Partners Synergy Meeting (IV)

10-11 July 2018

Geneva, Chateau des Penthes

1. Acronyms

ABC	Abacavir
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
ASLM	African Society for Laboratory Medicine
CDC	United States Centers for Disease Control
CHAI	Clinton Health Access Initiative
CPHL	Central Public Health Laboratory (Uganda)
DBS	dried blood spot
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EID	Early infant diagnosis
EFV	Efavirenz
EQA	External quality assessment
FTC	Emtricitabine
GDWG	Global Diagnostics Working Group
HCV	Hepatitis C virus
HEI	HIV exposed infants
HIV	Human immunodeficiency virus
IQC	Internal quality control
INS	Instituto Nacional de Saude (Mozambique)
ISO	International Organization for Standardization
LPV/r	Lopinavir/ritonavir
LSHTM	London School of Hygiene and Tropical Medicine
LTFU	Lost-to-follow-up
MOH	Ministry of Health
MSF	Medecins Sans Frontieres
M&E	Monitoring and Evaluation
NAT	Nucleic acid test
NHLS	National Health Laboratory Service (South Africa)
NVP	Nevirapine
PCR	Polymerase chain reaction
PHIA	Population-based HIV impact assessments
PLHIV	People living with HIV
PMTCT	Prevention mother to child transmission (of HIV)
POC	Point of care
QMS	Quality management system
RAL	Raltegravir
RCT	Randomized controlled trial

RDT	Rapid diagnostic test
SLIPTA	Stepwise Laboratory Quality Improvement Process Towards Accreditation
STI	Sexually transmitted infections
TAT	Turnaround time
TB	Tuberculosis
TDF	Tenofovir
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VL	Viral load

2. Introduction

Despite major progress in the global HIV response over past 15 years, HIV continues to be a public health challenge in all regions, with inequitable coverage of diagnosis, prevention strategies and treatment with antiretroviral drugs (ARVs). Effective interventions and services need to be targeted to individuals and populations most in need, while maintaining quality and efficiency in rapidly expanding programmes. Ending the HIV epidemic is feasible given the tools currently available and in the pipeline. Evidence being generated from randomized clinical trials (RCTs), implementation research, and programmatic experience must be translated into global policy. This is essential for high burden countries as they look to implement and expand effective HIV programmes.

WHO recently developed three global health sector strategies to cover HIV, viral hepatitis, and sexually transmitted infections (STIs). The strategies cover the period 2016-2021 and were endorsed by the Sixty-ninth World Health Assembly on 28 May 2016. The HIV outline both impacts targets and service coverage targets towards elimination of AIDS by 2030, and are tools that will help accelerate the global response.

Since 2013, WHO has recommended VL as the preferred approach to monitoring ART, this recommendation was further endorsed in 2016. The 90-90-90 fast-track targets by UNAIDS have added momentum by including a target of measuring viral suppression (90% of PLHIV on ART) as a key measure of success by 2020. Without adequate treatment monitoring, including for patients with advanced HIV disease, all existing and forthcoming treatment options would be compromised and a switch to alternative, more expensive, regimens would remain inappropriate. However, with the exception of South Africa and Botswana, countries with a high burden of HIV in Africa currently have a limited capacity to provide viral load for all patients.

A similar situation exists for early infant diagnosis (EID) of HIV. Testing closer to the point of care offers potential solutions to address gaps in laboratory based testing services, including provision of same day results. New technologies and approaches are being developed and piloted that offer opportunities for further scale-up, and need to be supported with WHO guidance and prequalification. Direct enabling by WHO will facilitate findings from Unitaid and other donor supported diagnostic grants on implementation research of laboratory-based and point of care (POC) technologies for VL and EID to provide valuable evidence on effective delivery mechanisms and value for money.

To date only a few countries have started introducing WHO recommendations and some of the novel innovations. Therefore, sharing the experience of early adopters will help countries gain a better understanding of the operational challenges and best practices as they consider the implementation of new and innovative strategies.

WHO is planning to organize a synergy meeting with key stakeholders in diagnostics to find concrete ways on how to improve and increase access to high quality diagnostics and understand the key activities of Unitaid grantees and other key stakeholders to discuss and determine how they can be translated into public health policy and ultimately have global patient impact.

3. Objectives and expected outcomes

a. General objective

The overarching objective of this synergy meeting is to convene key diagnostic stakeholders to discuss current projects and innovations in HIV diagnostics in order to inform the development of best practices guidance to support public health policy change.

b. Specific objectives

i. To review and refine diagnostic asks for suppliers, partners, regulatory bodies, and countries within the High-Level Vatican Diagnostics Initiative
ii. To disseminate key outcomes and conclusions for diagnostic consideration from the Infant meeting in April 2018
iii. To review and discuss POC EID scale-up and transition to sustainable funding sources as well as key priorities to improve early infant diagnosis
iv. To review progress in conventional viral load testing scale-up and brainstorm future treatment failure (viral load) algorithms for consideration with current and future drug regimens
v. To introduce the need and potential approaches to managing patients with advanced HIV disease
vi. To discuss the multiplex technology pipeline, best implementation practices, and perspectives across multiple disease programs, including TB, HIV, hepatitis, and HPV
vii. To review benefits and challenges of current diagnostic technologies and target product profiles for current and future needs
viii. To discuss how ongoing projects fit within the broader research/implementation landscape, research priorities, and needs for future public health policy change

c. Expected outcomes

It is anticipated that the meeting will generate discussion and provide insights on optimal approaches to strategically introduce innovations and address related key operational challenges, best practices, and learnings from the experiences of early adopters.

Expected outputs from the meeting will include:

1. A meeting report detailing the proceedings of the meeting and its participants as well as any key consensus decisions
2. Finalization of point-of-care target product profiles for CD4 for advanced HIV disease identification and early infant diagnosis
3. Refinement of Table 4.10 in the 2016 Consolidated ARV guidelines
4. Study mapping and priorities for treatment failure (viral load) algorithms considering current and future drug regimens

5. An Implementation/Operational Framework to be developed with grantees over the duration of projects for consideration of ongoing projects in the context of best practices development

4. Participants

Participants were Unitaid diagnostics grantees, key partners (CDC, USAID, Gates, Global Fund), and government representatives from 4-5 countries in the African region.

5. Key Outcomes

Vatican Diagnostics initiative

In December 2018, and building on similar consultations hosted by the Holy See in April and May 2016, and in November 2017[1], His Eminence Peter Appiah Kodowo Cardinal Turkson, Prefect of the Dicastery for the Promotion of Integral Human Development, will convene a *High-Level Dialogue to Assess Progress on and Intensify Commitment to Scaling Up Diagnosis and Treatment of Paediatric HIV.* The overarching purpose of the proposed fourth *High-Level Dialogue to Assess Progress on and Intensify Commitment to Scaling Up Diagnosis and Treatment of Paediatric HIV* is to address bottlenecks that limit access to EID products and programs and to scale up strategies that can quickly identify HIV-exposed children and link them to testing and treatment services. Leaders of major diagnostic and pharmaceutical companies, multilateral organizations, governments, regulators, faith-based and other organizations directly engaged in services to children living with HIV, and other key stakeholders will participate in the consultation with the intention to make joint commitments. In preparation for the final meeting in December 2018, and upcoming dinner conversation at AIDS 2018 in Amsterdam, the commitments and asks of each stakeholder were discussed and revisions made.

Early infant diagnosis

The *2016 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* presented innovative approaches to diagnosis and treatment; however, to date only a few countries have started to implement these innovations. Following the WHO regional workshop in Johannesburg, South Africa (June 2017), an expert meeting was convened in April 2018 to provide insight and promote discussion on these matters.

Some key diagnostic areas were discussed, including:

- **Indeterminate range for more accurate EID testing**: Data indicate that in countries not implementing an indeterminate range for NAT and where MCTC rates are low (<5%), 12.5% (76% of 16.5%) of non-negative EID results could be false-positive on initial testing with affected infants being potentially started on lifelong treatment unnecessarily. **Therefore, WHO now recommends that an indeterminate range should**

[1] Action plan for scaling up early diagnosis and treatment of children and adolescents. Pontifical Academy of Sciences, Vatican City, 2017 November 17. http://www.pedaids.org/wp-content/uploads/2018/02/Rome_Action_Plan_2017.pdf

be used to improve the accuracy of all nucleic acid-based early infant diagnosis assays.[2] Based on available information at the time the guidelines were developed, the optimal indeterminate range is considered to be the equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay.

- **Confirmatory testing**: A cost-effectiveness analysis undertaken to assess the value of confirmatory testing in different scenarios highlighted that confirmatory testing is indeed cost- effective.[3] Without confirmatory testing, this analysis showed that in settings with MTCT rates similar to those of South Africa, more than 10% of infants initiated on ART may in fact be HIV-uninfected. Confirmatory testing of positive test results using a new sample, as per WHO guidelines[4], may avoid this occurrence, although this policy is not consistently implemented. **It remains critical that programs ensure all HIV-exposed infants are retained and tested appropriately throughout the entire exposure period and all infants with a positive result receive a confirmatory test on a new sample**. Further, POC EID testing technologies can be used to confirm positive test results.
- How to manage indeterminate test results as well as considerations for treatment interruption of infants with discordant test results
- Implementation of POC EID testing
- Considerations for birth testing
- **Simplifying the EID algorithm and 9-month test**: In light of the challenges and recent data on the performance of RDTs around 9 months of age, **consideration can now be given to replacing RDT at 9 months with NAT** in the interests of minimizing the challenges of interpretation and simplifying the infant testing algorithm (see Figure 1 for the revised simplified EID algorithm).

Details can be found in the *HIV diagnosis and ARV use in HIV-exposed infants: a programmatic update* within the AIDS Free toolkit.[5]

While strengthening the molecular testing network and addressing key barriers remain critical, CDC and PEPFAR highlighted several key priorities, including:

a) improving confirmatory testing after the initial positive NAT result
b) new infant testing indicator introduced to better track and link infants
c) expanded case finding
d) determining final infection status of infants, partly through indicator adoption
e) implementation of the viral load and infant virologic testing scorecard tool
f) integration of LCQI (lab continuous quality improvement)
g) introduction of innovative testing approaches:
    i. strongly support POC EID within an optimized laboratory network

[2] Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.18). http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

[3] Dunning L et al. The value of confirmatory testing in early infant HIV diagnosis programmes in South Africa: A cost-effectiveness analysis. PLoS Medicine. 2017;14(11):e1002446.

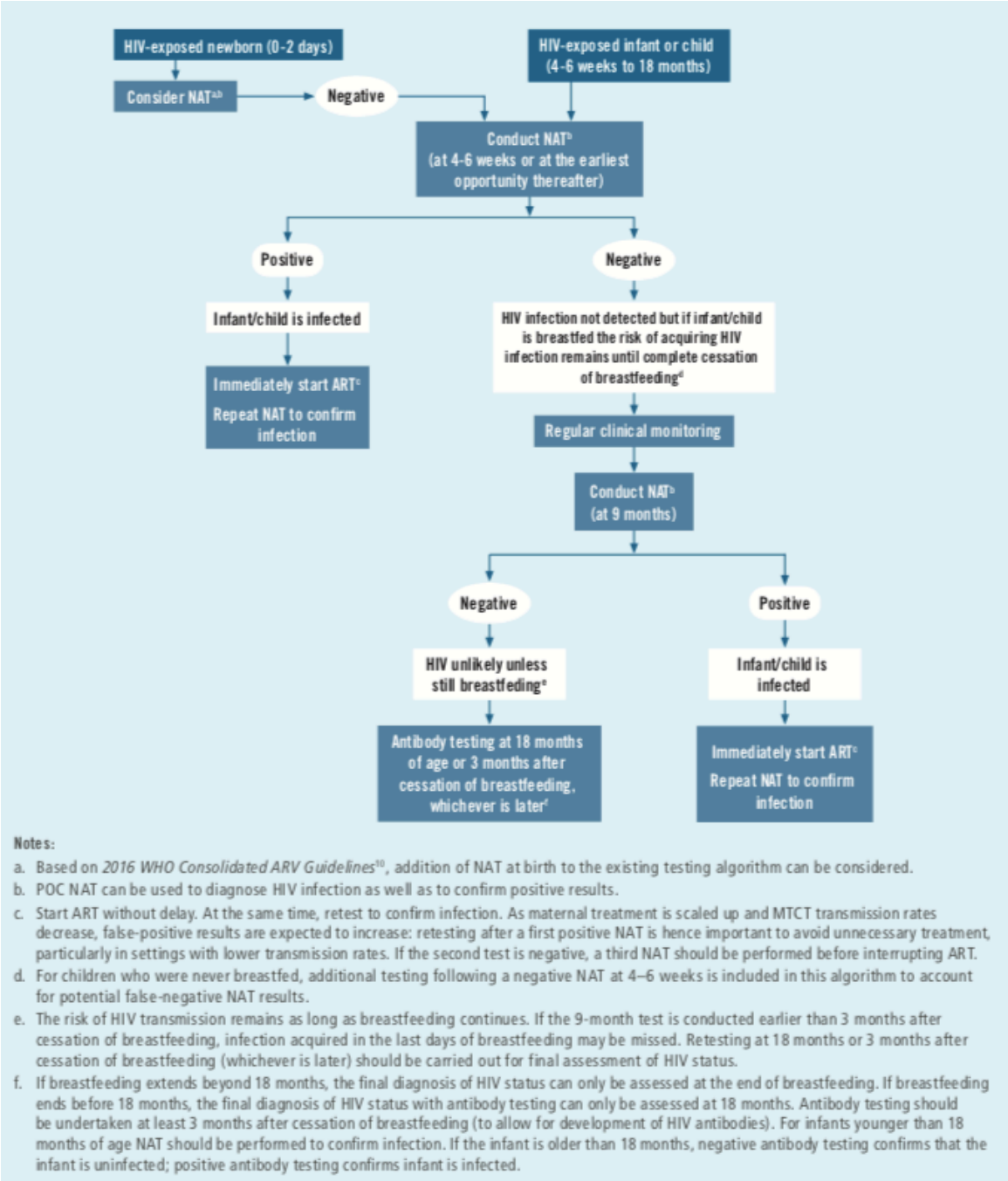
[4] WHO recommendations on the diagnosis of HIV infection in infants and children. Geneva: World Health Organization; 2010.

[5] AIDS Free toolkit: http://www.who.int/hiv/pub/paediatric/aids-free-toolkit/en/

ii. consideration for birth testing when 4-6 week EID coverage is high (>80%) and newborn treatment is available.

While the patient impact of implementing POC EID technologies has shown significantly improved turnaround times and treatment initiation rates, the cost-effectiveness and affordability of current technologies remains unclear. The Centre for International Economics has developed a costing model to provide a robust assessment of potential outcomes to help countries decide how to invest in POC EID. While it is still in development, the model will look at several scenarios of POC scale-up, including shifting conventional volumes to POC and expanding POC to increase EID coverage to 85%.

Figure 1. Revised and simplified early infant diagnosis algorithm.



Notes:

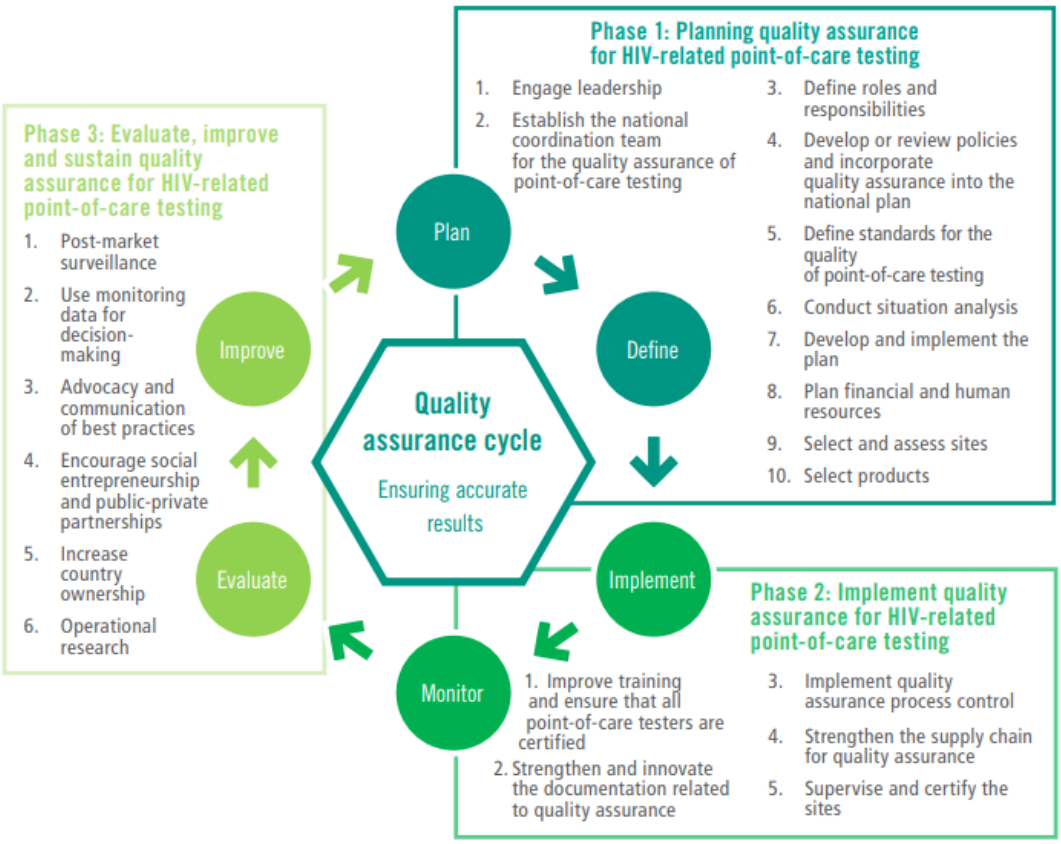
a. Based on *2016 WHO Consolidated ARV Guidelines*[10], addition of NAT at birth to the existing testing algorithm can be considered.
b. POC NAT can be used to diagnose HIV infection as well as to confirm positive results.
c. Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.
d. For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.
e. The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.
f. If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.

Source: *HIV diagnosis and ARV use in HIV-exposed infants: a programmatic update*, WHO 2018.

Through experiences with POC CD4, CHAI presented several critical pieces for consideration when implementing point-of-care technologies: product and site selection, training, mentorship, user certification, quality assurance (see Figure 2), connectivity and reporting, waste management, and supply chain management. Implementing POC CD4 increased access to on-site CD4 testing by 189% with successful implementation to a large national scale occurring under MOH leadership. Interestingly, >75% of devices across countries were still functional and operable four or more years after initial implementation. These lessons can be applied to implementation of additional POC

technologies, such as POC EID, which is expected to be implemented in at least 12 countries and 328 facilities by the end of 2018.

Figure 2. Quality assurance cycle: a continuous quality assurance and improvement process



Source: Improving the quality of HIV-related point-of-care testing: ensuring the reliability and accuracy of test results. WHO 2015.

Viral load

Viral load testing volumes have continued to increase considerably each year. Further, suppression rates are generally above 75% across countries (data from PHIAs and national databases); however, viral load testing coverage remains less than 60% in most countries. Unfortunately, viral suppression has been observed to be particularly low in children and adolescents (<70%). Several tools from the CDC and USAID exist to support various aspects of the viral load and EID testing cascades, including personnel, procurement & inventory, sample management, monitoring & evaluation, facility readiness, etc.[6] CDC has also developed enhanced adherence counselling materials.[7] Further, an interesting concept of viremia clinics was presented in which intensified support for all non-suppressed individuals are provided as well as case management for clients at risk or with viral non-suppression.

[6] AIDS Free USAID viral load and early infant diagnosis toolkit: https://aidsfree.usaid.gov/resources/vl-eid/
[7] US Centers for Disease Control Enhanced Adherence Counseling materials: https://www.dropbox.com/sh/o5z1lh0p8hakzy1/AAAcXy0TBCtzxzdcYBHB-GGGa?dl=0

The WHO treatment failure monitoring algorithm developed and recommended in 2013 was based on expert opinion and available drug regimens.[8] As drug resistance levels in some countries have risen and current and upcoming optimized ARVs have considerably different profiles, particularly with high barriers to drug resistance and better tolerability, it may be timely to review and modify the treatment failure monitoring algorithm.

There were several possible alternative options for the treatment failure algorithm discussed, including but not limited to:

- Treatment failure defined using only a single elevated viral load
- Earlier first viral load at 1 or 3 months after ART initiation
- Faster 2nd viral load after a 1st elevated viral load (1 month instead of the current 3 months)
- Faster return of viral load test results
- Lower threshold for treatment failure (undetectable/detectable or 400 copies/ml instead of the current 1,000 copies/ml)

Due to the differing drug resistance profiles of optimal ARVs, it may be possible that two treatment failure monitoring algorithms could be considered: one for patients on NNRTI-based regimens and another for patients on INI-based regimens. Several benefits and challenges were presented for each option, highlighting the need for further research:

- Currently, some variability exists in the treatment monitoring algorithm across countries, both with timing of tests and the threshold for determining treatment failure; however, approximately 50% of countries and the majority of high burden countries follow current WHO algorithm guidance.[9]
- One study has shown that a first viral load at 3 months results in superior virologic and treatment outcomes compared to a first viral load at 6 months.[10] However, it is worth better understanding whether an earlier first viral load may also result in more non-suppression observed if patients have not yet reached suppression with good adherence in the shorter timeframe, particularly with optimized ARVs.
- One study has been completed[11] and an additional in progress[12] to understand if the treatment failure threshold should be lowered. However, it is currently unknown if viral load testing using dried blood spot specimens or point-of-care technologies can accurately detect virus in those lower ranges. Furthermore, it is unknown if this phenomenon remains with patients on optimized ARVs.

[8] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.
[9] Putting HIV and HCV to the test: a product guide for point-of-care CD4 tests and laboratory-based and point-of-care HIV and HCV viral load tests; 3rd edition. MSF Access. July 2017. https://msfaccess.org/putting-hiv-and-hcv-test-3rd-ed-2017
[10] Kerschberger B et al. Superior virologic and treatment outcomes when viral load is measured at 3 months compared to 6 months on antiretroviral therapy.
[11] Hermans LE et al. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. Lancet Infect Dis. 2018 Feb;18(2):188-197.
[12] Amstutz A et al. SESOTHO trial ("Switch Either near Suppression Or THOusand") – switch to second-line versus WHO guided standard of care for unsuppressed patients on first-line ART with viremia below 1000 copies/mL: protocol of a multicenter, parallel-group, open-label, randomized clinical trial in Lesotho, Southern Africa. BMC Infect Dis. 2018 Feb 12;18(1):76.

- Faster results or second viral loads could be considered, especially for priority groups such as pregnant and breastfeeding women, children, adolescents, patients with advanced disease, etc.[13] Point-of-care viral load is one tool to support faster result provision. Several studies are ongoing to look at the impact of implementing POC VL.
- Finally, additional support structures could also improve viral load clinical utility and improved treatment monitoring including diagnostic integration using multidisease technologies, clinical reminders, mHealth patient alerts, strengthened clinical knowledge, and task-shifting of decision-making.

All of these studies will help inform future treatment failure monitoring algorithms; however, it will remain critical that key enablers remain to support drug switching, such as access to 2nd line treatment, decentralization and task-shifting of treatment services, remote switching decision support, and health care worker and client perceptions.

Advanced disease

There remains a significant burden of patients entering or re-entering care with advanced disease.[14] Tuberculosis and cryptococcal meningitis account for 50% of all AIDS-related deaths. Because of this, WHO released guidance in 2016 to support management of patients with advanced disease, including implementing a package of care.[15] Identification of patients with advanced disease relies primarily on using CD4 testing (CD4 < 200 cells/ul) as clinical and symptomatic screening can miss nearly 50% of those with advanced disease.[16]

MSF presented their experiences in implementing differentiated service delivery of stable patients in the community, primary health facility and hospital settings, as well as management of patients with advanced disease in similar settings.[17] A comprehensive package starting with an easy to use quantitative or semi-quantitative CD4 lateral flow assay will support quick and efficient identification of patients with advanced disease. This can then be followed by cryptococcal and tuberculosis testing using CrAg and TB-LAM tests, respectively. However, additional diagnostics are needed, such as to identify pneumocystis pneumonia, toxoplasmosis, and severe bacterial infections.

CHAI developed and presented initial forecasts for advanced disease diagnostics. Though viral load is being scaled up, CD4 is still recommended to support clinical management of patients. Therefore, 2018 demand for CD4 is expected to be 16 million tests. Nearly 82% of that volume will remain in 2022 for an expected 14 million CD4 tests. It is expected that the proportion of patients with advanced disease will remain flat at about 5.6 million patients/year; therefore, the forecast of additional diagnostics for these patients is forecasted to be between 2.7-

[13] Viral load monitoring resources, Southern Africa Medical Unit, Medecins Sans Frontieres: http://samumsf.org/en/resources/hiv/viral-load-monitoring

[14] Advanced HIV disease. Clinical Infectious Diseases supplement. 2018 Mar 4;66(suppl_2).

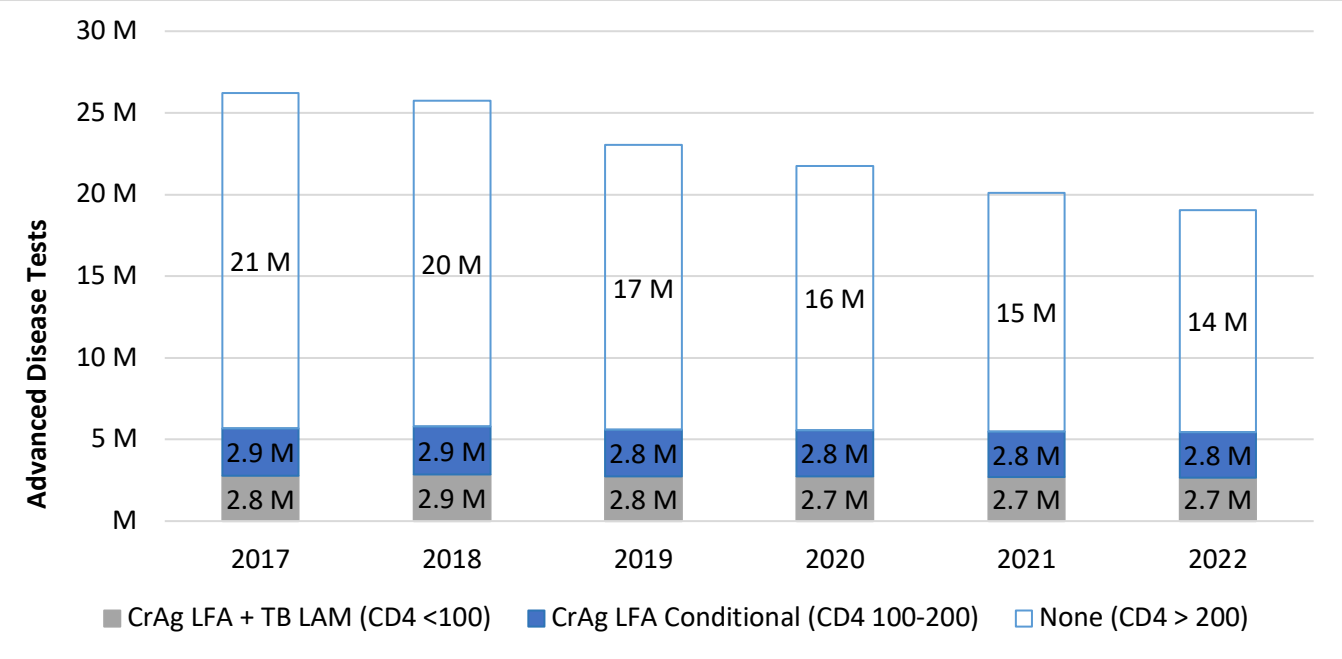
[15] WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; July 2017. http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

[16] Hakim J et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med. 2017 Jul 20;377(3):233-245.

[17] Advanced HIV disease resources, Southern Africa Medical Unit, Medecins Sans Frontieres: https://samumsf.org/en/resources/hiv/advanced-hiv-disease

5.6 million tests/year/test type. However, this need will only be met with increased funding and improved demand generation.

Figure 3. CrAg LFA and TB-LAM need per WHO guidelines – Global LMICs



Source: Clinton Health Access Initiative

Integration of diagnostic technologies

Several multidisease NAT technologies are on the market and in development, both for conventional laboratory and point-of-care settings.[18] Many of these technologies can test for several diseases on the same platform, including HIV (EID and viral load), tuberculosis, HCV viral load, and HPV. Key considerations for implementation of multidisease technologies were published in a joint document between the Global TB Programme and Department of HIV/AIDS at WHO.[19] Further, in order to maximum device utilization and investment and generate system efficiencies, a number of countries are moving towards integrating diagnostic services (Figure 4).

[18] Multi-disease diagnostic landscape for integrated management of HIV, HCV, TB and other coinfections. Geneva: Unitaid; January 2018.

[19] Considerations for adoption and use of multidisease testing devices in integrated laboratory networks. Geneva: World Health Organization; 2017.
http://www.who.int/tb/publications/2017/considerations_multidisease_testing_devices_2017/en/

Figure 4. Use of GeneXperts for diagnosing other diseases

Country (WHO classification)	Use of NTP GeneXpert for diagnosing other diseases (2017)	Other programs procuring GeneXpert machines (2016, 2017)	Implementation of Xpert Ultra cartridges in the public sector (2017)
South Africa	HCV VL, HIV-1 VL, HPV, NG/CT, C Diff, Carba R, Influenza	HIV, GXIV*	Procured and in use in the public sector
India	No	NA	In discussion**
Tanzania	HCV-VL, HIV-1 VL, HIV-1 qual/EID	No	Procured and in use in the public sector, plan to procure in 2018 (private sector)
Ethiopia	Piloting (HIV-1 qual/EID and HIV-1 VL)	Yes	Plan to procure in 2018
Kenya	No	No	Plan to procure in 2018
Nigeria	HCV-VL, HIV-1 VL, HPV, NG/CT	HIV	Plan to procure in 2018
Thailand	No	No	Do not have definitive plans
Myanmar	No	HIV, HCV	Procured but not yet in use in the public sector#
Philippines	No	No	Do not have definitive plans
Mozambique	No	No	Plan to procure in 2018
Pakistan	HCV VL, HIV-1 VL	No	Procured and in use in the public sector
Cambodia	NA	NA	Plan to procure
Viet Nam	No	NA	Plan to procure in 2018
Uganda	HIV-VL	NA	Plan to procure in 2018
DR Congo	No	No	Do not have definitive plans
Brazil	No	No	Plan to procure in 2018
Bangladesh	No	No	Do not have definitive plans
Russian Federation	NA	NA	Do not have definitive plans
Zimbabwe	HIV-1 VL, HIV-1 qual/EID	HIV	Procured, but not yet in use in the public sector
Afghanistan	No	No	Plan to procure in 2018
China	NA	NA	Do not have definitive plans

WHO: World Health Organization; NTP: National tuberculosis programme; HCV-VL: Hepatitis-C virus- viral load; HIV-VL: human immunodeficiency virus- viral load; HPV: human papilloma virus; NG/CT: Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT); C Diff: Clostridium Difficile; Carba R: Carbapenem resistance; Influenza: Detection of Flu A and Flu B with 2009 H1N1 Call Out; HIV-1 qual/EID: human immunodeficiency virus qualitative test/Early infant diagnosis; NA: not

Source: Cazabon D et al. 2018

Several laboratory-based technologies exist and/or are in development to allow for diagnostic integration and some are currently or will be entering the WHO TB endorsement process, such as the Roche COBAS TaqMan MDR TB, Abbott RealTime MTB Rif/Inh – both of these technologies have HIV, HBV, and HCV assays. Focusing on the Cepheid Xpert technology, STOP TB presented that by the end of 2017 there were nearly 9,500 total instruments and over 42,000 modules procured in 130 countries. Over 11 million MTB/RIF cartridges were procured in 2017. Utilization of this technology in particular has remained low at about 1.4 tests/module/working day (less than 50% of possible capacity).

Increased TB volumes are expected on existing devices as national programs implement new WHO guidelines; however, the total EID volumes across 15 countries represented less than 8.6% of total Cepheid Xpert capacity at less than 700,000 tests.[20] HIV viral load, HCV, and HPV testing could all have high volumes; however, patient prioritization for these additional tests, particularly for technologies at or near the point-of-care, may need to be considered. For example, patients with advanced HIV disease, pregnant women, children and adolescents, and patients suspected of treatment failure may be in more urgent need of HIV viral load testing. Therefore, careful patient and site mapping incorporating all disease areas and including the patient cascade (ie. loss to follow-up rates) will support optimized diagnostic integration.

[20] Source: Clinton Health Access Initiative

While some technologies require laboratory refurbishments (ie. installation of air conditioners, electrical backup, centrifuge, etc), it is also important to note that additional training may be necessary since different disease and test types may require different samples types, such as sputum, blood, plasma, dried blood spots, and vaginal swabs.

In order to successfully implement diagnostic integration using existing TB- or HIV-procured technologies, cost-sharing should be considered. For example, diagnostic integration may be better supported by TB programs and existing Xpert fleets through HIV, HCV, and/or HPV programs financing service and maintenance contracts, sample transportation systems, or additional device placements. Furthermore, CHAI has developed an Xpert integration tool to support mapping and costing of diagnostic integration.[21] The tool calculated the savings that can be realized by taking five main pieces of integration into account: equipment, S&M, connectivity, HR, mentoring & supervision; and subsequently allocating any savings to the relevant disease programs.

Three pilots were presented looking at integration of HIV testing within the TB testing networks in Malawi and Zimbabwe, both of which have extensive Cepheid GeneXpert platform investments. Both countries observed <35% utilization of the existing fleet and therefore conducted pilots at 10 and 11 health care facilities, respectively. The sites continued TB testing per the national guidelines, while also incorporating both EID (for all HIV-exposed infants) and viral load testing on the same Xpert devices. In Malawi, viral load tests were conducted for those suspected of treatment failure and patients needing a second viral load after an initial elevated, while in Zimbabwe viral load tests were requested at the discretion of the clinician/nurse, particularly for those suspected of treatment failure. In MSF's pilot in Zimbabwe[22], viral load samples were prioritized for patients who presented with advanced disease, pregnant women, adolescents, and suspected treatment failure patients.

In all three pilots, TB volumes were maintained, while as expected EID and VL volumes increased. However, overall GeneXpert utilization did not reach 70% at any health care facility in either country. Further, there were no increases in error rates and the test turnaround times and treatment initiation proportions for TB remained similar to those before the integration pilot. Overall, with careful planning, thoughtful mapping and cost-sharing, diagnostic integration was feasible, increased utilization without exceeding capacity, and was acceptable to health care workers and laboratory staff.

Product pipeline technologies

Conventional laboratory technologies offer the opportunity for high throughput, automated testing. Due to centralization, monitoring and management of laboratories can be simplified. However, these technologies often suffer from long test turnaround times, patient loss to follow-up, high labour and infrastructure costs, and the need for complex sample transportation networks. Uganda shifted from a slightly decentralized conventional laboratory network of eight labs to a highly centralized one lab system. This created efficiencies with lower overhead and human resource costs, faster in-laboratory test turnaround times, and better laboratory oversight

[21] Developed by the Clinton Health Access Initiative. Please reach out to Seth McGovern at sethmcgovern@clintonhealthaccess.org for access and/or additional information.

[22] Ndlovu Z et al. Multidisease testing for HIV and TB using the GeneXpert platform: A feasibility study in rural Zimbabwe. PLoS One. 2017 Mar 2;13(3): e0193577.

and management. Approximately 100 hubs exist around the country to support the more than 3,000 health care facilities (nearly 90% coverage); however, these hubs not only process samples for transportation to the national laboratory, but can also conduct CD4, tuberculosis, complete blood count, and other straightforward testing needs.

Several studies have highlighted the improved clinical benefits when implementing POC CD4 and POC EID for patient management.[23,24,25] Further, POC allows for significant decentralization of testing and more immediate clinical decision-making and reduced need for sample transportation. It is critical to ensure sufficient training and ongoing mentorship to ensure quality testing and clinician trust. EGPAF presented various implementation strategies can be considered when implementing POC; however, while hub and spoke may simplify the conventional laboratory system, the patient impact was significantly weaker than true point-of-care implementation.

Differences exist between technologies, both conventional and point-of-care, thus it is critical to compare technologies to determine the best fit for each setting. Mozambique, for example, has a clear placement process comprised of multiple stakeholders and considerations. When selecting and placing POC EID technologies, the priority remains to ensure placement at the point of care for maximum impact. Therefore, considerations include patient access, operator profile, patient flow, and clinical considerations as well as the typical technical considerations of the technology.[26] The system and program are led by the national programs to avoid 'parachute roll-out' (ie. dictated allocation) and 'partner prop-up' (ie. heavily supported hub and spoke systems). POC implementation success requires decentralization of monitoring and support as well as the need for connectivity to monitor remotely.

For HCV, though the product pipeline is rich, many are early in development and additional options, such as dried blood spots, require further analysis prior to implementation. FIND recently released a request for proposals to support diagnostics partners in the development of HCV diagnostics.[27]

6. Next Steps

Meeting participants identified several next steps that built and expanded on the expected outputs. These include:

[23] Vojnov L et al. POC CD4 testing improves linkage to HIV care and timeliness of ART initiation in a public health approach: a systematic review and meta-analysis. PLoS One. 2016 May 13;11(5):e0155256.
[24] Jani IV et al. Effect of point-of-care early infant diagnosis on antiretroviral therapy initiation and retention of patients. AIDS 2018 Jul 17;32(11):1453-1463.
[25] Mwenda R et al. Significant patient impact observed upon implementation of point-of-care early infant diagnosis technologies in an observational study in Malawi. Clin Infect Dis. 2018 Feb 27.
[26] Lehe JD et al. Evaluating operational specifications of point-of-care diagnostic tests: a standardized scorecard. PLoS One. 2012;7(10):e47459.
[27] FIND announces new wave of activities to address the challenges threatening hepatitis C elimination through potential diagnostic technologies, July 2018: https://www.finddx.org/news/find-announces-new-wave-activities-addressing-challenges-threatening-hepc-elimination/

1. Finalize and publish point-of-care CD4 and early infant diagnosis target product profiles
2. Refine Table 4.10 in the 2016 WHO Consolidated ARV guidelines
3. Update point of care testing quality handbook to develop a more holistic and comprehensive package of interventions for novel technologies
4. Develop an Implementation/Operational Framework with stakeholders over the duration of projects for consideration of on-going projects in the context of best practices development
5. Identify and disseminate evidence and information gaps for future guideline questions, particularly priorities for future treatment failure algorithms
6. Continue advocacy and efforts towards developing integrated laboratories across disease areas

Annex

AGENDA

Day 1: 10 July 2018

Time	Agenda	Presenter
09:00-9:30	**Welcome, introductions, meeting objectives:** Towards scaling up access to diagnostic technologies	WHO and Unitaid
9:30-10:30	**Vatican Diagnostics Initiative update and refinement of asks**	WHO/EGPAF/WCC
10:30-11:00	**Coffee/tea break**	
	Early infant diagnosis	Moderator: UNICEF
11:00-11:30	Diagnostic outcomes of Infant meeting	WHO – Lara Vojnov
11:30-11:45	**Discussion**	
11:45-12:00	Investment case	CIE – Sarina Lacey
12:00-12:15	EID priorities and POC EID scale-up	PEPFAR/CDC – Mackenzie Hurlston and Helen Dale
12:15-12:30	Experiences with POC	CHAI – Seth McGovern
12:30-13:00	**Discussion**	Alex Costa
13:00-14:00	**Lunch**	
	Viral load implementation and next steps	Moderator: NHLS
14:00-14:20	Viral load scale-up update	CDC – Heather Alexander
14:20-14:40	Future treatment failure algorithm consideration	WHO – Lara Vojnov
14:40-14:55	Treatment failure algorithms in use and consideration	MSF – Emmanuel Fajardo
14:55-15:10	Treatment failure-related studies completed / in progress	CHAI – Jilian Sacks
15:10-15:25	Treatment failure-related studies completed / in progress	CDC – Ritu Pati
15:25-16:00	**Discussion**	Sergio Carmona
16:00-16:30	**Coffee/tea break**	
	Advanced disease and HIV-related diagnostics	Moderator: WHO
16:30-16:50	Clinical management of advanced disease	MSF – Emmanuel Fajardo
16:50-17:10	Forecasting for advanced disease diagnostics	CHAI – Katie Pollak
17:10-17:30	HIV-related diagnostics and needs	WHO – Lara Vojnov
17:30-18:00	**Discussion**	Nathan Ford

Day 2: 11 July 2017

Time	Agenda	Presenter
	Integration of diagnostic technologies	Moderator: USAID & Global Fund
9:30-9:50	HIV perspective	MSF – Emmanuel Fajardo
9:50-10:10	TB perspective	GDF – Wayne van Gemert
10:10-10:30	HCV perspective	FIND – Sonjelle Shilton
10:30-10:50	HPV perspective	EGPAF – Jen Cohn
10:50-11:15	**Coffee and Tea Break**	
11:15-11:30	Cost sharing and integration challenges	CHAI – Seth McGovern
11:30-11:45	HIV/TB integration results	MOH Malawi – James Kandulu
11:45-12:00	HIV/TB integration results	Zimbabwe – Raiva Simbi
12:00-12:45	**Discussion**	Dianne Edgil & Eileen Burke
12:45-13:45	**Lunch**	
	Product pipeline	Moderator: ASLM & Unitaid
13:45-13:50	Scene set – product pipeline	
13:45-14:00	Programmatic and technical benefits and challenges of technologies	Zimbabwe – Raiva Simbi
14:00-14:15	Programmatic and technical benefits and challenges of technologies	Uganda – Charles Kiyaga
14:15-14:30	Programmatic and technical benefits and challenges of technologies	EGPAF – Esther Turunga
14:30-14:45	**Coffee and Tea Break**	
14:45-15:00	Programmatic and technical benefits and challenges of technologies	Mozambique – Tim Bollinger
15:00-15:15	Programmatic and technical benefits and challenges of technologies	FIND – Elena Ivanova
15:15-15:30	Target Product Profiles: POC CD4 and POC EID	WHO
15:30-16:00	**Discussion**	Pascale Ondoa & Smiljka de Lussigny
16:00-16:20	**Civil society perspectives**	ITPC – Bactrin Killingo
16:20-17:00	**Meeting wrap-up**	WHO and Unitaid

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