WHO EXPERT MEETING ON SHORT-TERM HIV DIAGNOSIS, TREATMENT INITIATION & MONITORING TECHNOLOGIES AND APPROACHES

Geneva, Switzerland
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The World Health Organization (WHO), with support from the Pangaea Global AIDS Foundation, and funding from the Bill & Melinda Gates Foundation, convened a meeting of experts in HIV diagnostics and HIV-related tests, to identify short-term optimization priorities for WHO and its partners in the scale-up of HIV serological diagnosis, HIV treatment initiation and treatment monitoring.

For this meeting, “short term” was defined as a 1-3 year timeframe, and the overall goal of the meeting was to identify the obstacles, challenges and opportunities to improve delivery of currently available laboratory technologies for HIV diagnosis, treatment initiation and treatment monitoring in resource-limited settings.

In particular, two specific objectives were set:

1. To define the principles and priorities for optimizing HIV diagnosis, treatment initiation & monitoring, utilizing currently available laboratory technologies.

2. To identify and propose strategies to overcome obstacles to the timely implementation of these priorities and principles, including (but not limited to) quality assurance, regulatory approval, cost, available international and national funding, lack of sufficient normative guidance, product manufacturing scale up, required healthcare capacity and accessibility

The recommendations of this meeting are intended to inform the development of WHO’s normative guidance to countries on how to make best use of existing diagnostic and testing technologies and approaches, as well as to provide some initial guidance to assay developers, policy makers, procurers and users on future strategies.

Treatment 2.0

The meeting was part of WHO’s commitment to the broader Treatment 2.0 Initiative, coordinated by WHO and the UNAIDS Secretariat, which aims to achieve radical simplification of all aspects of HIV treatment, including drugs, diagnostics and healthcare delivery systems, to reduce costs and to mobilize communities towards greater engagement in programme design and implementation in resource poor settings. Treatment 2.0 focuses on short – (1 to 3 years), medium – (4 – 6 years) and long – (7 to 10 years) term objectives to achieve and sustain universal access to treatment for all who need it and maximize the preventative benefits of HIV treatment.
Meeting Approach

While many of the priorities set out in this report have been identified previously, discussion at this meeting centered on key actions the WHO and other stakeholders can take immediately to improve the critical diagnostic elements of the HIV treatment and care continuum: HIV diagnosis, Antiretroviral treatment (ART) initiation, and ART monitoring.

While specific recommendations for each of these components were developed, three priorities stood out as common to all components:

| a) Strengthen processes of regulatory approval for diagnostics at the global and national level towards more rapid, transparent and consistent mechanisms |
| b) Provide timely, relevant normative guidance to countries, on the selection and use of diagnostics |
| c) Strengthen mechanisms for quality assurance and quality control |

Meeting participants also identified a series of possible agenda items for a future strategy-setting meeting scheduled for the June 2012, to determine medium and longer-term priorities.
Scaling up access to accurate HIV diagnosis is key to expanding access to HIV treatment and care. While it was noted that laboratory-based tests for HIV diagnosis continue to be used in some settings, in this meeting, attention was focused on the role of point of care (PoC) rapid tests (RTs). There is a growing trend towards the use of RTs, which brings HIV testing closer to affected communities and hard-to-reach populations, provides on-the-spot results and improves the likelihood of clients getting linked to HIV care and prevention services. At the same time, in clinical practice PoC rapid testing poses challenges in terms of the quality of tests themselves and consistency of use, including result reading and interpretation. Nonetheless, there was clear consensus that WHO needs to prioritize prequalification of RTs as well as systems for post-market surveillance of RTs to ensure that quality standards are maintained. In addition, all stakeholders need to ensure better systems to improve quality assurance (QA) and quality control (QC) procedures for rapid testing services. Specific discussion focused on three areas:

- Ensuring quality of services using PoC Testing
- Updating WHO guidance on testing strategies
- Opportunities for multi-disease diagnosis at PoC

A.1 Ensuring Quality of Services using PoC HIV Diagnostic Tests

**Key Recommendations**

- The WHO Prequalification Program for HIV rapid tests should be supported with the necessary resources, to conduct regular, robust and more timely evaluations of RTs. The results of these should be disseminated to both countries and procurement agencies
- In particular, the WHO Prequalification Program should address the current back-log of applications and review and consider for approval 10 to 15 products within a 1 year timeframe
- The WHO and other stakeholders should provide practical guidance to country policy makers, implementers and manufacturers on HIV RT selection, quality assurance/quality control and post market surveillance, to improve the reliability of current testing systems
Discussion

A key challenge for WHO is how to speed up the review of RT dossiers currently submitted for prequalification. The group considered that endorsement of a product class as a normative recommendation (rather than through pre-qualification of a specific product), might be one way to provide rapid guidance to countries. Above all, however, the commitment from the WHO to strengthen the capacity, speed and transparency of its Prequalification of Diagnostics Programme was considered indispensable.

In order to improve quality assurance/quality control of rapid tests and HIV testing services, the group considered that WHO should strengthen its support to implementers of grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), as well as provide technical assistance to the Global Fund’s Technical Review Panel on how to review applications containing QA/QC elements. The group recognized the value of simplified approaches to proficiency testing such as the use of control sera as dried tube specimens (DTS) using the approach developed by the CDC, and encouraged wider adoption of such approaches by stakeholders responsible for national level QA. In addition, RT result readers were discussed as a potentially useful way to make results reporting more objective as well as to better capture data on testing services.

A.2 Updating WHO guidance on testing strategies

**Key Recommendation**

- WHO should finalize and publish revised guidance on testing strategies for HIV diagnosis as soon as possible. This guidance should also include information to support national programmes in the selection of specific products and classes of products for use in national algorithms

Discussion

The group noted that country programmes are increasingly using RTs, but often without a clear understanding of which tests are appropriate for screening versus confirmation. As normative guidance on appropriate testing strategies is updated, WHO should send a strong message in support of the use of RTs, while recognizing that laboratory-based HIV testing services will still be important in some settings for both initial and confirmatory testing. It was recommended that WHO should seek to define the types of settings and users that could implement PoC HIV testing.
A.3 Multi-Disease Diagnosis

**Key Recommendation**

- Stakeholders should be encouraged to implement and gather evidence on the use of HIV testing combined with testing for other relevant diseases such as viral hepatitis, tuberculosis and syphilis
- WHO should call for a mapping of diagnostic needs and identify tests that could be “bundled” with HIV testing, in order to provide guidance on what types of such bundles need to be developed

**Discussion**

The group considered that there are opportunities to enhance the quality of care for people living with or at risk of HIV, by linking or “bundling” HIV testing with testing for co-morbidities such as tuberculosis (TB), syphilis and hepatitis B and C. In addition for patients who may be in need of treatment it may be valuable to bundle haematology and clinical chemistry testing with HIV testing. The group recommended that WHO should call for a mapping of diagnostic needs to identify tests that could be “bundled” with HIV testing, based on different regional patterns of disease.

The CD4 cell count is a key criterion for determining when to initiate antiretroviral therapy. While, laboratory-based CD4 counting has been essential to the scale up of HIV care services, recently developed PoC CD4 counting technologies offer the potential to further expand access to care. As HIV treatment is decentralized to settings where laboratory infrastructure is limited, PoC CD4 testing may enable health workers in lower tiers of the health system to initiate ART. The group focused its discussion on the role WHO can play in supporting timely prequalification assessment and programmatic implementation of these new technologies. Discussion centered on three areas

- Regulatory issues
- Improving access through normative guidance
- New technologies market identification and development.
B.1 PoC CD4 Regulatory Issues

Recommendations

- WHO should develop a rapid conditional prequalification mechanism for PoC CD4 Tests, and other diagnostic assays that meet key criteria. Conditional prequalification should follow after dossiers have been reviewed and site inspections performed.
- WHO should provide greater clarification to PoC CD4 assay developers and manufacturers on the prequalification assessment process (including the new conditional prequalification mechanism).

Discussion

While participants agreed that faster WHO prequalification is relevant for all HIV-related tests, the group identified a pressing and urgent need to develop a conditional prequalification mechanism to enable rapid approval of innovative testing platforms – such as PoC CD4 technologies. The intent of conditional prequalification would be to provide an interim WHO assurance of quality based on dossier review and site inspection. In order to be considered for conditional prequalification, the assay should be uniquely suited to filling an identifiable and critical public health need.

Once the conditional prequalification mechanism is better defined, this should be clearly communicated to assay developers, procurers and end users, including national regulatory authorities.

WHO should provide support to developers on dossier submission and clear guidance on how to undertake the required validation studies. This guidance will draw from existing institutional standards for the clinical evaluation of *in vitro* diagnostics. The group also noted that it is important to define operational benchmarks for rates of result misclassification and invalid readings when evaluating the performance characteristics of new assays.

Finally, given the importance of these recommendations, the group recommended that the WHO establish an internal working group (including the involvement of key external experts) to oversee and assist in the implementation of these recommendations.
B.2 Improving Access Through Timely, Relevant Normative Guidance

**Key Recommendations**

- WHO should provide rapid, normative guidance on the implementation of PoC CD4 cell count testing for countries
- WHO should recommend the review and updating of the 2008 Maputo Declaration on Strengthening Laboratory Systems, to include PoC CD4 Testing for HIV treatment initiation

**Discussion**

Better normative guidance from WHO should set out the criteria to determine what type of CD4 cell counting technology (including PoC and laboratory-based) is best to use in specific settings, (such as tertiary hospitals, antenatal clinics and rural health centres) with differing staff capacities and infrastructure, including stable electricity and availability of specimen collection, packaging and transport.

Participants also considered that as part of this guidance, WHO should recommend that in high burden countries, all secondary level facilities should have on-site CD4 testing availability, with a quality management programme and access to maintenance, service and reagents supply.

B3. Market Identification and Development

**Key Recommendations**

- In addition to rapid normative guidance, WHO should coordinate the development of a country-targeted decision-making framework for policy makers, which would set out the relative technical and cost benefits of various CD4 cell counting technologies
- WHO should advocate with international partners, particularly UNITAID, to identify opportunities to support the expansion of the global CD4 test market

**Discussion**

Included in the development of a decision-making framework for policy makers coordinated by WHO, should be:

- comprehensive and comparative costing of different CD4 tests
- identification of the appropriate use of CD4 testing for treatment monitoring as well as treatment initiation
- the appropriate performance characteristics of CD4 tests
- guidance for incorporation into existing laboratory networks and
relevance to the implementation of important national strategic objectives for HIV service delivery (for example, increased access to CD4 testing for pregnant women, achievement of universal treatment coverage, or prioritization of key affected populations).

The group noted that UNITAID could play a key role in helping to shape an expanded CD4 test market, using its expertise in helping to identify greater efficiencies in existing and future funding streams, innovative distribution, supply and equipment maintenance models, and the appropriate and efficient use of different product specifications.

The group considered that WHO should collaborate with partners to define more accurately the current, potential CD4 global market. Such a definition would include the total current market served, a projection of the total market potentially currently available, and potential equipment placement at HIV treatment sites that have adequate infrastructure and staffing.

The initial focus of global access to HIV treatment programs has been on the scale-up of first line therapy, bringing ARVs to those most in need. However, as programmes mature there is an increasing need to have access to accurate treatment monitoring. Treatment monitoring is essential to determine if first line therapy is working and to decide when to switch to a second line regimen. While current WHO guidelines emphasize the role of CD4 tests in monitoring the effectiveness of HIV treatment, viral load (VL) testing is standard of care in resource rich countries. The focus of discussion was on how to support the WHO in anticipating and helping countries prepare for new simplified (including PoC) VL testing technologies that are in advanced stages of development. The group centered its recommendations on

- Scaling-up access to current VL testing approaches
- Identifying target product profiles for PoC VL in different settings
- Managing longer term expectations on the potential of viral load in treatment monitoring.
C.1 Scaling Up Access to Current Viral Load Testing Approaches

Key Recommendations

- WHO should provide guidance to countries on how to select and use existing VL technologies
- WHO should develop standardized QA/QC protocols for existing VL platforms
- WHO should undertake further evaluation of dried blood spot (DBS) specimen collection on all VL platforms that permit its use

Discussion

WHO’s guidance to countries on the selection and deployment of existing Viral Load tests should include instrumentation, reagents, consumables, equipment maintenance, throughput, staff training, sample collection & transportation, and speed of obtaining results. The relative benefits of rental contracts over the outright purchase of equipment should be considered, as should the comparative advantages of open, as opposed to closed VL systems.

The group discussed dried blood spot specimen (DBS) collection technologies that have emerged in recent years. As well as conducting further evaluations of existing technologies, it was suggested that WHO should work with companies to validate DBS protocols and better define the impact on test sensitivity associated with use of DBS for treatment monitoring. The potential role of DBS on market development over the medium term was discussed, with some participants suggesting that its reliance on centralized laboratory systems may impact efforts to promote PoC treatment monitoring approaches. However, it was recognized that in the short to medium term, DBS offers an opportunity to address some of the challenges posed by laboratory-based VL technologies. In addition, increased access to viral load test results would improve provider understanding of how to use viral loads in the management of people on ART.

C.2 Target Product Profiles of PoC Viral Load Tests

The group developed and reviewed the following proposed target product profile (TPP) of VL PoC tests for resource-limited settings.

<table>
<thead>
<tr>
<th>Minimum requirements (for deployment at secondary level facilities)</th>
<th>Ideal requirements (for deployment at primary level facilities or in the community)</th>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Power Supply</td>
<td>Built in UPS</td>
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</tr>
<tr>
<td></td>
<td>Rechargeable battery</td>
</tr>
<tr>
<td>Sample Type</td>
<td>Venous whole blood/DBS using venous whole blood &amp; capillary whole blood</td>
</tr>
<tr>
<td>Cost</td>
<td>Less than current Viral Load, approximately the same as current CD4 Test</td>
</tr>
<tr>
<td>Equipment</td>
<td>Equipment Analyzer</td>
</tr>
<tr>
<td></td>
<td>Dust/Heat resistant</td>
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<tr>
<td></td>
<td>No moving liquids</td>
</tr>
<tr>
<td>Time to Result</td>
<td>2 hours</td>
</tr>
<tr>
<td>Limit of Detection</td>
<td>500 to 1000 copies/mL Qualitative or Semi-quantitative assays may be an option</td>
</tr>
<tr>
<td>Batching</td>
<td>Batched</td>
</tr>
<tr>
<td>Temperature/Stability</td>
<td>30°C Operation Ø cold chain</td>
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**Discussion**

In further articulating a PoC VL TPP, it was recommended that WHO and its partners engage now with developers of these new technologies – with a particular focus on validating what may be possible over the medium to long term, given technological limitations and opportunities.

In addition, it was considered that in informing temperature/stability components of the TPP, WHO should work with partners to collate data on storage and operating temperature conditions in clinics and laboratories, including the excursion ranges at which equipment and reagents are currently stored and distributed. It was noted that test stability at temperature extremes would be crucial. The TPP should also address throughput needs, and it was agreed that the WHO and other partners should work together to identify where patients are currently having viral load tests conducted and how many tests are run daily. It was also discussed that a more in-depth cost-
effectiveness analysis needs to be done to justify country investment in viral load testing versus additional treatment.

C.3 Managing Longer Term Expectations on the Potential of Viral Load in Treatment Monitoring

Key Recommendation

- WHO should develop a long-term framework for action to promote and prepare countries for the use of new viral load technologies

Discussion

The group noted that the role of VL has yet to be fully defined in monitoring treatment in resource-limited settings. The emergence of new PoC technologies will drive the extent to which VL is used over the medium to long term. Nonetheless, it was considered that WHO should play a leading role now in advocating for the importance of VL in the monitoring of HIV treatment. The recommendation that the WHO convene and coordinate with partners a global framework of action to promote VL has both a stakeholder mobilization component (including civil society and developers) and supports the Market Development and TPP recommendations set out earlier in the report. With partners such as UNITAID, the Global Fund and other cosponsors of UNAIDS, the WHO should propose a strategic phased implementation of VL testing, rooted in existing healthcare delivery system strengthening strategies. It should map laboratory capacity (including how to leverage EID, TB and private laboratories) and engage with the developers of emerging and existing technologies.
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