MEETING REPORT

WHO HIVResNet MEETING REPORT

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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, 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- and second-line antiretroviral therapy selection.

HIVResNet and its five working groups support the Global Action Plan on HIV drug resistance (https://www.who.int/hiv/pub/drugresistance/hivdr-action-plan-2017-2021/en). 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:

1. prevention and response;
2. monitoring and surveillance;
3. research and innovation;
4. laboratory capacity; and
5. governance and enabling mechanisms.

This meeting took place immediately before the 27th International Workshop on HIV Drug Resistance and Treatment Strategies in Johannesburg, South Africa, capitalizing on the presence of HIVResNet members, key opinion leaders and other WHO advisers. Annexes 1 and 2 present the meeting agenda and list of participants.

The meeting began with a review of recent changes in the antiretroviral therapy landscape in low- and middle-income countries from the WHO perspective. This includes the addition of dolutegravir (DTG)-based regimens as a preferred option for first-line therapy and observations regarding the safety of DTG for women of childbearing potential. These developments, in the context of increasing rates of pretreatment HIV drug resistance in many countries and especially among women, raise important issues that could affect WHO treatment guidelines. The five pillars of the Global Action Plan and the HIVResNet governance structure were also reviewed. This introduction was then followed by 10 thematically divided sessions of public health relevance.
WHO convened the HIVResNet meeting in Johannesburg, South Africa, on 21 October 2018. The meeting was attended by 60 HIV drug resistance experts from all over the world. The most important points discussed and conclusions from each session are summarized below.

Session 1: Sanger versus next-generation sequencing: optimal reporting thresholds for comparability and reproducibility

✓ Maximum identity to the Sanger consensus sequence was achieved at a threshold of 20%.

Session 2: Could a more affordable genotyping test affect its use in clinical practice in low- and middle-income countries and how?

✓ At least nine African countries among those who responded to the survey reported having national policies recommending the use of HIV drug resistance genotyping for people for whom second-line antiretroviral therapy regimens are failing. In some cases, reagent costs for sequencing of protease (PR), reverse-transcriptase (RT) and integrase (IN) may be as low as US$ 30 to US$ 50. HIV drug resistance testing was considered cost-effective for this group of people, since the cost of third-line antiretroviral therapy is high and levels of resistance to protease inhibitors (PIs) among second-line failures is relatively low (typically <40%).

Session 3: What is the risk of HIV drug resistance emerging among pre-exposure prophylaxis (PrEP) users in low- and middle-income countries?

✓ Data from clinical trials show that resistance is infrequent (3%) from oral tenofovir (TDF) + emtricitabine (FTC) PrEP if HIV-1 infection is not present when PrEP is started but is more common (41%) if TDF + FTC PrEP is started during undiagnosed acute HIV-1 infection. More data from programmes scaling up PrEP are needed.

Session 4: Dolutegravir roll-out in the context of non-nucleoside reverse-transcriptase inhibitor (NNRTI) pretreatment HIV drug resistance

✓ DTG roll-out has been slowed because of safety concerns for women of childbearing potential. This has complicated the recommended selection of optimal first-line antiretroviral therapy regimens in populations with elevated prevalence of pretreatment HIV drug resistance. In countries with NNRTI pretreatment HIV drug resistance prevalence >10%, WHO guidelines recommend urgently considering non-NNRTI (DTG or ritonavir-boosted atazanavir, ATV/r)-based first-line regimens for everyone initiating antiretroviral therapy.

✓ Informal poll among participants: in a country with NNRTI pretreatment HIV drug resistance >10%, no consistent access to contraception, for women starting first-line therapy: what regimen should be recommended?
  • Tenofovir, lamivudine/emtricitabine, dolutegravir (TLD): ~60%
  • Tenofovir, lamivudine/emtricitabine, efavirenz (TLE) with single (6 months) viral load testing and switch to ritonavir-boosted PI (PI/r) if needed: ~40%

Session 5: How can HIV drug resistance inform antiretroviral therapy switching strategy options?

✓ NNRTI resistance detected after the first viral load test >1000 copies/mL is present in >70% of those tested. Among people with NNRTI resistance, the likelihood of resuppression after adherence intervention is low. Any delay in switching patients to second-line antiretroviral therapy should therefore be avoided. The meeting participants discussed whether switch to second-line would be warranted for people receiving TLE with a single viral load >1000 copies/mL without waiting for a confirmatory second viral load test.

✓ Informal poll: meeting participants were comfortable with only one viral load to define NNRTI-based antiretroviral therapy failure when this would trigger switch to:
  • DTG-based second-line: ~100%; and
  • PI/r-based second-line: ~50%
Session 6: How do we interpret integrase genotypes for DTG?

✔ Interpretation of sequence data for integrase strand-transfer inhibitors (INSTIs) is well established but may continue to evolve as additional data become available (especially from people infected with non-B subtypes). There is a continued need for further research regarding the relationship between genotype, phenotype and clinical response for all antiretroviral drugs but especially DTG.

Session 7: What are the challenges and knowledge gaps related to the use of INSTIs in low- and middle-income countries?

✔ The efficacy of a switch from TLE to TLD among people with at least partial resistance to the nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) backbone (such as K65R ± M184V) remains an important unanswered question; relevant studies are underway.

Session 8: Country experience with DTG, viral failure and drug resistance

✔ Although suppression rates among people with DTG are good, we should continue to monitor those with viraemia for DTG resistance and to understand factors associated with non-suppression.

Session 9: Doravirine and new drugs in the pipeline: HIV drug resistance profile and potential role in HIV treatment in low- and middle-income countries

✔ Although potentially a promising option for antiretroviral therapy in low- and middle-income countries because of incomplete cross-resistance with efavirenz (EFV) and NVP, there are currently insufficient safety data for pregnant women, NNRTI-experienced people and drug–drug interaction concerns among people coinfected with TB to broadly recommend its use.

Session 10: How can we monitor progress in addressing the research gaps of the Global Action Plan?

✔ Working Group 3 (Research and Innovation) of the HIVResNet is actively reviewing progress on relevant research questions listed in the Global Action Plan (a list of “priority” research questions generated at the 2017 HIVResNet meeting) and tracking new questions as they arise as well as collating and interpreting evidence related to specific questions of public health importance.
SESSION 1: SANGER VERSUS NEXT-GENERATION SEQUENCING: OPTIMAL REPORTING THRESHOLDS FOR COMPARABILITY AND REPRODUCIBILITY

Presenter: Neil Parkin, Data First Consulting, USA (WHO consultant)

Summary of key points

• The WHO Global HIV Drug Resistance Laboratory Network and operational framework were reviewed.
• Capacity for integrase testing exists, and assay validations are ongoing.
• Next-generation sequencing is an emerging technology platform with several potential advantages, and some network laboratories are in the process of transitioning to it from conventional (Sanger) sequencing.
• To ensure comparability between next-generation sequencing and Sanger sequencing, data from samples provided by the virology quality assurance (VQA) programme (Rush University Medical Center) were tested in 10 laboratories and reported using different thresholds for low-abundance drug resistant variants. Maximum identity to the Sanger consensus sequence was achieved at a threshold of 20%, although sequence identity was only slightly lower at 15%. Interlaboratory agreement was high overall but lower when the reporting threshold was lower (such as 5% or 10%). This raises the need for standardizing assays in anticipation of the desire for more sensitive detection of low-abundance drug resistant variants using next-generation sequencing in the future.

Summary of discussion

• The performance of next-generation sequencing assays could be evaluated by a standardized panel of samples containing defined proportions of drug resistant variants (K. McCormick and J. Mellors, IDRW presentation #34). The VQA may be able to distribute this.
• The National HIV and Retrovirology Laboratory (Winnipeg, Canada) is also working on proficiency panels for external quality assurance purposes.
• Clinically relevant thresholds for low-abundance resistant variants are likely to vary by regimen; some data suggest that it may be as low as 1% for NNRTI, but this is unlikely to be transferable to PI/r or INSTI-based regimens.
SESSION 2: COULD A MORE AFFORDABLE GENOTYPING TEST AFFECT ITS USE IN CLINICAL PRACTICE IN LOW- AND MIDDLE-INCOME COUNTRIES AND HOW?

**Presenter:** Neil Parkin, Data First Consulting, USA (WHO consultant)

**Summary of key points**

- Among the 18 African countries that responded to the survey, nine have national policies recommending the use of HIV drug resistance genotyping for people for whom second-line antiretroviral therapy has failed: Botswana, Eswatini, Kenya, Lesotho, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

- The approximate testing volume is highest in South Africa (2000–3000 annually).

- The costs differ in each country but are considered relatively high, such as US$ 150 to US$ 200 per test, using in-house laboratory methods.

- The costs for commercially available kits or tests performed in central reference laboratories (next-generation sequencing or Sanger-based) and for new tests that may be available in the next 1–2 years (e.g. point mutation assays) were surveyed. Several commercial suppliers are working to reduce the cost for WHO laboratories (such as Abbott, ThermoFisher and ABL). In some cases, reagent costs for sequencing of PR, RT and IN may be as low as US$ 30–50.

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

**Summary of key points**

- The maximum assay cost at which genotyping is cost-effective for two scenarios was modelled.

- Genotyping can save costs by avoiding unnecessary switching to more expensive second- or third-line antiretroviral therapy regimens if drug resistance is not detected and by preventing disease progression among people with drug resistance who are appropriately switched.

- The cost–effectiveness of using HIV drug resistance testing to minimize switches from PI-based second-line to the most expensive third-line is influenced by the prevalence of resistance and the cost of the HIV drug resistance test.
  - If the prevalence of PI resistance among people for whom second-line has failed (PI/r-based antiretroviral therapy) is 10% compared with a standard of care action of switching everyone for whom treatment has failed to third-line antiretroviral therapy, HIV drug resistance testing is cost-effective to a maximum assay cost of approximately US$ 720.
  - If the prevalence of PI resistance is 50%, the maximum cost of the test is US$ 400.
  - If the prevalence of PI resistance is 80%, the maximum cost of the test is US$ 160.

- For people for whom first-line (DTG-based) regimens have failed, compared with a standard of care action of switching everyone to PI/r-based second-line antiretroviral therapy, the maximum assay cost is about US$ 125 if the prevalence of DTG resistance is 1%, US$ 112 if the DTG drug resistance prevalence is 10% and US$ 13 at 90%.

- These estimates do not consider several influential variables, including resource utilization (laboratory infrastructure requirements, fixed costs, specimen transport or results dissemination), opportunity costs or increased lifetime costs of care, if the intervention prolonged life expectancy.
Summary of discussion

• Drug sequencing strategies (within class) can affect the cost/benefit analyses. For example in the context of switching from second- to third-line, about half of LPV/r failures have cross-resistance to DRV/r, but ATV/r failures almost always susceptible to DRV/r.

• In the ACTG 5288 study of second-line failures (see Grinsztejn et al. Lancet HIV 2019 6(9): e588–600), more than half (56%) of participants without resistance to LPV/r who remained on second-line antiretroviral therapy did not achieve viral load suppression.

• PI failures without PI resistance also have less NRTI resistance (M184V), and switching ATV/r failures to LPV/r does not work very well – possibly because non-adherence is a pattern, and using DTG as third-line therapy may be better.

• The prevalence of PI resistance after second-line failure is typically 30–40%.

• The volume of genotype testing after first-line failure is probably too high given current capacity in low- and middle-income countries, even with very low failure rates. For example, in Botswana, people receiving DTG regimens have a failure rate of only 2% which would still require 20 000 tests per year.

• Genotyping may also be useful for detecting NRTI resistance; full NRTI backbone activity may be important for protecting against the development of resistance to DTG.

• In Kenya, genotyping is only done when switching from PI-based regimens due to practical concerns and cost limitations (PEPFAR not paying for it) – important to monitor viral load more carefully.

• More affordable DR testing is coming; other changes will affect the role of genotyping – so looking at cost–benefit now may be premature, because things are changing quickly.

• Additional data are needed to fully inform cost modelling.

• Modelling using a one-year time horizon is probably too short – five years might be better.

• Opportunity and other hidden costs are important.

• Switching people with suppressed viral loads on a second-line regimen to DTG saves a lot of costs; it may be useful to save specimens for later testing, such as using next-generation sequencing.
SESSION 3: WHAT IS THE RISK OF HIV DRUG RESISTANCE EMERGING AMONG PRE-EXPOSURE PROPHYLAXIS (PREP) USERS IN LOW- AND MIDDLE-INCOME COUNTRIES?

Presenter: John Mellors, University of Pittsburgh, USA

Summary of key points

• Resistance to FTC or TDF among subjects receiving oral TDF + FTC PrEP are more often a result of PrEP use during acute, undiagnosed HIV infection (12 of 26 cases, 46%) compared with true or suspected breakthrough infection (10 of 216 cases, 4.6%). Therefore it is important to exclude HIV-1 infections before starting PrEP.

• There have been five recent (published since 2017) case reports of oral TDF + FTC PrEP breakthrough infections with drug resistance.

• First-line antiretroviral therapy is likely to be effective for most PrEP seroconverters.
  – More data are needed; first-line DTG may be better than EFV.

• In an international observational cohort (GEMS), 3 of 5 PrEP seroconverter specimens tested had HIV drug resistance mutations.

• Resistance monitoring will likely be needed for any PrEP strategy once it is widely used in real-world, non-clinical trial settings.

• New PrEP modalities are in development that may have different profiles of resistance compared to oral TDF + FTC.
  – Dapivirine ring: no difference in the prevalence of resistance-associated mutations between the DPV and placebo arms of the ASPIRE study using a sensitive next-generation sequencing-based method.
  – Long-acting, injectable cabotegravir: no data yet, but since cabotegravir is an INSTI, PrEP-related resistance would not impair the efficacy of standard first-line regimens.

Summary of discussion

• Cross-resistance extensive between INSTIs.

• NRTI resistance from PrEP use during unrecognized acute infection has an unknown effect on efficacy of DTG + 2 NRTIs – does this affect the value of doing drug resistance testing?

• NNRTI resistance from PrEP with dapivirine is less of a concern with DTG coming.
SESSION 4: Dolutegravir Roll Out in the Context of Non-Nucleoside Reverse-Transcriptase (NNRTI) Pretreatment HIV Drug Resistance

DTG Roll-Out in PEPFAR-Supported Countries

Presenter: Elliot Raizes, United States Centers for Disease Control and Prevention, USA

Summary of key points

- PEPFAR focus countries are in various stages of planned transition from TDF, lamivudine (3TC)/ FTC, EFV first-line regimens (TLE) to TDF, 3TC + FTC, DTG (TLD).

- In early 2018, countries were planning to have between 40–100% of the people initiating antiretroviral therapy receive TLD (all African countries except South Sudan >75%).

- In June and July 2018, after reports of safety concerns regarding the use of DTG in women of childbearing potential, these percentages dropped to between 2% and 55%.

- A modelling study (Phillips et al., Lancet 2019; 6: e116–27) designed to predict the most effective and cost-effective future antiretroviral therapy regimen policy in sub-Saharan Africa, accounting for drug resistance and the potential effects of dolutegravir on the risk of neural tube defects, concluded the following.

  - There are substantial net public health benefits for women of childbearing age using TLD compared with avoiding DTG for such women.

  - The benefits of a policy using TLD in people currently on first-line or second-line regimens, without any dependence on viral load or consideration of use of zidovudine rather than tenofovir, outweighed the risks.

  - There is potential for improving the death rate for AIDS related causes among people receiving antiretroviral therapy exceeding 1 per 100 person-years compared with continuing the current policy; with more than 15 million people receiving antiretroviral therapy in sub-Saharan Africa, this suggests that the means exist to prevent 150 000 from dying from AIDS-related causes per year.

- PEPFAR expects countries to continue with their planned TLD transition start dates from fiscal year 2019 (October 2018–September 2019) work plans.

- All men and adolescent boys (≥30 kg and ≥10 years of age) should be switched to TLD as early as possible.

- Until more information is available, women of reproductive potential living with HIV (including adolescent girls 10–19 years of age) can take EFV-based regimens as a safe and effective first-line regimen.
**DTG AND COUNTRY RESPONSE TO PRETREATMENT HIV DRUG RESISTANCE**

**Presenter:** Silvia Bertagnolio, WHO, Switzerland

**Summary of key points**


- In countries with pretreatment NNRTI resistance prevalence >10%, WHO guidelines recommend urgently considering non-NNRTI-based first-line regimens for everyone initiating antiretroviral therapy.

- DTG is the preferred first-line antiretroviral therapy in accordance with WHO guidelines.

- The transition from EFV- to DTG-based first-line antiretroviral therapy is slow because of challenges associated with DTG safety concerns among women.
  - DTG scale-up is ongoing in men.
  - EFV is still used for women despite pretreatment NNRTI resistance >10%. When DTG cannot be used, adopting alternative non-NNRTI regimens such as those based on a boosted PI is challenging because of their higher cost.

**HOW DO PRETREATMENT HIV DRUG RESISTANCE SURVEY DATA INFORM NATIONAL ANTIRETROVIRAL THERAPY GUIDELINES? EXPERIENCE FROM UGANDA**

**Presenter:** Christine Watera, Ministry of Health, Uganda and Uganda Virus Research Institute, Uganda

**Summary of key points**

- In the 2016/2017 pretreatment HIV drug resistance survey in Uganda, 15% of the people initiating antiretroviral therapy had NNRTI resistance; among women, it was 16%.

- National antiretroviral therapy guidelines (second edition, September 2018) state that “the guidelines have recommended optimizing antiretroviral therapy using dolutegravir-based regimen as preferred first-line for eligible people living with HIV in light of the rising levels of pre-treatment HIV drug resistance to NNRTIs”.
  - For women of childbearing potential, the preferred first-line regimen is TLE
  - An amendment is being considered that would entail initiating women of reproductive age on TLE followed by viral load testing at three months and switching to ATV/r-based antiretroviral therapy if the viral load is not <1000 copies/mL based on a single viral load test.

**Summary of discussion**

- High pretreatment HIV drug resistance in the population may overestimate the risk to an individual person. Although it does indicate need for earlier action, countries may have some breathing room to sort out whether the safety concerns with DTG can be confirmed with larger numbers of people.
  - We need a threshold to trigger public health action; it is a question of relative risk. What are most concerning are the trends for an increasing prevalence of resistance over time.
  - Other reasons also contribute to the need to move away from NNRTI-based antiretroviral therapy, so precise estimates of pretreatment HIV drug resistance are not critical.

- In countries with pretreatment NNRTI resistance exceeding 10%, what are the options for women of childbearing potential?
  1. Continue with EFV, despite the increased risk of failure related to NNRTI resistance.
2. Use DTG, despite the possible increased risk of neural tube defects among children.

3. Use ATV/r, despite the increased cost.

- Most studies examining associations between pretreatment HIV drug resistance and outcome used different NRTI backbones than those mostly used now and NVP and not EFV. Is the risk of viral failure lower with TDF + FTC + EFV? Only 2 of 13 studies used TDF; is FTC better than 3TC? TDF better than AZT? etc.

- In the PROMISE study, people with *single* K103N still respond, but the risk of failure increased if there were NNRTI+NRTI mutations (presented at IDRW 2018, abstract 13).

- Linkage may also be important: K103N + NRTI DRMs on the same genome could confer a different risk for failure than a mixture of viruses with K103N but no NRTI DRMs vs. with NRTI DRMs but no K103N.

- Recommending ATV/r first-line may be difficult because of limited drug availability and cost. Good to keep EFV as an option. Consider DTG in the context of better access to contraception and link to or integrate with decentralized sexual and reproductive health services.

- Pretreatment HIV drug resistance is associated with suboptimal response: so perhaps it is better to overestimate the potential harm of NNRTI resistance?

- Suggestion to model the impact of earlier viral load testing (such as three months after starting antiretroviral therapy instead of six months) for people receiving EFV in countries with high pretreatment HIV drug resistance?

- The antiretroviral therapy guidelines should be more context-dependent and flexible based on certain important factors, such as drug availability in different countries

  - Point from the United States Centers for Disease Control and Prevention: “Are we entering the era of not one size fits all? WHO guidelines are one size fits all, and this may not be appropriate anymore?” Response: WHO guidelines do provide multiple options for countries depending on their situation, including individual choice, where possible.

- Informal poll: in a country with high (>10%) pretreatment HIV drug resistance to NNRTI and no access to contraception, for women starting first-line therapy – what regimen should be recommended?
  - TLD: ~60%
  - TLE with single (six months) viral load testing and switch to PI/r if needed: ~40%
**SESSION 5: HOW CAN HIV DRUG RESISTANCE INFORM ANTIRETROVIRAL THERAPY SWITCHING STRATEGY OPTIONS?**

**Presenter:** Lara Vojnov and Silvia Bertagnolio, WHO, Switzerland

**Summary of key points**

- Antiretroviral therapy switching guidelines are informed by viral load testing, which is currently recommended to be done at six and 12 months after initiating antiretroviral therapy and then annually thereafter.
  - If viral load exceeds 1000 copies/mL, the test should be repeated following adherence counselling.
- The WHO guidelines on antiretroviral therapy switching will be revised in 2020:
  - Data on the prevalence of HIV drug resistance can inform the revision, especially among people treated with NNRTI-based regimens with one detectable viral load. The prevalence of NNRTI resistance when failure to suppress viral loads is detected after a single viral load test can be as high as 90%. Thus, the long-term impact of adherence interventions on viral load resuppression in these populations, and therefore the utility of a second viral load test before switching – especially when the viral load testing coverage is low and the turnaround time of viral load results is delayed – should be re-examined.

**PROGRAMMATIC CONSIDERATIONS ON THE IMPLEMENTATION OF THE VIRAL LOAD ALGORITHM: EXPERIENCE FROM UGANDA**

**Presenter:** Christine Watera, Ministry of Health, Uganda and Uganda Virus Research Institute, Uganda

**Summary of key points**

- Viral load testing is becoming routine in Uganda.
- There are significant programmatic challenges to adhering to the WHO-recommended algorithm.
  - For example, only 21% of 66 333 people with viral load >1000 copies/mL (July–December 2017) had viral load repeated after six months; of those with viral load >1000 copies/mL confirmed, only 50% were switched to second-line. Many are therefore left on a failing regimen.
- The survey of acquired drug resistance at 12 months done in 2017 showed that >90% had NNRTI resistance after a single viral load >1000 copies/mL.
CONSIDERATIONS ON USING A SINGLE VIRAL LOAD TO TRIGGER SWITCH IN PEOPLE FOR WHOM NNRTI-BASED ANTIRETROVIRAL THERAPY HAS FAILED: A MODELLING EXERCISE

Presenter: Amir Shroufi, Médecins Sans Frontières, South Africa

Summary of key points

- Mathematical modelling was used to predict the effect of a policy of defining failure of first-line EFV-based regimens by a single viral load >1000 copies/mL in sub-Saharan Africa.
- The model predicts an 18% reduction in mortality if the definition of first-line EFV-based failure is changed from two to a single viral load >1000 copies/mL and an increase of 2.6% in the percentage of people receiving antiretroviral therapy having viral load <1000 copies/mL (the third 90 in the 90–90–90 targets).
  - This would be accompanied by a large increase in the number of people switched to second-line without drug resistance.

VIRAL LOAD RESUPPRESSION AMONG PEOPLE RECEIVING EFV WITH AND WITHOUT ACQUIRED DRUG RESISTANCE AT FIRST ELEVATED VIRAL LOAD

Presenter: Suzanne McCluskey, Harvard Medical School, USA

Summary of key points

- A study of programmatic data from Uganda shows that people with drug resistance at the first viral load >1000 copies/mL have a low chance of resuppressing after adherence intervention: only 37% resuppressed after a single viral load >1000 copies/mL.
  - Other published studies report rates ranging from 20% to 45%.
- Even if resuppression is achieved, the long-term response is suboptimal compared with people who never had viral load >1000 copies/mL (Hermans et al., CROI 2018).
- In data from a cohort study in Uganda, adherence was not a predictive factor for failure to resuppress among people with NNRTI resistance after a single viral load test >1000 copies/mL.
- People with no drug resistance detected at the time of a single viral load >1000 copies/mL had much higher rates of resuppression than those with drug resistance.

VIRAL LOAD RESUPPRESSION AMONG PEOPLE RECEIVING SECOND-LINE PI-BASED ANTIRETROVIRAL THERAPY WITH AND WITHOUT ACQUIRED DRUG RESISTANCE

Presenter: Lucas Hermans, University Medical Center Utrecht, Netherlands

Summary of key points

- Viral rebound occurs frequently: ~30% at viral load >1000 copies/mL based on a single viral load at week 48, ~50% resuppression after adherence counselling and repeat viral load testing.
- Low prevalence of resistance after a single viral load (typically 10–30%).
  - Switching to third-line after first viral load >1000 copies/mL may be premature.
- The risk of viral load rebound after resuppression on second-line antiretroviral therapy is unknown.
- No data were found on the drug resistance prevalence at rebound, only after prolonged failure.
- Tools for insight into adherence and resistance are needed to yield insight into the underlying causes of viral rebound.
Summary of discussion

- Need to consider the ongoing risk of accumulation of drug resistance mutations and transmission while the person is viraemic.

- ACTG 5230 (people for whom first-line therapy has failed who are kept on treatment for a relatively long time) observed high-level NRTI and NNRTI resistance. They were switched to LPV/r monotherapy and then TDF + 3TC added later if needed. The people with less NRTI drug resistance experienced drug failure more rapidly. Similar results from other studies, such as EARNEST. The likely explanation is that when people who are adherent experience drug failure, they have more drug resistance and tend to be more adherent on second-line therapy. So can NRTI or NNRTI resistance be used to predict success on PI-based second-line therapy? NRTI resistance that accumulates might not prevent the activity of PI-based second-line therapy.

- Informal poll: is the group comfortable with a single viral load to define NNRTI-based antiretroviral therapy failure and trigger a switch to
  - DTG based second-line: ~100%; and
  - PI/r based second-line: ~50%.
    a. ATV/r- or LPV/r-based second-line therapy? This could affect the answer.

- What about the number of viral load tests to define PI/r-based antiretroviral therapy failure and trigger switch to third-line?
  - One viral load test – none
  - Two viral load test – none
  - Two viral load tests and drug resistance testing – all.

- If only a single viral load test was available to identify failures and trigger a switch, when should it be done after initiation of antiretroviral therapy (TLD or TLE)?
  - One month: only one vote
  - Three months: ~50%
  - Six months: ~50%
SESSION 6: HOW DO WE INTERPRET INTEGRASE GENOTYPES FOR DTG?

Presenter: Robert Shafer, Stanford University, USA

Summary of key points

- Candidate mutations for inclusion in a list for surveillance of transmitted drug resistance for integrase was proposed.
  - This includes 25 "major non-polymorphic" mutations at 12 positions.
  - An additional 15 rare, non-polymorphic mutations can be considered.
- Prediction of DTG resistance based on integrase genotype data is based on cumulative in vivo data (such as clinical outcomes) and in vitro data (such as phenotypic susceptibility data).
- Studies using in vitro (cell culture) selection of DTG-resistant viruses have reported R263K (8 of 17 selections), S153F, T or Y (7/17), H51Y (4/17), G118R (2/17), E138K (1/17) and E92Q (1/17) in multiple subtypes.
- Although not observed in clinical trials, changes in the integrase coding region have been reported in observational cohorts and case reports of previously INSTI-naive people for whom DTG-based antiretroviral therapy has failed. A systematic review is underway and has thus far identified 21 such cases. INSTI resistance–associated mutations observed so far include: T66I, G118R, E138K, Q148K, N155H, E157Q, G163E and R263K. R263K was most common (n = 14).
- Penalty scores for these INSTI resistance–associated mutations and combinations have been established (http://hivdb.stanford.edu/dr-summary/mut-scores/INSTI).

Summary of discussion

- Stanford University HIV Drug Resistance Database (HIVdb) algorithm (14 positions involved) compared with the International AIDS Society USA (only six positions) – is there a risk of overestimating the resistance from secondary positions?
- Many mutations selected in vitro by DTG impart fitness defects.
- R263K has been seen among people for whom DTG has failed but not accompanied by a decline in phenotypic susceptibility.
  - Whether these people might resuppress with improved adherence is unknown.
- Further research is needed on the relationship between genotype, phenotype and clinical response for all antiretroviral drugs, but especially DTG.
SESSION 7: WHAT ARE THE CHALLENGES AND KNOWLEDGE GAPS RELATED TO THE USE OF INTEGRASE STRAND-TRANSFER INHIBITORS (INSTIS) IN LOW- AND MIDDLE-INCOME COUNTRIES?

Presenter: Dan Kuritzkes, Brigham and Women’s Hospital, USA

Summary of key points

- Pre-existing thymidine analogue mutations and M184V are unlikely to reduce the efficacy of TLD regimens.
  - M184V could – at least partly – reverse the resistance to TDF imparted by thymidine analogue mutations.
- The effect of pre-existing K65R on the efficacy of TLD is still unknown.
  - Note that K65R confers cross-resistance to FTC + 3TC.
- No data are available to date on the activity of bictegrevir for treatment-experienced people, but it is likely similar to DTG.
- Shared mutations can result in cross-resistance among INSTIs.
- The efficacy of DTG declines with increasing resistance to raltegravir (RAL)
- In vitro and in vivo data support the efficacy of DTG against HIV-2.

Summary of discussion

- Studies in the pipeline to inform how NRTI drug resistance (65R/184V) affects the efficacy of TLD?
  - DAWNING study reanalysis (International AIDS Society): the number of active NRTIs was not associated with reduced response, but everyone had at least one active NRTI.
  - A new study – PEPFAR and ACTG collaboration: 1500 people starting or switching to DTG, emphasis on being viraemic at entry, people with TB etc. – hoping to start before the end of 2018.
  - Médecins Sans Frontières in South Africa (University of Cape Town): ~200 viraemic people receiving TLE switch to TLD, doing intensive follow-up including viral load, baseline genotyping.
- Are we missing integrase resistance? That is, could the determinants of DTG resistance lie outside the integrase coding region? Or is this an in vitro phenomenon only? That is, changes in gp41 or the polypurine tract.
- Is double-dose DTG better than normal dose after previous exposure to RAL?
  - Anecdotally, a few people not doing well on once-daily DTG (not necessarily after RAL failure) do better with twice-daily DTG.
  - Is there a difference between people with RAL exposure or documented RAL resistance? Exposure with viraemia is enough to be worried about?
- Question about RAL in infants: DTG will soon be approved for children older than three years – why use RAL for neonates?
- Increase dose of DRV in third-line therapy after failure of other second-line PI/r antiretroviral therapy?
  - The guidelines recommend 600 mg twice daily if the person has used PIs before.
SESSION 8: COUNTRY EXPERIENCE WITH DTG, VIRAL FAILURE AND DRUG RESISTANCE

EXPERIENCE FROM BRAZIL

**Presenter:** Ricardo Diaz, Federal University of São Paulo, Brazil

**Summary of key points**

- The recommended first-line antiretroviral therapy in Brazil is TLD, except for pregnant women or people with TB, who should be tested for drug resistance by genotyping and given TLE if no NNRTI resistance is detected, otherwise TDF + 3TC + RAL.

- DTG has been available since January 2017.

- As of August 2018, of the 581,064 people receiving antiretroviral therapy, 143,239 were receiving DTG.
  - 85,344 initiated DTG-containing regimens.
  - 57,895 switched to DTG-containing third-line antiretroviral therapy or due to intolerance etc.

- In 2017, 54,175 people initiated antiretroviral therapy using a DTG-based regimen, and 26,417 switched from a RAL-containing regimen to a DTG-containing regimen.
  - 77% of the people who initiated antiretroviral therapy in 2017 were using a DTG-based regimen and 17% an EFV-based regimen.

- The rates of suppressed viral loads are high (≥90% after about eight months), with more rapid response and higher suppression rates among people initiating TLD compared with TLE.

- Genotyping of people for whom TLD has failed: although the failure rates are low, the numbers are significant (~5000).
  - So far only 48 genotypes completed; one person identified with R263K.

- Accessory INSTI resistance-associated mutations (such as T124A) were detected at relatively high prevalence among DTG-treated viraemic people, with no data on the prevalence of these drug resistance-associated mutations among people for whom treatment did not fail.

EXPERIENCE FROM KENYA

**Presenter:** Evelyn Wangari, United States Centers for Disease Control and Prevention, Kenya

**Summary of key points**

- The 2018 edition of the guidelines on the use of antiretroviral drugs was launched in August.

- TLD is recommended for first-line therapy and TLE as an alternative.

- Nationwide transition for all adults on first-line therapy to TLD or TLE in the next 8–12 months.

- Adults with suppressed viral loads receiving current first-line therapy are eligible for transition to the recommended or alternative regimens, including DTG.

- As of August 2018, 22,154 people are receiving TLD.
  - 92% have suppressed viral loads.
EXPERIENCE FROM BOTSWANA

Presenter: Ava Avalos, Careena Centre for Health, Botswana

Summary of key points

- TLD was recommended as a first-line regimen in June 2016.
- >82 200 treatment-naive people initiated DTG-containing regimens as of 30 June.
  - Viral load suppression rates are high (>95%).
  - No INSTI mutations have been observed to date.
- Among highly treatment-experienced people switched to DTG-containing regimens, 79% (74 of 93) achieved viral load <400 copies/mL.
  - Among the 19 treatment failures, four had INSTI resistance–associated mutations (3 were failing RAL-containing regimens prior to the switch).
- Will switch to TAF when the donated TLD stocks used up (are there any safety data for TAF in pregnancy?).

Summary of discussion

- Although the suppression rates are good, we should continue to monitor those with viraemia for DTG resistance and to understand factors associated with non-suppression.
  - We can also check for adherence by measuring drug levels, such as TDF and FTC in dried blood spots by mass spectrometry.
- Mechanisms of DTG resistance not involving mutations in integrase in vitro have still not been seen clinically, but we should keep looking, such as by whole-virus genome sequencing before and after DTG treatment and possibly intact virus phenotyping.
SESSION 9: DORAVIRINE AND NEW DRUGS IN THE PIPELINE: HIV DRUG RESISTANCE PROFILE AND POTENTIAL ROLE IN HIV TREATMENT IN LOW- AND MIDDLE-INCOME COUNTRIES

Presenter: Dan Kuritzkes, Brigham and Women’s Hospital, USA

Summary of key points

- Doravirine (DOR) is a novel, next-generation NNRTI with a unique resistance profile.
  - It is active against HIV with common NNRTI resistance mutations (K103N, Y181C, G190A, K103N/Y181C and E138K).
- Clinical trials report good efficacy among antiretroviral therapy–naive adults.
- NNRTI-resistance mutations emerged among seven of 747 (0.9%) participants in DOR Phase 3 trials.
  - The mutations observed included A98G, V106A, I or M, Y188L, H221Y, P225H and F227C/R.
  - Five of the seven had cross-resistance to EFV (phenotypic fold change in EC_{50} >3), three of seven to etravirine (fold change >2.9) and four of seven to rilpivirine (fold change >2).
- There are limited data on efficacy among NNRTI-experienced people and pregnant women.
- Rifampicin substantially affects DOR trough concentrations (cannot be co-administered), which would prevent its use in areas where TB coinfection rates are high.
- No comparative trials of DOR versus DTG (the current standard of care).
- Although potentially a promising option for antiretroviral therapy in low- and middle-income countries, insufficient safety data for pregnant women and NNRTI-experienced people and drug–drug interaction concerns for people with TB prevent considering its use broadly.

Summary of discussion

- In subtype C, V106M is a single nucleotide change. Is the resistance barrier lower for subtype C?
  - No increased rates of failure were observed in Phase 2 trials in geographical areas where subtype C is prevalent.
- Could DOR be used after TLE failure?
  - Depends on the NRTI backbone resistance; there are no data on efficacy if NRTIs are partly active (such as M184V). Maybe it could be used with a boosted PI for people with virus resistant to INSTI and NRTIs.
- Is DOR active against HIV-2?
  - Not aware of data on this, but DOR selects V106I and Y188L so this might indicate reduced activity against HIV-2.
SESSION 10: HOW CAN WE MONITOR PROGRESS IN ADDRESSING THE RESEARCH GAPS OF THE GLOBAL ACTION PLAN?

**Presenter:** Roger Paredes, IrsiCaixa AIDS Research Institute, Spain

**Summary of key points**

- The tasks assigned to Working Group 3 (Research and Innovation) of the HIVResNet are:
  - to 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; and
  - to collate and interpret evidence related to specific questions of public health importance, such as the WHO surveillance drug resistance mutations list, clinical relevance of low-abundance drug-resistant variants and how HIV drug resistance affects treatment outcomes.

- The 2017 HIVResNet meeting generated a long list of priority research questions.

- HIVResNet Working Group 3 plans to implement the tasks listed above by:
  - assessing the progress made in filling the various gaps (peer-reviewed publications, abstracts at meetings); and
  - promoting innovative research to address tier 1 questions.

- The level of sophistication for tools, compendia etc. will depend on the funding available.

- Link to United States National Institutes of Health requests for applications, collaborations and repository for new procedures, such as whole-genome sequencing for non-INSTITI resistance, PI/r etc.

**Summary of the discussion**

- The United States National Institutes of Health has funded several groups working on topics such as:
  - clinical significance of low-abundance drug-resistant variants;
  - suppression of viral loads on antiretroviral therapy despite drug resistance;
  - treatment failure with no in vitro phenotypic resistance; and
  - correlations between genotype, phenotype and outcome.

- Need to have a specimen repository – call for collaborations via the Working Group?
## ANNEX 1. MEETING AGENDA

### 21 October 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30</td>
<td>Welcome and introductions</td>
<td>Silvia Bertagnolio, WHO</td>
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<tr>
<td>8:40</td>
<td>What is new in WHO HIVResNet?</td>
<td>Silvia Bertagnolio, WHO</td>
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<tr>
<td>9:10</td>
<td><strong>Session 1: Sanger versus next-generation sequencing:</strong> optimal reporting thresholds for comparability and reproducibility</td>
<td>Neil Parkin, Data First Consulting, WHO consultant</td>
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<tr>
<td>9:25</td>
<td>Discussion</td>
<td>All (moderator: Tamyo Mbisa, Public Health England)</td>
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<tr>
<td>9:35</td>
<td><strong>Session 2: Could a more affordable genotyping test affect its use in clinical practice in low- and middle-income countries and how?</strong></td>
<td>Gillian Hunt, South Africa National Institute of Communicable Diseases</td>
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<tr>
<td>9:55</td>
<td>Discussion</td>
<td>All (moderator: Emily Hyle, Massachusetts General Hospital)</td>
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<tr>
<td>10:25</td>
<td><strong>Session 3: What is the risk of HIV drug resistance emerging among pre-exposure prophylaxis (PrEP) users in low- and middle-income countries?</strong></td>
<td>John Mellors, University of Pittsburgh</td>
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<tr>
<td>10:40</td>
<td>Discussion</td>
<td>All (moderator: John Mellors)</td>
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<td>10:55</td>
<td>Break</td>
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<td>11:05</td>
<td><strong>Session 4: Dolutegravir roll-out in the context of non-nucleoside reverse-transcriptase inhibitor (NNRTI) pretreatment HIV drug resistance</strong></td>
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<td>11:05</td>
<td>DTG roll-out in PEPFAR-supported countries</td>
<td>Elliot Raizes, United States Centers for Disease Control and Prevention</td>
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<tr>
<td>11:15</td>
<td>DTG and country response to pretreatment HIV drug resistance</td>
<td>Silvia Bertagnolio, WHO</td>
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<td>11:25</td>
<td>How do pretreatment HIV drug resistance survey data inform national antiretroviral therapy guidelines? Experience from Uganda</td>
<td>Christine Watera, Ministry of Health, Uganda and Uganda Virus Research Institute</td>
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<tr>
<td>11:40</td>
<td>Discussion</td>
<td>All (moderator: John Mellors)</td>
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<tr>
<td>12:00</td>
<td>Lunch</td>
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<tr>
<td>13:00</td>
<td><strong>Session 5: How can HIV drug resistance inform antiretroviral therapy switching strategy options?</strong></td>
<td>Lara Vojnov and Silvia Bertagnolio; WHO</td>
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<tr>
<td>13:20</td>
<td>Programmatic considerations on implementing the viral load algorithm: experience from Uganda</td>
<td>Christine Watera, Ministry of Health, Uganda and Uganda Virus Research Institute</td>
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<tr>
<td>13:30</td>
<td>Considerations on using a single viral load to trigger switch among people for whom NNRTI-based antiretroviral therapy has failed: a modelling exercise</td>
<td>Amir Shroufi, Médecins Sans Frontières</td>
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<td>13:45</td>
<td>Viral load resuppression among people receiving EFV with and without acquired drug resistance at first elevated viral load</td>
<td>Suzanne McCluskey, Harvard Medical School</td>
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<td>14:00</td>
<td>Viral load resuppression among people receiving second-line PI-based antiretroviral therapy with and without acquired drug resistance</td>
<td>Lucas Hermans, University Medical Center Utrecht</td>
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<tr>
<td>14:15</td>
<td>Discussion</td>
<td>All (moderator: John Mellors)</td>
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<td>Time</td>
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<td>14:40</td>
<td><strong>Session 6: How do we interpret integrase genotypes for DTG?</strong></td>
<td>Robert Shafer, Stanford University</td>
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<td>15:00</td>
<td>Discussion</td>
<td>All (moderator: Annemarie Wensing, University Medical Center Utrecht)</td>
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<td>15:20</td>
<td><strong>Session 7: What are the challenges and knowledge gaps related to the use of integrase strand-transfer inhibitors (INSTIs) in low- and middle-income countries?</strong></td>
<td>Dan Kuritzkes, Brigham and Women’s Hospital</td>
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<td>15:50</td>
<td>Discussion</td>
<td>All (moderator: Dan Kuritzkes)</td>
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<td>16:20</td>
<td>Break</td>
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<tr>
<td>16:35</td>
<td><strong>Session 8: Country experience with DTG, viral failure and drug resistance</strong></td>
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<td>16:35</td>
<td>Experience from Brazil</td>
<td>Ricardo Diaz, Federal University of São Paulo</td>
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<td>16:45</td>
<td>Experience from Kenya</td>
<td>Evelyn Wangari, United States Centers for Disease Control and Prevention, Kenya</td>
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<td>16:55</td>
<td>Experience from Botswana</td>
<td>Ava Avalos, Careena Centre for Health</td>
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<tr>
<td>17:05</td>
<td>Discussion</td>
<td>All (moderator: John Mellors)</td>
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<tr>
<td>17:20</td>
<td><strong>Session 9: Doravirine and new drugs in the pipeline: HIV drug resistance profile and potential role in HIV treatment in low- and middle-income countries</strong></td>
<td>Dan Kuritzkes, Brigham and Women’s Hospital</td>
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<tr>
<td>17:35</td>
<td><strong>Session 10: How can we monitor progress in addressing the research gaps of the Global Action Plan?</strong></td>
<td>Roger Paredes, IrsiCaixa AIDS Research Institute</td>
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<tr>
<td>17:55</td>
<td>Discussion</td>
<td>All (moderator: John Mellors)</td>
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<tr>
<td>18:15</td>
<td>Summary of the discussion</td>
<td>John Mellors, University of Pittsburgh</td>
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<td>18:30</td>
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**ANNEX 2. LIST OF PARTICIPANTS**

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<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>City</th>
<th>Country</th>
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<tbody>
<tr>
<td>Elfriede Agyemang</td>
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<tr>
<td>Ava Avalos</td>
<td>Careena Centre for Health</td>
<td>Gaborone</td>
<td>Botswana</td>
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<td>Solange Baptiste</td>
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<td>Trinidad and Tobago</td>
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<td>George Bello</td>
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<td>Silvia Bertagnolio</td>
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<td>Mohamed Chakroun</td>
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<td>Fatim Cham</td>
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<td>Joy Chang</td>
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<td>Keith Crawford</td>
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<td>Gillian Hunt</td>
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<td>Emily Hyle</td>
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<tr>
<td>Hezhao Ji</td>
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<td>Michael Jordan</td>
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<td>Pontiano Kaleebu</td>
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<td>David Katzenstein</td>
<td>Stanford University</td>
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<tr>
<td>Shaukat Khan</td>
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<td>Boston, MA</td>
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<td>Anneleen Kiekens</td>
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<tr>
<td>Dan Kuritzkes</td>
<td>Brigham and Women’s Hospital and Harvard Medical School</td>
<td>Boston, MA</td>
<td>USA</td>
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<td>Swarali Kurle</td>
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<td>Johanna Ledwaba</td>
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<td>Tamyo Mbisa</td>
<td>Public Health England</td>
<td>London</td>
<td>UK</td>
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<td>Suzanne McCluskey</td>
<td>Massachusetts General Hospital, Harvard Medical School</td>
<td>Boston, MA</td>
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<tr>
<td>Kevin McCormick</td>
<td>University of Pittsburgh</td>
<td>Pittsburgh, PA</td>
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<td>John Mellors</td>
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<tr>
<td>Anita Mesic</td>
<td>Médecins Sans Frontières</td>
<td>Amsterdam</td>
<td>Netherlands</td>
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<td>Kiren Mitruka</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>Michelle Moorhouse</td>
<td>Wits Reproductive Health and HIV Institute</td>
<td>Johannesburg, Gauteng</td>
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<td>Mahomed-Yunus Moosa</td>
<td>University of KwaZulu-Natal</td>
<td>Durban</td>
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<td>Fausta Mosha</td>
<td>WHO Regional Office for Africa</td>
<td>Harare</td>
<td>Zimbabwe</td>
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<tr>
<td>Sikhulile Moyo</td>
<td>Botswana-Harvard AIDS Institute Partnership</td>
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<td>Nuttada Panpradist</td>
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<td>Roger Paredes</td>
<td>IrsiCaixa AIDS Research Institute</td>
<td>Badalona, Catalonia</td>
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<td>Neil Parkin</td>
<td>Data First Consulting</td>
<td>Belmont, CA</td>
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<td>Atlanta, GA</td>
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<td>Andrew Phillips</td>
<td>University College London</td>
<td>London</td>
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<tr>
<td>Elliot Raizes</td>
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<td>Atlanta, GA</td>
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<td>Winnipeg, MB</td>
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<td>Robert Shafer</td>
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*Via WebEx.*
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www.who.int/hiv