HIV DRUG RESISTANCE

WHO HIVRESNET MEETING REPORT

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JOHANNESBURG, SOUTH AFRICA, 11–12 NOVEMBER 2017

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EXECUTIVE SUMMARY

The WHO HIVResNet met on 11–12 November 2017 in Johannesburg, South Africa. The following list summarizes major consensus points.

Use and sequencing of dolutegravir (DTG) in low- and middle-income countries

- DTG is a potent integrase inhibitor. DTG is highly potent for treatment-naive individuals, and little HIV drug resistance is expected to emerge if adequate adherence is maintained.
- Data are lacking on DTG use in settings with limited or no viral load monitoring. Programmatic issues such as drug stock-outs can result in poor adherence and can subsequently lead to emergence of DTG resistance.
- The substitution of DTG for efavirenz (EFV) for people already taking EFV-based first-line antiretroviral therapy (ART) is ideally accompanied by viral load testing. The risk of viral failure and the subsequent emergence of HIV drug resistance among people with viral suppression is likely to be minimal. However, for people with viral non-suppression, the probability of dual resistance to both tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC) may be high (50% based on the TenoRes study). Because of lack of data on long-term viral suppression outcomes among people with TDF + 3TC resistance who are receiving DTG-based ART, switching to a ritonavir-boosted protease inhibitor (PI) is preferable. Alternatively, using DTG with an optimized backbone (based on the results of HIV drug resistance testing, if available) may be considered.
- In settings in which viral load test results are unavailable at the time of a planned substitution of TDF + 3TC plus EFV to TDF + 3TC plus DTG, the most prudent choice is to wait for viral load test results to avoid a change to functional monotherapy or to use DTG with an optimized nucleoside reverse-transcriptase inhibitor (NRTI) backbone (Table 1).
- Based on the available evidence, the genetic barrier to resistance of DTG appears to be higher than that of non-nucleoside reverse-transcriptase inhibitors (NNRTI) but lower than that of ritonavir-boosted PIs. However, this genetic barrier may not necessarily correlate directly with the drug's effectiveness, and more research is needed to answer this question.

Recommended approach to DTG transition for people receiving TDF + 3TC plus EFV

Viral load	Recommendation from HIVResNet
<1000 copies/ml[a]	Stay on EFV-based ART or replace EFV with DTG (TDF + 3TC plus DTG)
Unknown	Stay on EFV until viral load is determined or use zidovudine (AZT) + 3TC plus DTG
Unknown but clinically failing	Switch to a PI plus AZT + lamivudine (3TC) (or a PI plus TDF + 3TC) or DTG plus AZT + 3TC
>1000 copies/ml	Switch to a PI plus AZT + 3TC (or a PI plus TDF + 3TC) or DTG plus AZT + 3TC

[a] The group noted a potential issue among people with viraemia with viral load <1000 copies/ml and with K65R.

- As DTG is introduced in low- and middle-income countries, viral and drug resistance outcomes need to be closely monitored; thus, HIV drug resistance surveillance remains critical to inform care and treatment guidelines and programme functioning.
  - Surveillance of pretreatment HIV drug resistance is important to establish baseline polymorphic profiles of the integrase gene in HIV-1 non-subtype B, which may be associated with DTG clinical response or non-response in various subtypes and populations. Ongoing assessment of NRTI pretreatment drug resistance will remain important and relevant both for its possible and as yet unknown impact on ART based on DTG plus two NRTIs and to measure the population burden of NRTI resistance caused by pre-exposure prophylaxis with TDF + 3TC.
  - Surveillance of acquired HIV drug resistance and robust nationally representative measures of viral load suppression and retention are critical to assess programme functioning with respect to DTG roll-out and viral and HIV drug resistance outcomes.

Potential use of HIV drug resistance testing for managing people living with HIV in low- and middle-income countries

WHO currently recommends using HIV drug resistance testing for people for whom second-line ART based on darunavir/ritonavir is failing after using DTG-based first-line ART.

Potential use of HIV drug resistance testing for managing people living with HIV in low- and middle-income countries

ART scenario	Purpose
Failure of DTG-based ART	To minimize unnecessary switching (if there is no integrase inhibitor drug resistance)
Failure of PI-based ART	To minimize unnecessary switching (if there is no PI drug resistance)
Start of EFV-based ART	To assess EFV resistance in countries with no access to DTG

In the future, as HIV drug resistance testing becomes more widely available, its use should be linked to clearly definable actions by health-care workers. In addition, consideration should be given to whether or not the same action could be taken without resistance testing.

A future role of HIV drug resistance testing could be considered in the following priority groups of people.

Other potential groups were considered for future HIV drug resistance testing: (1) people starting DTG-based ART, to minimize functional DTG monotherapy; (2) people starting PI-based ART, to minimize functional PI monotherapy; and (3) people starting DTG-based ART with previous use of raltegravir (RAL) who may have acquired DTG resistance due to RAL exposure.

Point-mutation assays and point-of-care assays

- A point-mutation assay developed as a point-of-care assay would provide several theoretical advantages to people living with HIV, health-care providers and health-care programmes.
- Pilot studies and clinical outcome data are needed to establish whether the potential advantages of point-mutation assays, implemented following a centralized point-of-care assay or near-point-of-care assay model, outweigh the disadvantages for various applications.
- Because point-mutation assays detect only a subset of possible resistance mutations, they are unlikely to be suitable for surveillance applications in which the full-length sequence is needed to capture data on all mutations and to detect transmission networks.
- Further research areas identified for point-of-care assays and point-mutation assays include:
  - impact assessment studies and operational research to guide the placement of point-of-care resistance tests;
  - evaluating training needs, developing monitoring and implementation guidelines for using point-of-care point-mutation assays in low- and middle-income countries, developing global quality assurance and quality control parameters for point-mutation assays and developing external quality assurance for validating assays;
  - considering sustainability, supply-chain management and market demands, especially in countries investing heavily in centralized HIV drug resistance testing; and
  - integrating viral load and drug resistance tests into point-of-

care point-mutation assays, in which the viral load is measured first and drug resistance is reflexively tested among individuals with viral failure. This testing algorithm could reduce costs, since most of the people living with HIV are expected to have viral suppression.

HIV-1 integrase resistance testing

- Increasing laboratory capacity within the WHO HIVResNet laboratory network to genotype the integrase region of HIV-1 for surveillance purposes is important, since integrase inhibitors are rolled out widely in low- and middle-income countries.
- The minimum region of HIV-1 integrase to be genotyped for surveillance purposes was defined as codons 51 to 263.
- Participants generally agreed that, when conducting surveillance, there is no cost benefit in excluding the protease region during sequencing, since data on PI resistance still needs to be accumulated.

Next-generation sequencing

- Within the WHO HIVResNet laboratory network, any laboratory considering a transition to next-generation sequencing should first assess the need. No laboratory needs to rush to implement it. Any assessment for readiness for transition to next-generation sequencing should include: testing volume, laboratory capacity and the development by the WHO HIVResNet of standard operating procedures and methods for HIVResNet labs.
- Laboratories should not report variants presenting at less than 15% in a specimen
- A guidance document should be developed to elaborate standardized next-generation sequencing methods (wet laboratory and data analysis) to enable the comparability of results between laboratories. WHO is well positioned to lead this activity, and this document should build on the strengths and limitations of next-generation sequencing outlined above. A subgroup of HIVResNet laboratory members and researchers have begun this work.
- Opportunity exists to engage in dialogue with manufacturers of next-generation sequencing to reduce costs.

Dried blood spot (DBS) and HIV drug resistance testing

- Plasma can be promoted as the gold standard; however, when use of plasma is not feasible, DBS may be used as specimens for an HIV drug resistance survey. However, when DBS are used for surveys, the survey sample size should be increased to account for an amplification failure rate that is larger than anticipated.
- DBS are an important alternative to plasma for genotyping. WHO has developed guidance on collecting, processing and storing DBS. Although WHO's standard operating procedures on DBS collection, processing, storage and handling are largely adequate, proper implementation in the field must be more strongly emphasized. Current guidance recommends that DBS be stored at room temperature with desiccant and humidity indicator for a maximum of 14 days from the day of collection to storage at –20 °C or –80 °C. Based on survey data, it was suggested that the guidance document