiretroviral drug guidelines</td>
<td>Increased uptake of latest guidance for quality HIV programmes</td>
</tr>
</tbody>
</table>

- Support WHO in producing HIV drug resistance surveillance reports by reviewing and commenting on draft versions
- Support modelling on HIV drug resistance as required
- Support WHO and/or countries in analysing HIV drug resistance survey data to ensure high-quality HIV drug resistance survey results to guide antiretroviral therapy programme and public health responses at the national and global levels

- Work plan and focus areas
- Working Group 2 has consultative terms of reference and supports WHO in developing and reviewing normative guidance on surveillance

- Accomplishments in 2019
Support the interpretation of Global AIDS Monitoring and quality of care indicators relevant to the HIV drug resistance data presented in WHO’s 2019 HIV drug resistance report

Quality of care indicators relevant for HIV drug resistance – revised and harmonized definitions (Working Group 2 plus an additional 20 experts and country programme representatives)

Recommendations made on updating existing HIV drug resistance survey methods

New approaches for acquired drug resistance survey: laboratory-based survey method leveraging remnant viral load specimens

» Facility-based survey method for surveillance of HIV drug resistance in populations taking pre-exposure prophylaxis (PrEP)

Modelling to support WHO guidelines on first-line antiretroviral therapy regimen

» Alternative regimens in first line if DTG not available in settings with high levels of non-nucleoside reverse-transcriptase inhibitor (NNRTI) pretreatment HIV drug resistance

» Impact of neural tube defects and DTG transition in the context of HIV drug resistance background levels

Table 2. Planned activities 2020–2021, Working Group 2

<table>
<thead>
<tr>
<th>Activities and products</th>
<th>Purpose</th>
<th>Expected country impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated HIV drug resistance strategy</td>
<td>Reflect updated survey guidance in the DTG era</td>
<td>Simplified and updated HIV drug resistance surveillance strategy</td>
</tr>
</tbody>
</table>
| Update HIV drug resistance survey methods:  
  • Acquired drug resistance survey: laboratory-based (remnant specimen)  
  • Surveys of pretreatment HIV drug resistance | Simplified laboratory-based acquired drug resistance survey method leveraging remnant viral load specimens from people with unsuppressed viral loads  
  Pretreatment drug resistance: increased precision in women in countries not moving to DTG | Facilitate the implementation of acquired drug resistance survey; decreased costs and quicker results, actionable results |
| Operational guidance to support surveillance implementation and toolkit | Support the implementation of HIV drug resistance surveys | Facilitate survey planning and implementation |
| WHO HIV drug resistance database | Support data management and capacity strengthening for data and sequence quality assurance and interpretation | High-quality data for country reports and country ownership |
| Updated definitions and targets for quality of care indicators relevant to HIV drug resistance | Support integration with global indicators; updated targets reflecting new definitions | Support clinic-level quality initiatives |
| National and global targets to monitor Global Action Plan implementation | Support countries, regions and WHO headquarters in monitoring the implementation of the Global Action Plan on HIV drug resistance | Support the implementation of the Global Action Plan on HIV drug resistance – defined indicators and country-targets for Global Action Plan implementation |
| Country-adapted protocols and data analysis aligned with WHO concept notes | Protocols aligned with WHO guidance (laboratory and epidemiological data); quality-assured data and analyses for country reports | Country-adapted protocol (data sets) designed to maximize generate high-quality data for decision-makers |
Working Group 3 – Research and innovation

Presenter: Roger Paredes, IrsiCaixa AIDS Research Institute, Co-Chair, Working Group 3

Summary of key points

- Working Group 3 – objectives
  - Encourage and monitor progress on relevant and innovative research, leading to interventions that will have the greatest public health impact on minimizing HIV drug resistance
  - Fill and monitor knowledge gaps on HIV drug resistance for newer antiretroviral drug drugs and the impact of service delivery interventions to increase viral load suppression and contain HIV drug resistance

- Work plan and focus areas
  - Review and update WHO on progress on relevant research questions listed in the Global Action Plan or new questions as they arise during the period of the Global Action Plan; globally defined tier 1 and tier 2 HIV drug resistance–related research priorities as defined in the Global Action Plan
  - Collate and interpret evidence related to specific questions of public health importance: WHO surveillance drug resistance mutations list, clinical relevance of low-abundance drug-resistant variants and impact of HIV drug resistance on treatment outcomes
  - Written contribution to the WHO Global Action Plan progress report

- Accomplishments in 2019
  - Publication of integrase inhibitor surveillance transmitted drug resistance mutations list

- Planned activities 2020–2021 (Table 3)
  - Winnipeg consensus for next-generation sequencing pipeline analysis quality standards
  - Consensus around Sanger 20% threshold as gold-standard sensitivity cut-off for drug resistance mutation detection
    - Winnipeg consensus demonstrating increasing “noise” at next-generation sequencing reporting threshold below 20%
  - Point-of-care advances
    - Oligonucleotide ligation assay (OLA)-Simple (both RNA and DNA)
      - Validated in 228 multi-clade patient specimens (dried blood spot (DBS), peripheral blood mononuclear cell (PBMC), plasma) compared with Sanger 99.6% and 98% sensitivity
      - Reagent cost <$US 20, including extraction turnaround time less than four hours with less than 10 minutes hands-on time
      - Demonstration projects planned in Kenya, Mexico, South Africa and Zimbabwe
    - Viral load (V)-OLA-Simple
      - Streamlined viral load and drug resistance testing using single RNA extraction and amplification. End-point viral load assay providing visual florescence signals that can be observed by eyes under blue LED light, thus eliminating the need for real-time quantitative polymerase chain reaction (qPCR) machine
  - Documenting the proportion of PrEP users newly infected in New York City showing drug resistance
    - 30% of PrEP users acquiring HIV show M184V versus 2% among never-PREP users

Table 3. Planned activities 2020–2021, Working Group 3

<table>
<thead>
<tr>
<th>Activities and products</th>
<th>Purpose</th>
<th>Expected country impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVResNet communication platform (Slack)</td>
<td>Foster communication and exchange of research protocols, manuscripts and grant opportunities</td>
<td>Enhanced integration of researchers in countries with the global research community</td>
</tr>
<tr>
<td>Teleconference every six months</td>
<td>Update information</td>
<td>As above</td>
</tr>
<tr>
<td>Yearly report</td>
<td>Update information</td>
<td>As above</td>
</tr>
</tbody>
</table>
Working Group 4 – Laboratory capacity

Presenter: Gillian Hunt, National Institutes of Communicable Diseases, South Africa, Co-Chair, Working Group 4

Summary of key points

- Working Group 4 – objectives
  - Support the production of laboratory-related technical guidance documents
  - Map progress in developing innovative HIV drug resistance diagnostics
  - Support countries in assessing and strengthening genotyping laboratories, capacity-building, internal and external quality assurance and quality control procedures, including proficiency panels and post-testing sequence analysis and quality control and specific laboratory procedures
  - Review of applications from laboratories seeking WHO designation
  - Work with candidate or designated laboratories to strengthen one or more aspects of their standard operating procedures to support WHO quality assurance and quality control processes
  - Develop training materials, provide training, or perform special studies and duties such as investigating the use of dried blood spots in HIV drug resistance surveillance and monitoring and producing dried blood spot proficiency panels
  - Review of applications from laboratories seeking WHO designation

- Work plan and focus areas
  - Operational framework updates
  - Webinars held for network laboratories (once for each two groups of regions according to time zones)
  - New version of quality control tool developed with capacity for integrase sequences
  - DBS amplification rates analysed and assessed
  - Supporting virology quality assurance contract for external quality assurance move to Duke University
  - Three Working Group 4 teleconferences held in June
  - Working Group 4 meeting in Johannesburg – International HIV Drug Resistance Workshop
  - External quality assurance for next-generation sequencing HIV drug resistance genotyping symposium (led by Public Health agency of Canada laboratory in Winnipeg, Canada)

- Accomplishments in 2019
  - Operational framework updates
  - Webinars held for network laboratories (once for each two groups of regions according to time zones)
  - New version of quality control tool developed with capacity for integrase sequences
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  - Supporting virology quality assurance contract for external quality assurance move to Duke University
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- Planned activities 2020–2021 (Table 4)
Working Group 5 – Governance and enabling mechanisms

**Presenter:** Tobias Rinke de Wit, AIGHD, Amsterdam, Netherlands, Co-Chair, Working Group 5

**Summary of key points**

- **Working Group 5 – objectives**
  - Ensure that country ownership and enabling mechanisms (advocacy, awareness, coordinated action and sustainable funding) are in place to support action on HIV drug resistance
  - Advocacy and communication: advocacy and awareness of the burden and impact of HIV drug resistance among policy-makers, health-care workers, communities, patients and civil societies is key but generally insufficient
  - Sustainable funding: global partners and national governments should commit to funding HIV drug resistance surveillance activities in countries, strengthening health-care systems and building laboratory capacity to achieve universal viral load testing coverage and develop HIV drug resistance capacity
  - Country ownership (coordination, integration and alignment): governance and ownership of HIV drug resistance prevention, monitoring and response is a critical element of a well-functioning antiretroviral therapy programme

- **Work plan and focus areas**
  - Awareness, education and demand creation as and where needed
  - Frame HIV drug resistance in broader context: Sustainable Development Goals, universal health coverage, quality of care and link to other topical issues (DTG, PrEP, sexual and reproductive health and rights etc.)
  - Simplify language, increase visuals for different audiences with clear messaging to communities of people living with HIV and service providers
  - Building evidence around key issues
  - “What’s out there”: comprehensive landscaping analysis of the causes of HIV drug resistance, identification of gaps and main national and global issues
  - Develop community indicators to monitor quality of HIV care to minimize HIV drug resistance to be incorporated in the Global Action Plan mid-term report
  - Test community indicators and triangulate with facility indicators (such as early warning indicators)
Advocacy
- Formulate advocacy plan and identify champions

Fundraising
- Accomplishments in 2019

Landscaping
- Leuven University: identifying and visualizing HIV drug resistance key elements
- Landscaping of HIV drug resistance as a wicked problem
  - To create a visual overview of all known elements influencing HIV drug resistance and their interactions with each other, from three perspectives: local influencers, international experts and people living with HIV:
    - To better understand the dynamics of HIV drug resistance in order to plan targeted interventions
    - Understand the perception of factors influencing HIV drug resistance of international experts, local influencers and people living with HIV to identify possible gaps or overlaps between science and practice
    - Identify which data need to be collected for quantitative analysis
    - Identify possible gaps in the literature
  - As a basis for simplifying language, blogs and short video productions

Positioning HIV drug resistance as a quality indicator
- Joep Lange Institute workshops with the International Treatment Preparedness Coalition to collect evidence and to build a framework for community-based mobile HIV treatment and care quality indicators
- Formulation of a proposal to evaluate these community indicators

Fund raising
- Submit proposal for potential funding through the Amsterdam dinner 2020 event

Advocacy
- HIV drug resistance symposium in Amsterdam on 11 November 2019

Challenges
- Increased civil society representation in all working groups for more efficient cross-sharing
- Time and financial constraints: difficult to get professionals to participate, excessive reliance on volunteering
- Limited progress in organizing country ownership and coordinated actions

Planned activities 2020–2021 (Table 5)

Table 5. Planned activities 2020–2021, Working Group 5

<table>
<thead>
<tr>
<th>Activities and products</th>
<th>Purpose</th>
<th>Expected country impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landscape of HIV drug resistance, publications, simplified text, videos in coordination with WHO World AIDS Day</td>
<td>Identify important root causes of HIV drug resistance, select priority areas for simple language-supported awareness-raising</td>
<td>Identification of priority areas of local HIV drug resistance interventions and increased awareness among stakeholders</td>
</tr>
<tr>
<td>Action plan for implementing and testing community-quality monitoring through (mobile-digital) indicators</td>
<td>Raise awareness among target populations: patients, doctors, communities, nurses, policy-makers and payers</td>
<td>Increased HIV drug resistance awareness among pertinent target populations</td>
</tr>
<tr>
<td>Menu of HIVResNet activities for Amsterdam dinner 2020–2021</td>
<td>Fundraising for HIVResNet activities</td>
<td>More funds available for HIVResNet to provide guidance to countries</td>
</tr>
<tr>
<td>Generic texts to engage civil society to advocate within their health ministry for including in Global Fund applications</td>
<td>Brief and engage civil society</td>
<td>More funds available in countries for addressing HIV drug resistance</td>
</tr>
<tr>
<td>Stimulate HIV drug resistance advocacy events</td>
<td>Raise awareness and advocacy with key decision-makers and funders</td>
<td>More awareness in countries for addressing HIV drug resistance</td>
</tr>
</tbody>
</table>
SESSION 2: TECHNICAL SESSIONS ON NRTI BACKBONE OPTIMIZATION

Discussant 1: Abacavir (ABC)/XTC (3TC or FTC) resistance among infants younger than 18 months diagnosed with HIV: results from a WHO global report

Presenter: Seth Inzaule, WHO

Summary of key points

- Introduction
  - Wide-scale access to services to prevent the mother-to-child transmission of HIV has resulted in a significant decline in vertical HIV transmission
    - Globally in 2019, the coverage of services to prevent the mother-to-child transmission of HIV was estimated to be 82%
  - The few children who become infected are at high risk of developing HIV drug resistance
  - Studies show a rise in pretreatment HIV drug resistance, including nucleoside reverse-transcriptase inhibitor (NRTI) resistance with wide-scale access to maternal lifelong antiretroviral therapy

- WHO-recommended first- and second-line antiretroviral therapy (~53% antiretroviral therapy coverage among children in low- and middle-income countries as of 2019)
  - First-line treatment recommendations
    - <1 month: raltegravir (RAL) + zidovudine (AZT) + lamivudine (3TC)
    - <20 kg: lopinavir/ritonavir (LPV/r) + abacavir (ABC) + 3TC
    - >20 kg: dolutegravir (DTG) + ABC + 3TC
  - Second-line treatment recommendations
    - After DTG first line: LPV/r + two NRTI drugs
    - After protease inhibitor (PI) in first-line: DTG + two NRTI drugs
- WHO’s nationally representative survey method for HIV drug resistance among infants younger than 18 months aims to estimate the prevalence of NRTI pretreatment drug resistance among infants newly diagnosed with HIV
  - Nine surveys (2684 infants) were implemented during 2012–2018 in the following countries (Fig.1.): Cameroon, Eswatini, Malawi, Mozambique, Nigeria, South Africa, Togo, Uganda and Zimbabwe (see WHO’s HIV drug resistance report 2019)
  - In the aggregated analysis: half of newly diagnosed infants has efavirenz (EFV)/nevirapine (NVP) resistance
- Subanalysis of WHO 2019 report data showed no difference in the prevalence of NRTI resistance by age ≤12 weeks versus >12 weeks. However, the findings showed significantly higher levels of NRTI resistance in surveys done after versus before the adoption of lifelong antiretroviral therapy for pregnant women
- Overall, the high levels of NRTI resistance observed in surveys were primarily driven by ABC and XTC resistance; the prevalence of NRTI resistance appears to be higher in recent surveys potentially due to wide-scale access to lifelong maternal antiretroviral therapy. The conclusion is supported by a high prevalence among infants exposed to maternal antiretroviral therapy (up to one in three infants)
- The results suggest: (1) the need to accelerate transition to PI-based antiretroviral therapy; (2) the need to understand the impact of ABC + XTC resistance on DTG and PI regimens for children; and (3) the need to accelerate access to other NRTIs, including islatavir.
Discussant 2 and 3: Clinical implications of ABC resistance among infants starting first-line antiretroviral therapy

Presenter: Robert Shafer, Stanford University
Presenter: Lisa Frenkel, University of Washington

Summary of key points

This presentation seeks to respond to the following questions.

- Many infants starting antiretroviral therapy with perinatal acquisition of resistance to ABC + XTC are starting ABC-based first-line antiretroviral therapy. Should we be worried? What is the best first-line NRTI option for children with perinatally acquired resistance to ABC + XTC: continue using ABC (current recommendation), use AZT or promote the use of tenofovir alafenamide (TAF) where possible and available?
- Children for whom AZT + 3TC + EFV is failing have often multiple thymidine analogue-associated mutations (TAMs) conferring resistance to both AZT and ABC. Which second-line NRTI should be combined with DTG for an effective regimen: TAF or ABC?
- Is TAF going to be the most suitable antiretroviral drug for these people to overcome drug resistance?

**Background**

Among infants newly diagnosed with HIV, ABC + XTC dual resistance is high in some countries (up to 30%). ABC + XTC is the recommended NRTI in first-line (in combination with LPV/r if <20 kg or DTG if >20 kg). Alternative regimens include ABC + 3TC + NVP.

Fig. 1. *NRTI resistance by antiretroviral drug among children newly diagnosed with HIV*

![Graph showing NRTI resistance by antiretroviral drug among children newly diagnosed with HIV](image)

Source: WHO infant surveys.
Discussion

- Children failing AZT + 3TC + NVP are switched to ABC + XTC + LPV/r or ABC + XTC + DTG. There is a danger of cross-resistance between ABC and AZT.
- The EARNEST trial and other second-line studies show minimal impact of NRTI resistance on boosted PI-based regimens. However, these studies did not include adults on ABC NRTI backbone; can we extrapolate?
- The median fold reduction in susceptibility as defined by the PhenoSense Assay was reviewed for M184V/I DRM patterns on AZT, TDF and ABC. Mutation patterns with and without TAMS were defined.
- The impact of M184V and TAMs on viral load response following ABC intensification was reviewed.
- The clinical activity of ABC + 3TC versus TDF + FTC was reviewed as was the clinical activity of AZT + 3TC + ABC.

Conclusions

1. ABC + 3TC is inferior to TDF + XTC and TAF + XTC in terms of antiviral activity and genetic barrier to resistance.
2. ABC + 3TC is usually (but not always) superior to AZT + 3TC in terms of antiviral activity.
3. Triple NRTI (ABC + 3TC + AZT) should be considered for infants starting antiretroviral therapy or for infants for whom NNRTI-based first-line antiretroviral therapy is failing and switched to LPV/r or DTG to reduce the risk of providing a regimen with a compromised NRTI backbone.
4. When AZT + 3TC + EFV with TAMs fails children, which second-line NRTI should be combined with DTG for an effective regimen?
   - Failure of first-line AZT + 3TC + EFV may select TAMs + M184V
   - Stanford penalty scores for T215Y + M184V: ABC = 25 (low-level resistance), TDF = 0 (susceptible)
   TAF can be used with 3TC + DTG for children >25 kg, and DAWNING suggests that TAF + 3TC + DTG will likely suppress viral replication, despite TAMs + M184V.
5. What is the role of TAF?
   TAF may play a role, since DAWNING suggests that TAF + 3TC + DTG will likely suppress viral replication, despite TAMs + M184V. TAF may be considered in combination with 3TC and DTG for children for whom AZT + 3TC + EFV has failed.

Discussant 4: NRTI resistance: implications for antiretroviral therapy for children in Uganda and Cameroon

Presenter: Eleanor Namusoke-Magongo, Ministry of Health, Uganda

Summary of key points

Uganda

- Most low- and middle-income countries use NVP + 3TC + AZT in the absence of LPV/r pellets. With the potential increase in DTG and LVP/r-based formulations for children, most currently plan or are transitioning to DTG + ABC + XTC (infant >20 kg) or PI + ABC + XTC (infant <20 kg). There is a risk of XTC resistance and cross-resistance to ABC (from TAMs), and this risk may be higher among infants with unsuppressed viral loads.
- Data on resistance prevalence and mutation patterns among children younger than six years in Uganda were reviewed.
   - The 35 children <6 years had the following resistance prevalence and patterns: 85% NVP + EFV; 88% (ABC); 85% XTC; 21% AZT; 18% TDF; 85% ABC + XTC. Children with ABC resistance had the following mutation patterns: M184V 6%; M184V + Y115F, L74V) 21%; L74V 3%; 184V+ >3 TAMS 15%; M184V + >1 TAM 9%; M184V only 35%.
   - Uganda is actively moving children with suppressed viral loads from AZT + 3TC to ABC + 3TC in accordance with WHO guidelines. Given the high levels of ABC + XTC resistance partly because of TAMs from AZT, there are two main questions: How effective are current NRTI backbones for second-line antiretroviral therapy? What options do resource-limited countries have?
- To address these questions, Uganda is proactively transitioning children taking AZT + 3TC with suppressed viral loads to ABC + 3TC to preserve AZT + 3TC for second-line antiretroviral therapy.
- Children and adolescents are being viral load tested every six months to facilitate early identification of suspected failure.
- Uganda proposes HIV drug resistance testing for each child for whom a PI-based regimen has failed.
- The priorities for HIV drug resistance testing are as follows:
  - Infants born to mothers for whom treatment has failed
  - People for whom a DTG or PI anchor regimen has failed regardless of line of care
All children with exposure to first-line treatment based on either AZT + 3TC or ABC + 3TC for whom treatment is failing.

- People for whom second-line antiretroviral therapy is failing, including pregnant and lactating women
- People for whom third-line antiretroviral therapy is failing, including pregnant and lactating women

Cameroon

Like Uganda, Cameroon is in the process of transition. Cameroon has proposed the following observations and actions for optimized NRTI backbone (Table 6).

Table 6. Observations and actions from NRTI backbone – Cameroon

<table>
<thead>
<tr>
<th>Observation in children</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>~50% EFV + NVP pretreatment resistance</td>
<td>Transition to PI/r-based first-line antiretroviral therapy</td>
</tr>
<tr>
<td>~10% NRTI pretreatment drug resistance (ABC + XTC)</td>
<td>ABC for initial antiretroviral therapy + viral load monitoring every six months</td>
</tr>
<tr>
<td>~80% dual class resistance at first-line failure (70% on NNRTI-based antiretroviral therapy)</td>
<td>HIV drug resistance testing: failure on PI/r-based antiretroviral therapy or failure on first-line antiretroviral therapy after multiple NRTI substitutions</td>
</tr>
</tbody>
</table>

Discussant 5: TDF resistance among adults for whom EFV-based first-line antiretroviral therapy is failing

Presenter: Seth Inzaule, WHO

Summary of key points

- Background
  - WHO guidelines recommend optimizing the NRTI backbone during the switch to second-line antiretroviral therapy: for example, TDF + XTC + first line → AZT + XTC + second line.
  - Recent second-line studies with PIs (here, here and here) suggest better treatment outcomes for people with no active NRTI backbone, potentially because of:
    » Better adherence
    » Residual NRTI activity
    » Hypersensitivity of AZT or TDF by M184V XTC resistance
    » High PI potency.

- Nevertheless, whether the same effect may be seen with DTG is uncertain (WHO-recommended second-line antiretroviral therapy for people for whom first-line NNRTIs are failing).
- The DAWNING study suggests high efficacy of DTG when used with at least one active NRTI backbone.

- WHO HIV drug resistance survey data from people receiving first-line antiretroviral therapy from eight low- and middle-income countries between 2015 and 2018 was analysed with the following aims:
  - To assess the prevalence of NRTI drug resistance among people for whom first-line antiretroviral therapy is failing in low- and middle-income countries reviewed from WHO’s HIV drug resistance report 2019; and
  - To predict the magnitude of population at risk if TDF + XTC is maintained while transitioning (first-line) or switching to TLD (second-line).

- Despite high heterogeneity suggesting country-specific differences in the prevalence of NRTI drug resistance, which may limit generalizability and limit power to provide precise estimates of HIV drug resistance outcomes, hence wide confidence intervals, the following conclusions were drawn:
  - Most people were receiving TDF-based antiretroviral therapy, about 20% with unsuppressed viral loads.
    » Transitioning to TLD in the absence of viral load may affect about 6% of the population receiving long-term antiretroviral therapy and another 2% who have resistance to both TDF and AZT.
    » Optimizing the NRTI backbone – TDF to AZT during second-line switch – has the potential to benefit only 30% of the people for whom antiretroviral therapy is failing from a resistance perspective.
  - A sizeable population of people receiving long-term antiretroviral therapy are taking AZT: about 20% with unsuppressed viral loads.
    » Transitioning to TLD in the absence of viral load may benefit about 94% of the population receiving long-term antiretroviral therapy and another 2% who have resistance to both TDF and AZT.
    » Optimizing the NRTI backbone – AZT to TDF during second-line switch – has the potential to benefit only 70% of the people for whom antiretroviral therapy is failing from a resistance perspective.
  - Overall close treatment monitoring (viral load testing and population-based drug resistance survey) is required when people are transitioned or switched to DTG despite the backbone used.
Discussant 6: Optimal NRTI backbone for people for whom TDF + XTC + EFV is failing and were switched to DTG-based antiretroviral therapy

Presenter: Juliana Da Silva, United States Centers for Disease Control and Prevention

Summary of key points

- The major theme covered was: What should be the NRTI backbone for DTG-containing second-line antiretroviral therapy when a public health approach is used? The presentation considered:
  - Published literature
    - TDF + FTC versus AZT + 3TC
      - HIV RNA <400 copies/mL 84% versus 73%, TDF + FTC + EFV versus AZT + 3TC + EFV, respectively.
      - Increased adverse events resulting in discontinuation in AZT group compared with the TDF group.
  - Fig. 2 summarizes the scenarios and viral load suppression outcomes and associated emergence of HIV drug resistance.

- Conclusions
  - Ease of programmatic implementation is paramount in PEPFAR.
    - Procurement and distribution of DTG singles and AZT + 3TC at a large scale are barriers.
    - Providing more complex guidance for health-care workers may impair implementation.
  - Emergence of DTG resistance is likely inevitable and has been seen in clinical trials for second-line use.
  - The benefits of WHO-recommended NRTIs must be weighed against likely decreased adherence and side-effects of AZT.
  - The impact of possible emerging DTG resistance on overall suppression of viral loads should consider pre-transition suppression rates, dual NRTI acquired drug resistance and viral load testing coverage.

Fig. 2. Summary of viral load scenarios and suppression outcomes with the associated emergence of HIV drug resistance

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Viral suppression rates (VL&lt;1000)</th>
<th>Viral non suppression attributable to 2NRTI group</th>
<th>Viral non suppression attributable to 2NRTI (amongst virologic failures)</th>
<th>Emerging drug resistance (Failing 1st line and ART naive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point estimates from metanalysis</td>
<td>A 97.6% 0.1% 4.0% 0.20%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B 96.1% 1.6% 40.5% 3.85%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low 2NRTI prevalence (24.7%, 25th percentile)</td>
<td>A 97.5% 0.1% 2.0% 0.20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B 96.6% 1.0% 28.7% 2.41%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High 2NRTI prevalence (49.2%, 75th percentile)</td>
<td>A 97.6% 0.1% 5.0% 0.20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B 95.7% 2.0% 47.6% 4.94%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High VS/low 2NRTI</td>
<td>A 97.6% 0.0% 2.0% 0.10%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B 96.9% 0.7% 23.8% 1.81%</td>
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<td></td>
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</tr>
<tr>
<td>Low VS/high dual NRTI</td>
<td>A 97.4% 0.3% 10.0% 0.40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B 93.5% 4.1% 63.5% 10.00%</td>
<td></td>
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</tr>
</tbody>
</table>
Discussant 7: Optimal NRTI backbone for individuals for whom TLD is failing and are switched to PIs

Presenter: Roger Paredes, IrsiCaixa AIDS Research Institute, Barcelona, Catalonia

Summary of key points

- Prevalence of TDF + XTC resistance in DTG failures
  - Selection of NRTI resistance after DTG failure is extremely rare to non-existent in randomized controlled trails among integrase strand transfer inhibitor (INSTI)–naive people (FLAMINGO, ARIA, SINGLE, SPRING-2, GS-1489, GS1490, GEMINI, ASPIRE, NEAT 022, GS-1878, GS-1844, GS-1961).
  - There are anecdotal cases of DTG resistance emerging when DTG fails.

- Are boosted PIs expected to overcome the impact of NRTI resistance?
  - The risk of PI resistance is low but cumulative during failure.
  - NRTI resistance predicts higher odds of suppressed viral loads in combination with PIs. Possible reasons:
    - Proxy for adherence
    - Residual activity of AZT, stavudine and TDF in the presence of TAMs
    - In the presence of M184V:
      - Residual 3TC activity (0.5 log viral load drop)
  - Viral suppression outcomes of boosted PI second-line antiretroviral therapy
    - A systematic review reported the following:
      - By intention-to-treat analysis, viral loads were suppressed for 69% (95% confidence interval [CI] 58–79%) of people treated at week 48 (4558 participants, 14 studies), and for 61% (95% CI 47–75%) at week 96 (2145 participants, eight studies). Pre-existing resistance to NRTIs increased the likelihood of suppressed viral loads. Major PI resistance mutations occurred in a median of 17% (interquartile range, 0–25%) of the population with unsuppressed viral loads and increased with the duration of second-line antiretroviral therapy. One third of the people receiving PI-based second-line antiretroviral therapy with continued NRTI use in sub-Saharan Africa did not have suppressed viral loads, although PI resistance was infrequent among people with viraemia. Significant challenges remain in implementing viral load monitoring. Optimizing definitions and strategies for managing second-line antiretroviral therapy failure are research priorities.
  - TDF + XTC was the NRTI used in >70% of the participants in EARNEST and was much better tolerated than AZT + 3TC.
SESSION 3: FUTURE SCOPING: INNOVATIONS TO IMPROVE HIV DRUG RESISTANCE SURVEILLANCE AND ABILITY TO PROVIDE BETTER QUALITY AND PERSON-CENTRED HIV CARE

Presentation 1: Results from a survey on the use of HIV drug resistance testing in Africa

Presenter: Fatim Cham, WHO Regional Office for Africa

Summary of key points

A survey of HIV drug resistance testing was performed in the WHO African Region.

Survey purposes

- Collect information in the WHO African Region that will inform WHO about the demand for resistance testing and its intended use.
- Follow up on the cost associated with HIV drug resistance testing in the Region.
- Initiate discussions regarding WHO prequalification and regulatory oversight of quality standards for HIV drug resistance tests and assays.

Table 7. HIV drug resistance testing policy by country

<table>
<thead>
<tr>
<th>Policy for HIV drug resistance testing</th>
<th>Number of countries</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9</td>
<td>Burkina Faso, Burundi, Central African Republic, Eritrea, Ethiopia, Liberia, Sierra Leone, South Sudan</td>
</tr>
<tr>
<td>Adults and children for whom second-line antiretroviral therapy has failed</td>
<td>7</td>
<td>Benin, Côte d'Ivoire, South Africa, Uganda, United Republic of Tanzania, Zambia, Zimbabwe</td>
</tr>
<tr>
<td>Adults and children for whom first- or second-line antiretroviral therapy has failed</td>
<td>4</td>
<td>Algeria, Botswana, Cameroon, Rwanda</td>
</tr>
<tr>
<td>Adults for whom second-line antiretroviral therapy has failed</td>
<td>1</td>
<td>Malawi</td>
</tr>
<tr>
<td>Adults for whom first-line DTG has failed and children for whom first- or second-line antiretroviral therapy has failed</td>
<td>1</td>
<td>Guinea</td>
</tr>
<tr>
<td>Adults for whom first-line DTG has failed and adults for whom second-line antiretroviral therapy has failed</td>
<td>1</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Adults for whom second-line antiretroviral therapy has failed</td>
<td>3</td>
<td>Democratic Republic of the Congo, Kenya, Nigeria</td>
</tr>
</tbody>
</table>
Summary of key points

• Background
  - Overview of current laboratory assessment techniques of HIV drug resistance: phenotyping and genotyping
    » Phenotyping: directly measures drug susceptibility; complex to perform; expensive; not used in low- and middle-income countries; important source of data for deriving genotype interpretation systems, especially for new drugs
    » Genotyping: indirectly assessed drug susceptibility, relatively less complex than phenotyping assays and also relatively less expensive. Genotyping primarily used for HIV drug resistance surveillance in low- and middle-income countries; the use for individual patient management is limited in low- and middle-income countries but increasing.
  - Genotyping assay methods
    » Sanger-based sequencing
      » Most common technology
      » Existing infrastructure and expertise
      » Kits and (mostly) home-brew
      » Sensitivity for low-abundance drug-resistant variants ~20%
    » Next-generation sequencing (NGS)
      » Potential for greatly increased sensitivity to low-abundance drug-resistant variants
      » Potential for cost reduction (given sufficient scale)
      » Simplified (to the user) data processing
  - Point mutation assays
    » Test for limited number of specific changes in sequence associated with drug resistance
      » Need to know which drug-resistance mutations to target (still undefined for DTG)
    » Simpler, less expensive than full sequencing
    » Potential for decentralized or point-of-care implementation
      » Use existing equipment, such as GeneXpert?
    » Potential for reduced cost
• Ideal quality assurance must be balanced with feasibility in low- and middle-income countries
• Table 8 provides an overview of the features of HIV drug resistance testing kits
• Questions on the road to a target product profile for development for HIV drug resistance tests
  - What is the market size?
    » Market assessment
      » Prediction of the number of tests expected
        » For different applications
        » In different countries
      » Essential for test developers and funders
      » Examples:
        » Clinton Health Access Initiative HIV diagnostics market forecasts
        » WHO forecast of the global demand for HIV monitoring and diagnostic tests (2016–2021)
  - What are the minimum and optimal assay characteristics (including cost) for the use of HIV drug resistance testing in low- and middle-income countries?
    » Description of targets for various test characteristics (often “minimal” and “optimal”) that should be met
    » Dependent on intended use (“use case”)
    » Essential for test developers and funders
    » Can be applied to evaluating existing products (such as for new applications or to identify unmet needs) or proactively for new tests
  - An example of use cases and target product profiles for tests of recent HIV infection
• Use cases, assay characteristics and minimal and optimal targets for HIV drug resistance testing in low- and middle-income countries
  - Possible use cases
    » Surveillance versus patient management (applies to all below)
    » In countries relying on EFV-based first-line antiretroviral therapy
    » In countries relying on DTG-based first-line antiretroviral therapy
    » After failure of PI/r-based antiretroviral therapy
    » Variations on this theme for second- and third-line antiretroviral therapy
    » PrEP users (before, during, after?)
    » To guide next antiretroviral therapy regimen selection
<table>
<thead>
<tr>
<th>Test (manufacturer)</th>
<th>Coverage</th>
<th>Assay type</th>
<th>Analysis and reporting software</th>
<th>Equipment requirements</th>
<th>Availability</th>
<th>Regulatory status</th>
<th>Kit excludes</th>
<th>Cost (US dollars)</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViroSeq (Abbott)</td>
<td>PR, RT, IN</td>
<td>Sanger sequencing</td>
<td>ViroSeq</td>
<td>PCR machine, ABI 3130 sequencer</td>
<td>Now</td>
<td>PR/RT: FDA, CE-IVD IN: RUO (ISO 13485)</td>
<td>On request</td>
<td>Discounted for WHO-designated laboratories</td>
<td></td>
</tr>
<tr>
<td>HIV-1 Genotyping Kit (ThermoFisher/CDC)</td>
<td>PR, RT (IN&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Sanger sequencing</td>
<td>Exatype (Hyrax)</td>
<td>PCR machine, ABI sequencer</td>
<td>Now (PR-RT) 2020 (IN)</td>
<td>RUO (ISO 13485)</td>
<td>NA extraction</td>
<td>30–50</td>
<td>Variable based on location</td>
</tr>
<tr>
<td>DeepChek-HIV (ABL)</td>
<td>PR, RT, IN</td>
<td>Sanger sequencing or NGS</td>
<td>ViroScore-HIV or DeepChek-HIV</td>
<td>PCR machine, any Sanger/NGS sequencer</td>
<td>Now</td>
<td>CE-IVD (January 2020)</td>
<td></td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Sentosa SQ HIV (Vela)</td>
<td>PR, RT, IN</td>
<td>NGS (Ion Torrent)</td>
<td>Sentosa SQ</td>
<td>Ion Torrent sequencer</td>
<td>Now</td>
<td>CE-IVD</td>
<td></td>
<td>200 (2016)</td>
<td></td>
</tr>
<tr>
<td>PANDAA qDx (Aldatu)</td>
<td>RT 65, 103, 106, 181, 184, 190</td>
<td>Point mutation assay (semi-quantitative)</td>
<td>Excel template (provided)</td>
<td>Real time RT-PCR machine</td>
<td>Now</td>
<td>TBD</td>
<td>NA extraction</td>
<td>25</td>
<td>Volume pricing</td>
</tr>
<tr>
<td>OLA Simple</td>
<td>RT 65, 103, 106, 181, 184, 190</td>
<td>Point mutation assay (qualitative)</td>
<td>n/a</td>
<td>PCR machine</td>
<td>2020 (for collaboration)</td>
<td>TBD</td>
<td>&lt;20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Test kit (one kit per person)</td>
<td></td>
</tr>
<tr>
<td>Discidium</td>
<td>RT 103, 184</td>
<td>Point mutation assay (qualitative)</td>
<td>n/a</td>
<td>PCR machine</td>
<td>2019</td>
<td>TBD</td>
<td>NA extraction</td>
<td>~10&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Solid-phase melting curve analysis (Insilixa)</td>
<td>RT 65, 103</td>
<td>Point mutation assay (qualitative)</td>
<td>Signal processing and sequence ID software</td>
<td>CMOS biochip</td>
<td>TBD</td>
<td>TBD</td>
<td>unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>In progress
<sup>b</sup>Anticipated pricing, reagent costs only
Everyone versus children only or pregnant women only

To assess adherence

Assay characteristics for consideration

» Sensitivity for amplification (minimum viral load or input copy number needed for reliable result)
» Sensitivity for detection of low-abundance drug-resistant variants (input copy number dependent)
» Specimen type(s)
» Region(s) covered (PR, RT, IN)
» Subtype coverage
» Cost
» Throughput (tests per week)
» Equipment stability, storage requirements, etc.
» Time to results
» Operator training
» Biosafety
» Data capture and transfer

In conclusion, several genotyping method and kit options exist, and more are in development. However, a system of defined use cases and target product profiles has not been established to help to guide their most appropriate use. An international effort to achieve this is needed, but funding has not been identified.

Presentation 3: Cost–effectiveness of HIV drug resistance testing among people for whom first- and second-line antiretroviral therapy has failed

Presenter: Emily Hyle, Massachusetts General Hospital, Boston, USA

Summary of key points

» Background (here, here and here)
  » Previous modelling analyses have demonstrated high value of standard (non-INsti) genotype to investigate failure to suppress viral loads with first-line NNRTI-based antiretroviral therapy to distinguish:
    » Failure to suppress viral loads due to resistant virus, leading to regimen switch

» Failure to suppress viral loads due to susceptible virus, leading to considering barriers to suppression (adherence and stock-outs)

» Key parameters have included:
  » Prevalence of drug resistance
  » Cost of second-line antiretroviral therapy
  » Likelihood that people will switch to a new regimen if offered

WHO now recommending DTG for everyone:

» Transmitted integrase inhibitor drug resistance is very rare
  » <1% in most surveillance studies
  » Three case reports in the United States of de novo DTG-resistance among treatment-naive people

» Acquired drug resistance is also rare
  » Some data indicate that it may be on the rise in the United States and Europe

» DTG-based regimens are potent
  » Some with DTG resistance or other INSTI mutations may suppress on DTG regimens despite resistance

Objective: To examine the clinical and economic impact of drug resistance testing for adults with failure to suppress viral loads on first-line TLD in South Africa

» South Africa's per capita GDP (US$ 6100) to be the cost–effectiveness threshold

» Previously validated CEPAC-I simulation model used

Strategies:

» TLD: people with failure to suppress viral loads continue on TLD with additional opportunities to resuppress after each episode of enhanced adherence counselling

» Genotype: people with failure to suppress viral loads due to resistant virus switch to PI + 2 NRTI, whereas people with failure to suppress viral loads and susceptible virus continue TLD

» PI + 2 NRTI: everyone with failure to suppress viral loads switch to PI + 2 NRTI

Tables 9 and 10 summarize the results
Table 9. Undiscounted clinical and cost outcomes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Alive at five years</th>
<th>Suppressed and alive at five years</th>
<th>Life-years</th>
<th>Cost (US dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLD</td>
<td>72%</td>
<td>90%</td>
<td>22.4</td>
<td>13 800</td>
</tr>
<tr>
<td>Genotype</td>
<td>72%</td>
<td>90%</td>
<td>22.6</td>
<td>15 000</td>
</tr>
<tr>
<td>PI + 2 NRTI</td>
<td>68%</td>
<td>88%</td>
<td>21.1</td>
<td>17 100</td>
</tr>
</tbody>
</table>

Table 10. Discounted clinical, cost and cost–effectiveness outcomes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Life-years</th>
<th>Costs (US dollars)</th>
<th>Incremental cost–effectiveness ratio (US dollars per life-year saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLD</td>
<td>13.9</td>
<td>9 000</td>
<td>–</td>
</tr>
<tr>
<td>Genotype</td>
<td>14.0</td>
<td>9 800</td>
<td>11 220</td>
</tr>
<tr>
<td>PI + 2 NRTI</td>
<td>13.1</td>
<td>11 000</td>
<td>Worse clinical outcomes and higher cost</td>
</tr>
</tbody>
</table>

- Model limitations
  - Influential parameters with wide range in possible values given uncertainty
    - However, this is also a major strength of the modelling approach, which assesses the impact of different values on the outcomes of interest
  - Not explicitly modelled:
    - HIV transmission
    - Changes in the prevalence of drug resistance over time
    - Changes in adherence over time
  - Conclusions
    - Genotype is clinically preferred for people receiving TLD with failure to suppress viral loads versus ongoing TLD even at low prevalence of failure to suppress viral loads with resistance
    - Empirical switch to second-line PI is not clinically or economically preferred until unrealistically high prevalence of failure to suppress viral loads with resistance
    - Findings are sensitive to the likelihood of suppression of viral loads for TLD- or PI-based-regimens depending on resistance and/or adherence

Presentation 4: Challenges with resistance testing in DBS and plasma specimens from people with low-level viraemia

Presenter: Paul Sandstrom, National HIV and Retrovirology Laboratory, JC Wilt Infectious Diseases Research Centre, Public Health Agency of Canada

Summary of key points
- Issues affecting HIV drug resistance genotyping in low-level viraemia
  - Effect on HIV drug resistance target amplification
  - Consequence to DBS-based surveillance for failure to suppress viral loads and HIV drug resistance prevalence and failure to suppress viral loads
  - Precision, reliability and interpretation of HIV drug resistance results (especially low-abundance drug resistance mutations: is it even possible below 1000 copies?)
  - Can centralized (DBS and plasma spot cards) and decentralized point-of-care or near point-of-care viral load testing protocols support a lower failure threshold?
- Overall, 4312 of 4915 (88%) low-level viraemia assays attempted produced usable sequences
Successful results were obtained from 74% of a sample with viral loads <250 copies/mL from approximately 90% of samples with viral loads >250 copies/mL.

Importantly, the requirement of a backup or secondary PCR protocol progressively increased with decreasing viral loads.

Results were similar regardless of subtype; other studies have shown non-B low-level viraemia impact on success rates.

Samples with lower viral loads tended to have fewer observed mixtures compared with those with higher viral loads, which may be related to the total number of input template copies amplified from the sample.

- Sensitivity and reliability of drug resistance mutations, from two DBS, at increasing viral loads (Fig. 3)
- Can current viral load protocols support low-level viraemia below 1000 copies/mL (Fig. 4)?

Fig. 3. Sensitivity and reliability of drug resistance mutations from DBS at increasing viral load values

Fig. 4. Quantification of viral load using DBS by viral load copy number

<table>
<thead>
<tr>
<th>HIV Hologic</th>
<th>Expected log cp/ml</th>
<th>Plasma hologic log cp/ml</th>
<th>DBS average log cp/ml Hologic conversion</th>
<th>DBS average log cp/ml our conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>8.35</td>
<td>8.46</td>
<td>8.48</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>7.55</td>
<td>7.00</td>
<td>7.12</td>
<td>7.19</td>
</tr>
<tr>
<td>M3</td>
<td>6.44</td>
<td>6.77</td>
<td>5.74</td>
<td>5.76</td>
</tr>
<tr>
<td>M4</td>
<td>5.43</td>
<td>5.86</td>
<td>4.64</td>
<td>4.67</td>
</tr>
<tr>
<td>M5</td>
<td>4.58</td>
<td>4.77</td>
<td>3.38</td>
<td>3.40</td>
</tr>
<tr>
<td>M6*</td>
<td>3.57</td>
<td>3.44</td>
<td>2.94</td>
<td>2.97</td>
</tr>
<tr>
<td>M7*</td>
<td>2.72</td>
<td>2.56</td>
<td>2.94</td>
<td>2.97</td>
</tr>
<tr>
<td>M8</td>
<td>2.50</td>
<td>1.61</td>
<td>TND for DBS</td>
<td></td>
</tr>
</tbody>
</table>

For DBS- Quantification below 1000 copies/ml becomes difficult

Source: J C Wilt Infectious Diseases Research Centre, Public Health Agency of Canada
SESSION 4: THINK TANK PRIORITIES FOR WHO AND HIVRESNET LOOKING FORWARD

The WHO HIV drug resistance secretariat and the HIV drug resistance Global Action Plan working group priorities were reviewed at the meeting through individual group round tables and a questionnaire to help the prioritization exercise. The figures and tables below summarize the results of the prioritization effort. Overall, up to 37 participants expressed a preference; not all participants answered all questions.

**Fig. 5. WHO secretariat priorities**

![WHO secretariat priorities chart]

With respect to WHO secretariat activities (Fig. 5), the majority of the participants believe that the following were high priorities (top 5 scored high priority):

1. Gather and use best available HIV drug resistance evidence to inform antiretroviral drug guidelines
2. Regularly develop technical guidance on HIV drug resistance surveillance to support country implementation
3. Support sustainability of the activities thought resource mobilization and identify mechanisms to promote in country sustainability of HIVDR-related work through integration and ownership
4. Support the development of global HIV drug resistance reports
5. Support and manage quality assurance of HIV drug resistance survey data

**Fig. 6. Working Group 1 priorities**

![Working Group 1 priorities chart]

Identify strategies to improve sub-optimal quality of care to prevent and respond to HIVDR, for use in national and global decision making

Best practices around quality of HIV care
Creation of a resource library of HIV specific quality of care operational tools
Community-based assessment of quality of care of HIV services
Review of national progress on GAM HIV services quality indicators
Quality scoping call for 2020 WHO guidelines
WHO global learning lab
With respect to Working Group 1 activities (Fig. 6), the majority ranked the following three items as high priorities (top 3 scored highest priority):

1. Identifying strategies to improve suboptimal care
2. Identifying best practices around the quality of HIV care
3. Creating a resource library of HIV-specific quality of care best practices

**Fig. 7. Working Group 2 priorities**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update HIVDR survey methods (ADR lab, PDR, PrEP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO HIVDR database</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operational guidance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor GAP implementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country adapted protocols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Updated definitions and targets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With respect to Working Group 2, the majority surveyed identified the following as priorities activities (top 3 scored the highest priority) (Fig. 7):

1. Provide technical input to WHO to update HIV drug resistance survey methods, as needed
2. Support further development of the WHO HIV drug resistance database
3. Develop operational guidance related to survey implementation

With respect to Working Group 3 priorities, the group ranked as high priority many research activities (Table 11). The effect of pre-existing resistance to the NRTI backbone on the efficacy of DTG-based antiretroviral therapy was ranked as the highest research priority.

**Table 11. Working Group 3 priorities**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer collection matrices for HIV drug resistance testing</td>
<td>41%</td>
<td>47%</td>
<td>12%</td>
</tr>
<tr>
<td>Correlation of genotype and phenotype and clinical significance for all mutations</td>
<td>30%</td>
<td>58%</td>
<td>12%</td>
</tr>
<tr>
<td>Clinically significant thresholds of low-abundance NNRTI-resistant variants</td>
<td>53%</td>
<td>26%</td>
<td>21%</td>
</tr>
<tr>
<td>Levels of viral suppression and acquired HIV drug resistance among people receiving second-line boosted PIs in low- and middle-income countries, with particular focus on atazanavir/ritonavir</td>
<td>15%</td>
<td>62%</td>
<td>23%</td>
</tr>
<tr>
<td>Simple and affordable next-generation sequencing bioinformatics algorithms</td>
<td>32%</td>
<td>41%</td>
<td>26%</td>
</tr>
<tr>
<td>Activity</td>
<td>Priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost–effectiveness analysis tools for use in countries for financing and advocacy of optimized treatment</td>
<td>Low: 29%</td>
<td>Medium: 42%</td>
<td>High: 29%</td>
</tr>
<tr>
<td>Clinical impact of raltegravir-based antiretroviral therapy among children infected with NRTI-resistant HIV</td>
<td>Low: 26%</td>
<td>Medium: 35%</td>
<td>High: 38%</td>
</tr>
<tr>
<td>Impact of K65R/M184V mutations on the efficacy of Truvada®-based PrEP</td>
<td>Low: 13%</td>
<td>Medium: 46%</td>
<td>High: 40%</td>
</tr>
<tr>
<td>Efficacy of DTG administered twice daily as a strategy to increase the potency of the regimen among individuals with a partly active NRTI backbone</td>
<td>Low: 22%</td>
<td>Medium: 34%</td>
<td>High: 44%</td>
</tr>
<tr>
<td>Minimum set of mutations for PIs, NTRIs and NNRTIs and INSTIs for clinical purposes for point mutation technology</td>
<td>Low: 15%</td>
<td>Medium: 39%</td>
<td>High: 45%</td>
</tr>
<tr>
<td>Clinical impact of dolutegravir administered twice daily among children for whom raltegravir-based antiretroviral therapy has failed</td>
<td>Low: 26%</td>
<td>Medium: 26%</td>
<td>High: 47%</td>
</tr>
<tr>
<td>HIV drug resistance emerging in programmes scaling up PrEP</td>
<td>Low: 8%</td>
<td>Medium: 44%</td>
<td>High: 47%</td>
</tr>
<tr>
<td>Simple algorithm for interpreting HIV drug resistance for use by caregivers</td>
<td>Low: 14%</td>
<td>Medium: 39%</td>
<td>High: 47%</td>
</tr>
<tr>
<td>Validated local, inexpensive and sustainable corrective actions to minimize the emergence and transmission of preventable drug-resistant virus</td>
<td>Low: 13%</td>
<td>Medium: 38%</td>
<td>High: 49%</td>
</tr>
<tr>
<td>Simple and affordable point-of-care HIV drug resistance assays</td>
<td>Low: 9%</td>
<td>Medium: 36%</td>
<td>High: 54%</td>
</tr>
<tr>
<td>Cost–effectiveness of individualized HIV drug resistance testing for people for whom a boosted PI or DTG-based regimen has failed to minimize unnecessary switches to subsequent lines</td>
<td>Low: 5%</td>
<td>Medium: 38%</td>
<td>High: 57%</td>
</tr>
<tr>
<td>Inexpensive, simple, easy-to-interpret tests that combine viral load and HIV drug resistance testing that can be used to minimize unnecessary switches to subsequent regimens</td>
<td>Low: 6%</td>
<td>Medium: 35%</td>
<td>High: 59%</td>
</tr>
<tr>
<td>Simplifying resistance testing (point of care leading to clinical validation, K65R/M184V rapid molecular testing (GeneXpert, etc.) to evaluate residual TDF/FTC backbone activity?</td>
<td>Low: 8%</td>
<td>Medium: 28%</td>
<td>High: 64%</td>
</tr>
<tr>
<td>Affordable, simple and easy-to-use point-of-care tests to measure drug levels to distinguish people for whom treatment has failed because of poor adherence versus resistance</td>
<td>Low: 6%</td>
<td>Medium: 28%</td>
<td>High: 66%</td>
</tr>
<tr>
<td>Response of tenofovir, 3TC and DTG in populations at high risk of suboptimal adherence (such as adolescents) and among people with TB and HIV</td>
<td>Low: 3%</td>
<td>Medium: 30%</td>
<td>High: 67%</td>
</tr>
<tr>
<td>Optimal viral load switching algorithm to minimize the emergence of resistance</td>
<td>Low: 8%</td>
<td>Medium: 24%</td>
<td>High: 68%</td>
</tr>
<tr>
<td>Impact of novel drug delivery methods (such as long-acting drug formulations) on the selection of HIV drug resistance</td>
<td>Low: 6%</td>
<td>Medium: 26%</td>
<td>High: 68%</td>
</tr>
<tr>
<td>Levels of viral suppression and prevalence and pattern of HIV drug resistance mutations among people for whom DTG-based antiretroviral therapy has failed in low- and middle-income countries</td>
<td>Low: 5%</td>
<td>Medium: 16%</td>
<td>High: 78%</td>
</tr>
<tr>
<td>Effect of pre-existing resistance to the NRTI backbone on the efficacy of DTG-based antiretroviral therapy (Can we safely switch people for whom first-line TLE has failed to TLD instead of AZT + 3TC + DTG?)</td>
<td>Low: 0%</td>
<td>Medium: 13%</td>
<td>High: 86%</td>
</tr>
</tbody>
</table>
With respect to Working Group 4 priorities, the majority reported the following four activities as high priority (top 4 scored as highest priority) (Fig. 8):

1. Develop a quality standard for HIV drug resistance testing for patient management to guide countries without national regulatory bodies that have expertise in quality assurance for HIV drug resistance genotyping and distinguish standards for this purpose versus public health surveillance

2. External quality assurance management of HIV drug resistance laboratories within HIVResNet (annual proficiency panel for plasma and DBS-based genotyping and dry panels for sequence analysis and post-testing sequence quality assurance)

3. Support assay validation for genotyping using DBS and integrase

4. Quality assurance and resistance interpretation of HIV drug resistance national survey sequence data

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Fig. 8. Working Group 4 priorities

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With respect to Working Group 5 priorities (Fig. 9), the majority ranked the top three priorities as:

1. Landscaping of HIV drug resistance, publications, simplified text, videos in coordination with WHO and World AIDS Day

2. Development of generic text to engage civil society to advocate within health ministries for including HIV drug resistance in Global Fund applications

3. Stimulate HIV drug resistance advocacy events and community engagement

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Fig. 9. Working Group 5 priorities
ANNEX 1. RESULTS FROM PARTICIPANT QUESTIONNAIRE ON PRIORITY TECHNICAL QUESTIONS

The questions in the participant questionnaire and the responses obtained are below. Session numbers reference relevant sessions described above.

1) Session 2: NRTI backbone acquired drug resistance and antiretroviral therapy optimization, for children
   a. Based on what you have heard during this session, do we have enough evidence to suggest that we need a different NRTI backbone in first-line for children (i.e. moving away from ABC)?
      _____ Yes (77%)
      _____ No

   » 31 respondents answered question 2a with a yes or no: 77% ticked yes and 23% ticked no. One respondent said they were unsure. Of those who replied no, two provided a rationale. One wrote that their choice of no is predicated upon the use of DTG or LPV/r as first line. In addition, this respondent noted that the "Odyssey trial has just completed enrolment and will likely answer this question with evidence. If children behave like adults, NRTI resistance will have no bearing on the efficacy of LPV/r- or DTG-based regimens: Odyssey – NTC 02259127". The second wrote that there is a "need to look at incidence of M184V and L74V or K65R at country level, if >10%, especially with PI/DTG, [this would necessitate a] change in regimen".

   If yes, what would you suggest as options?
      _____ TAF + XTC (90%)
      _____ AZT + XTC
      _____ 3TC or FTC alone without a second NRTI
      _____ Other:

   » 20 respondents answered the second part of question 2a. 90% preferred TAF + XTC and 10% preferred AZT + 3TC. Four respondents who had ticked yes also wrote that NRTI backbone selection should be optimized by drug resistance testing since there is limited choice of antiretroviral drugs. Two respondents who had ticked yes stated that the need for a different NRTI backbone in first-line for children depended on surveillance data and the prevalence of documented NRTI resistance. TAF + XTC was cited as being advantageous since it is administered once daily. One individual queried the possibility of using second-generation NNRTIs in the population and another noted that newer classes of drug may "allow us to move away from NRTI backbone and the current three-drug paradigm".

   b. Based on what you have heard during this session, do we have enough evidence to suggest that we need a different NRTI backbone in second line for children?
      _____ Yes (57%)
      _____ No

   » 28 respondents answered question 2b: 57% ticked yes and 43% ticked no. One respondent who did not answer this question wrote, "Yes and no, except in areas where [there is] high ABC resistance, [it would] be simpler to use TAF for all infants and children." However, the same respondent added that "ideally the mother is virally suppressed; diagnosed accurately then treated with TAF + XTC + DTG or much less good LPV/R". Two individuals suggested using HIV drug resistance genotyping to choose the NRTI backbone in this scenario. One respondent commented that their choice would depend on the country context and what antiretroviral drugs are available.

   If yes, what would you suggest as options?
      _____ TAF + XTC (94%)
      _____ AZT + XTC
      _____ 3TC or FTC alone without a second NRTI
      _____ Other:
17 of 18 respondents answered the second part of question 2b with a choice of either TAF + XTC or AZT + XTC. 94% recommended TAF + XTC and 6% recommended AZT + XTC. One respondent suggested an “other” regimen; specifically, DTG + PI/r. A nineteenth respondent stated that they “felt inadequate to judge”. Two respondents who ticked yes underscored their preference for HIV drug resistance genotyping to guide antiretroviral drug selection. One respondent qualified their choice of TAF + XTC by adding that it should be administered with DTG. Finally, one individual suggested using DTG in combination with a ritonavir-boosted PI.

2) Session 3: NRTI backbone acquired drug resistance and antiretroviral therapy optimization, for adults

a. Based on what you have heard during this session, do we have enough evidence to suggest that we maintain tenofovir + XTC NRTI backbone in second line for adults for whom TDF + XTC + EFV has failed and switching to DTG?

___ Yes (60%)
___ No (40%)

If no, what would you suggest as options?

___ AZT + XTC (100%)
___ 3TC or FTC alone without a second NRTI
___ Other: ______________________________

Three of 14 respondents opted for AZT/3TC. One respondent suggested 3TC or FTC alone.

35 respondents responded to Question 3a. 60% responded yes and 40% responded no.

Of those replying yes to question 3a, some provided added explanations:

» “As above, no data … show [whether] NRTI activity predicts or [does not predict] failure on InSTI regimens.”

» “We still need more studies, but the alternative of AZT + 3TC is much worse”

» “Not enough evidence, but practically may be best from care aspect.”

» “Because we have viral load monitoring.”

» “But need more data with K65R.”

» “Suggest they do suppress but why are not Botswana data available? Those who switched with M184V + K65R – what can be done to expedite data? Would get data as cohorts available. Additional data [are needed] before changing guidelines based on assumptions. If were wrong, this could select for more DTG resistance.”

» “Despite lack of evidence, TDF + XTC had predicted advantages of AZT + 3TC; would not recommend DTG + 3TC only.”

» “Additional data needed but preferably use TDF + /XTC with close treatment monitoring.”

Of those replying no to question 3a, some provided explanations:

» “AZT + 3TC [should be used] until results from NADIA, ARTIST and ACTG study [are available].”

» “Keep current recommendations until more data are available.”

» “We need studies similar to EARNEST to select second-line.”

» “This is a discussion is about tolerance of imperfection. It is important to understand …the effect of leaving patients on failing TLE (knowing switch rated to second line are small) and delaying uptake of a better regimen.”

» “AZT + XTC; data first! extensive resistance to tenofovir in low- and middle-income countries compared to western situation, more time on failing regimens different subtypes, look at PI failure in second-line (adherence issue – if resistance more extensive than even reported in western countries, not sure how much).”

b. Based on what you have heard during this session, do we have enough evidence to suggest that we maintain tenofovir + XTC NRTI backbone in second line for adults for whom TDF + 3TC + DTG has failed and switching to PIs?

___ Yes (65%)
___ No (35%)

34 respondents replied to this question: 65% ticked yes and 35% ticked no. One respondent who replied no wrote: “Same as prior NRTI activity not correlated with increased risk of failure.” Another wrote: “No and no since most failure to suppress viral loads with DTG antiretroviral therapy due to non-adherence would help with adherence, if high viral load persists would check for HIV drug resistance.” Two respondents who ticked yes provided additional comments. One wrote: “Yes, because viral load monitoring in place.”
If no, what would you suggest as options?

_____ AZT + XTC
_____ 3TC or FTC alone without a second NRTI
_____ Other: ____________________________

> Among those providing an explanation for question 3b, four recommended AZT + XTC. Two said AZT was toxic. One recommended TDF + FTC + DTG, one asked why there was any need to change at all, one suggested focusing on adherence counselling and two suggested HIV drug resistance genotyping to guide therapy.

3) Session 4: future innovations for HIV drug resistance testing

a. Based on what you have heard during this session, under what circumstances or for which populations could HIV drug resistance testing be considered for patient management?

- DTG first-line failures: 31 respondents, yes 87%, no 13%. One individual responding no cited very low to no acquired DTG resistance among thousands of people taking DTG-based antiretroviral therapy.
- PI-based failures: 34 respondents, yes 94%, no 6%. One respondent suggested that it would not be needed if drug level testing were available and another clarified the response by citing that drug resistance testing supports shifting from second to third line.
- Children: 32 respondents, yes 100%, no 0%. One responded added, “If on boosted PI.”
- Pregnant women: 29 respondents, yes 93%, no 7%. One respondent who ticked yes clarified the response by saying that pregnant women would be a lower priority than the three other groups above. One individual who replied no stated “adherence counselling”, and one who left the question blank wrote: “maybe point-of-care viral load testing first.”

If no, are there other circumstances or populations in which HIV drug resistance testing can be prioritized?

Eight respondents provided an answer to this question and suggested the following situations:

> To add further data to the modelling work presented: “Emily Hyle model [using HIV drug resistance among people receiving DTG to minimize switch to second line] was very appealing – requires more scrutiny, and real-life experiment in high HIV drug resistance setting could be considered.”
> “Drug levels may be cheaper and should be considered; see Hermans et al.”
> “Adolescents initiating antiretroviral therapy if their mother used antiretroviral therapy as TCT.”
> “Children”
> “PrEP”
> “If money/capacity not a problem, do it! I would prioritize pregnant women and children.”
> “In people who have received adherence sessions and/or after drug levels [suggesting adherence].”
> “In people failing DTG-based after drug level monitoring documents adherence.”

b. From the presentations we know that several low- and middle-income countries are using drug resistance testing for clinical management of people for whom PI has failed, using tests with unknown performance characteristics. Therefore, is a target product profile needed for drug resistance testing in low- and middle-income countries?

_____ Yes 81%
_____ No

> 31 respondents replied to this question. 81% responded yes and 19% responded no. Among those replying yes, one respondent qualified the answer by saying that there is a need, but this should not preclude countries from using other tests. One respondent who was against development of a target product profile wrote that it would stifle new innovation. One additional individual wrote that they were undecided.

If no, how can we ensure high quality drug resistance testing in low- and middle-income countries?

> Three individuals provided suggestions on how high-quality drug resistance testing can be assured in the absence of a target product profile.
For feasibility, we can implement regular proficiency testing and quality assurance of sequences generated (FASTA format). The target product profile may depend on context as drug resistance testing performance could also be affected by subtype diversity (the case of west and central Africa where validated in-house assays may be useful).

“Cost prohibitive and standard external quality assurance is sufficient instead of prequalification. I feel we did this when we developed the point-of-care mutations list.”

“You will suppress innovative techniques and low-cost local optimal solutions. Proficiency panels [are a way to maintain quality] or a review of FASTA files, if proficiency panels are too expensive.”

c. From the presentations and your experience, should WHO and partners prioritize the development of a simplified drug resistance testing report for clinicians?

_____ Yes (74%)
_____ No

35 respondents replied to this question. 74% ticked yes and 26% ticked no. Three respondents added that both types of reports are needed. One respondent who ticked no wrote: “I think people with significant HIV drug resistance should be managed by experts who understand these reports.” Many who ticked yes felt that both a simplified report and the traditional more complex report were required and that both should be given to healthcare providers.

If no, how can we ensure high-quality drug resistance testing in low- and middle-income countries?

Among those replying no, the following responses were elicited:

”Current drug resistance testing reports are well understood and also serve as educational tools. A key component for drug resistance testing report is expert opinion, which guides clinical recommendations.”

“I am concerned that clinicians may interpret ‘green’ as if the drug can be used, when it may be suboptimal because of archived resistance.”

“Unsure whether this is a priority. Focus on drug level testing for less complex feedback to clinician.”

“Interpretation [of standard drug resistance reports] is important.”

“Consider development of a ‘levelled report’, providing both simple and detailed information.”

d. Based on what you have heard in this session, should countries be attempting to measure resistance in patients with low-level viraemia?

_____ Yes (50%)
_____ No

34 individuals replied to this question. 50% ticked yes and 50% ticked no. Among those replying no, two cited technology concerns (“technology not yet ready”) and one stated that clinicians do not know how to act on drug resistance test results and doing drug resistance testing at low viral loads would be confusing. One individual who responded yes qualified the answer by saying, “For research purposes only now.”

If yes, for plasma: above what threshold?

19 individuals responded to this question. The following thresholds with their corresponding prevalence were: >50 copies/mL – 21%; >200 copies/mL – 32%; >400 copies/mL – 32%; >500 copies/mL – 16%. One individual who left the question blank wrote, “[The] threshold depends on context, since settings with wide viral diversity have more challenges (>200 Europe, >400 South Africa, and higher threshold for western and central Africa).”

If yes, for DBS: above what threshold?

8 individuals replied to this question. The following thresholds with their corresponding prevalence were: >50 copies/mL – 0%; >200 copies/mL – 25%; >500 copies/mL – 38%; >1000 copies/mL – 37%. Three people who did not respond to this portion of the question wrote that results from DBS would be unreliable.
## ANNEX 2. MEETING AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:15</td>
<td>Welcome and introductions</td>
<td>Meg Doherty and Irene Mukui</td>
</tr>
<tr>
<td>8:25</td>
<td>New WHO operating model and programme of work: opportunities and risks for HIV drug resistance</td>
<td>Meg Doherty</td>
</tr>
<tr>
<td>8:45</td>
<td>HIV drug resistance @WHO: what’s on the agenda?</td>
<td>Silvia Bertagnolio</td>
</tr>
<tr>
<td>9:15</td>
<td>HIVResNet Working Group 2: monitoring and surveillance</td>
<td>Michael Jordan</td>
</tr>
<tr>
<td>9:25</td>
<td>HIVResNet Working Group 3: research and innovation</td>
<td>Roger Paredes</td>
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<tr>
<td>9:35</td>
<td>HIVResNet Working Group 4: laboratory capacity</td>
<td>Gillian Hunt</td>
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<tr>
<td>9:45</td>
<td>HIVResNet Working Group 5: governance and enabling mechanisms</td>
<td>Tobias Rinke de Wit</td>
</tr>
<tr>
<td>9:55</td>
<td>Q&amp;A: work accomplished and planned from WHO and HIVResNet Working Groups 1–5</td>
<td>Irene Mukui and Tobias Rinke de Wit</td>
</tr>
<tr>
<td>10:10</td>
<td>Break</td>
<td></td>
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<tr>
<td>10:25</td>
<td>ABC + XTC resistance among infants ≤18 months diagnosed with HIV: results from the WHO global report</td>
<td>Seth Inzaule</td>
</tr>
<tr>
<td>10:40</td>
<td>Clinical implications of ABC resistance among infants starting first-line antiretroviral therapy</td>
<td>Lisa Frenkel</td>
</tr>
<tr>
<td>10:50</td>
<td>NRTI resistance: implications for antiretroviral therapy for children in Uganda and Cameroon</td>
<td>Eleanor Namusoke-Magongo; Joseph Fokam</td>
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<tr>
<td>11:00</td>
<td>Viewpoints and group discussion</td>
<td>Moderator: Lisa Frenkel</td>
</tr>
<tr>
<td>11:25</td>
<td>TDF resistance in adults for whom EFV-based first-line antiretroviral therapy has failed: results from the WHO HIV drug resistance global report</td>
<td>Seth Inzaule</td>
</tr>
<tr>
<td>11:35</td>
<td>Optimal NRTI backbone for individuals on a second-line DTG-based regimen for whom an EFV-based regimen has failed in first-line</td>
<td>Juliana Da Silva</td>
</tr>
<tr>
<td>11:45</td>
<td>Optimal NRTI backbone for individuals on a second-line PI-based regimen for whom a DTG-based regimen in first-line has failed</td>
<td>Roger Paredes</td>
</tr>
<tr>
<td>11:55</td>
<td>Viewpoints and group discussion</td>
<td>Moderators: Ava Avalos, Francois Venter</td>
</tr>
<tr>
<td>12:20</td>
<td>Lunch</td>
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<tr>
<td>Time</td>
<td>Topic</td>
<td>Presenter(s)</td>
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<tr>
<td>13:05</td>
<td>Use of routine HIV drug resistance testing in African countries</td>
<td>Fatim Cham</td>
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<tr>
<td>13:10</td>
<td>HIV drug resistance test options: technology landscape, costs, gaps and opportunities</td>
<td>Neil Parkin</td>
</tr>
<tr>
<td>13:35</td>
<td>Cost–effectiveness of HIV drug resistance testing among people for whom first- and second-line antiretroviral therapy has failed</td>
<td>Emily Hyle (remote)</td>
</tr>
<tr>
<td>13:55</td>
<td>Challenges with resistance testing in DBS and plasma specimens from patients with low-level viraemia</td>
<td>Paul Sandstrom</td>
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<tr>
<td>14:05</td>
<td>Group discussion</td>
<td>Moderator: Carole Wallis</td>
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<tr>
<td>14:25</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>14:40</td>
<td>Working Group 1: prevention and response</td>
<td>Charles Holmes (remote)</td>
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</tbody>
</table>

**Session 4: Looking forward – priorities for WHO HIVResNet and partners**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>14:50</td>
<td>Priority-setting exercise</td>
<td>Moderators: Tobias Rinke de Wit, Irene Mukui</td>
</tr>
<tr>
<td>15:55</td>
<td>Next steps and closing comments</td>
<td></td>
</tr>
<tr>
<td>16:00</td>
<td>Adjourn</td>
<td></td>
</tr>
</tbody>
</table>
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