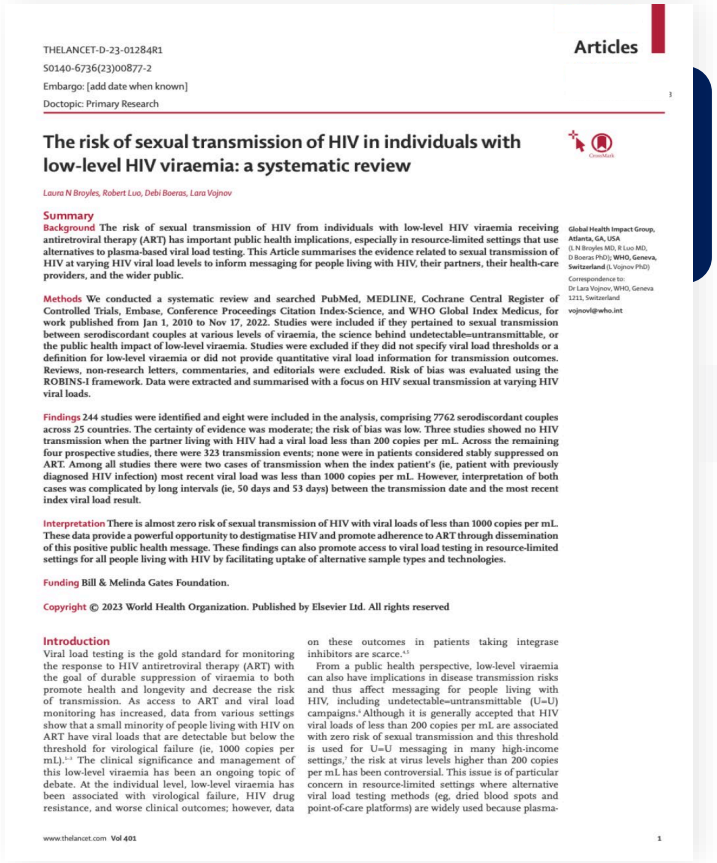
World Health Organization

The Role of HIV Viral Suppression in Improving Individual Health and Reducing Transmission

Robert Luo, MD, MPH
Department of Global HIV, Viral Hepatitis and Sexually Transmitted Infections Programmes

Evidence Improving Public Health Messaging



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Doctopic: Primary Research

Articles

The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review

Laura N Broyles, Robert Luo, Debi Boeras, Lara Vojnov

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Summary

Background The risk of sexual transmission of HIV from individuals with low-level HIV viraemia receiving antiretroviral therapy (ART) has important public health implications, especially in resource-limited settings that use alternatives to plasma-based viral load testing. This Article summarises the evidence related to sexual transmission of HIV at varying HIV viral load levels to inform messaging for people living with HIV, their partners, their health-care providers, and the wider public.

Methods We conducted a systematic review and searched PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, Embase, Conference Proceedings Citation Index-Science, and WHO Global Index Medicus, for work published from Jan 1, 2010 to Nov 17, 2022. Studies were included if they pertained to sexual transmission between serodiscordant couples at various levels of viraemia, the science behind undetectable=untransmittable, or the public health impact of low-level viraemia. Studies were excluded if they did not specify viral load thresholds or a definition for low-level viraemia or did not provide quantitative viral load information for transmission outcomes. Reviews, non-research letters, commentaries, and editorials were excluded. Risk of bias was evaluated using the ROBINS-I framework. Data were extracted and summarised with a focus on HIV sexual transmission at varying HIV viral loads.

Findings 244 studies were identified and eight were included in the analysis, comprising 7762 serodiscordant couples across 25 countries. The certainty of evidence was moderate; the risk of bias was low. Three studies showed no HIV transmission when the partner living with HIV had a viral load less than 200 copies per mL. Across the remaining four prospective studies, there were 323 transmission events; none were in patients considered stably suppressed on ART. Among all studies there were two cases of transmission when the index patient's (ie, patient with previously diagnosed HIV infection) most recent viral load was less than 1000 copies per mL. However, interpretation of both cases was complicated by long intervals (ie, 50 days and 53 days) between the transmission date and the most recent index viral load result.

Interpretation There is almost zero risk of sexual transmission of HIV with viral loads of less than 1000 copies per mL. These data provide a powerful opportunity to destigmatise HIV and promote adherence to ART through dissemination of this positive public health message. These findings can also promote access to viral load testing in resource-limited settings for all people living with HIV by facilitating uptake of alternative sample types and technologies.

Funding Bill & Melinda Gates Foundation.

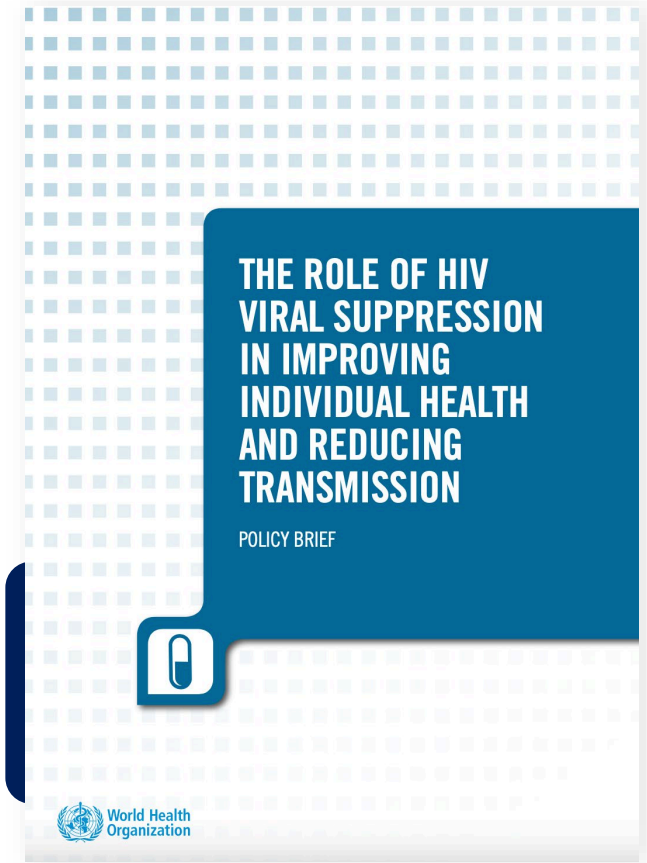
Introduction

Viral load testing is the gold standard for monitoring the response to HIV antiretroviral therapy (ART) with the goal of durable suppression of viraemia to both promote health and longevity and decrease the risk of transmission. As access to ART and viral load monitoring has increased, data from various settings show that a small minority of people living with HIV on ART have viral loads that are detectable but below the threshold for virological failure (ie, 1000 copies per mL).[1–3] The clinical significance and management of this low-level viraemia has been an ongoing topic of debate. At the individual level, low-level viraemia has been associated with virological failure, HIV drug resistance, and worse clinical outcomes; however, data on these outcomes in patients taking integrase inhibitors are scarce.[4,5]

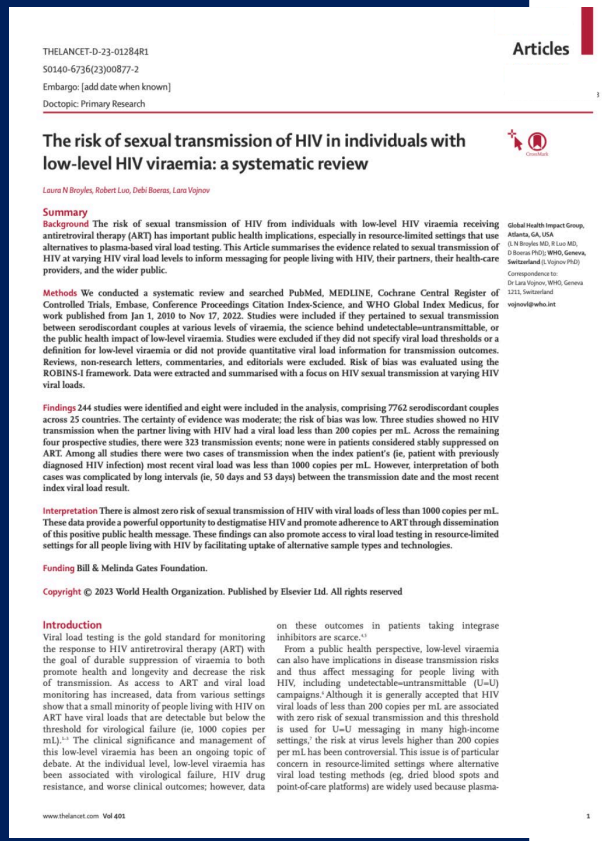
From a public health perspective, low-level viraemia can also have implications in disease transmission risks and thus affect messaging for people living with HIV, including undetectable=untransmittable (U=U) campaigns.[6] Although it is generally accepted that HIV viral loads of less than 200 copies per mL are associated with zero risk of sexual transmission and this threshold is used for U=U messaging in many high-income settings,[7] the risk at virus levels higher than 200 copies per mL has been controversial. This issue is of particular concern in resource-limited settings where alternative viral load testing methods (eg, dried blood spots and point-of-care platforms) are widely used because plasma-

Evidence consolidation and review of the risks of sexual HIV transmission based on viral load levels

Reflecting on the benefits and harms of the evidence, clear, positive messaging, stigma, discrimination, and criminalization



Risk of Sexual Transmission when PLHIV Have Lower Viral Loads



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Three studies showed no HIV transmission when the HIV-positive partner had a viral load less than 200 copies/mL. Most transmission events occurred when the HIV-positive partner had a viral load between 30,000 and 750,000 copies/mL.

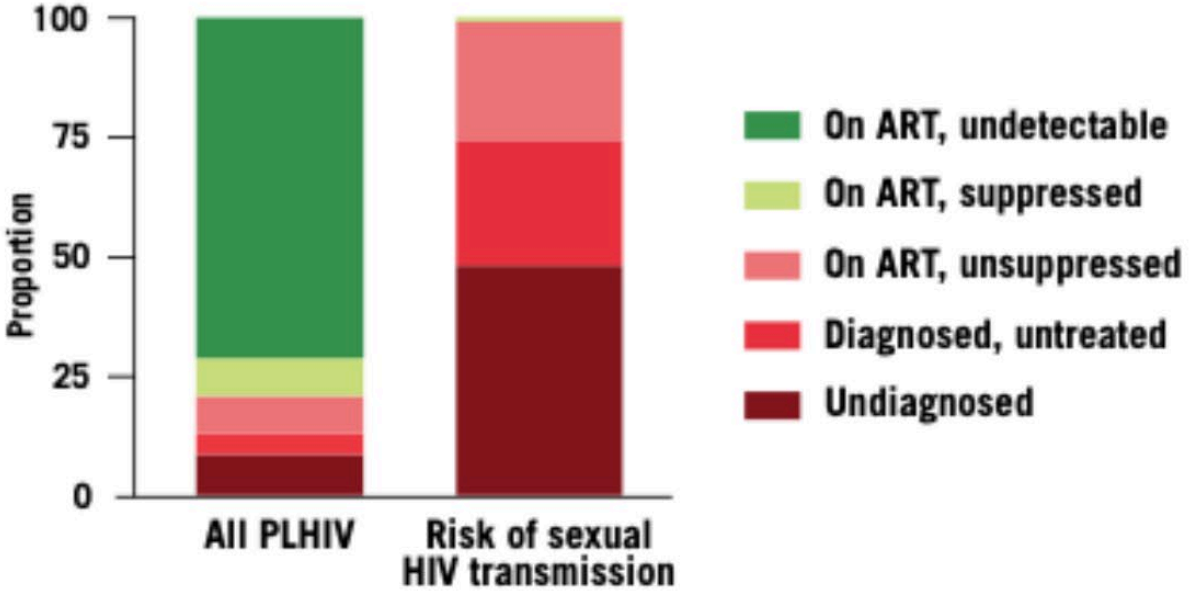
Across the remaining four prospective studies, there were 323 transmission events; none were in patients considered stably suppressed on ART.

Among all studies, there were two cases of transmission when the index patient's most recent viral load was less than 1000 copies/mL (~700 and ~850 copies/mL). However, in both cases the index case viral load test was taken 50+ days prior to the transmission event.

No studies were identified evaluating the transmissibility of HIV through the sharing of injection drug use equipment when a person's viral load is less than 1000 copies/mL.

The majority of people living with HIV are not at risk of sexually transmitting HIV

Proportion of viral load categorization of all people living with HIV and by risk of sexual transmission



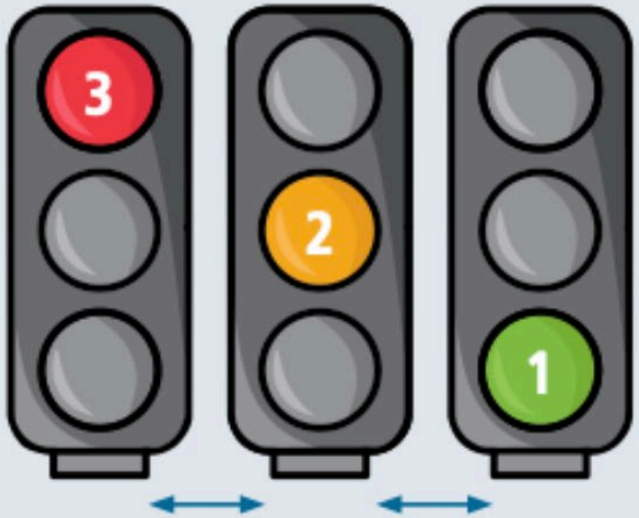
People living with HIV who have an undetectable viral load have zero risk of transmitting HIV to their sexual partner(s).

People living with HIV who have a suppressed but detectable viral load have almost zero or negligible risk of transmitting HIV to their sexual partner(s).

Clear, Celebratory Messaging for People Living With HIV

World Health Organization

Three categories of viral load levels

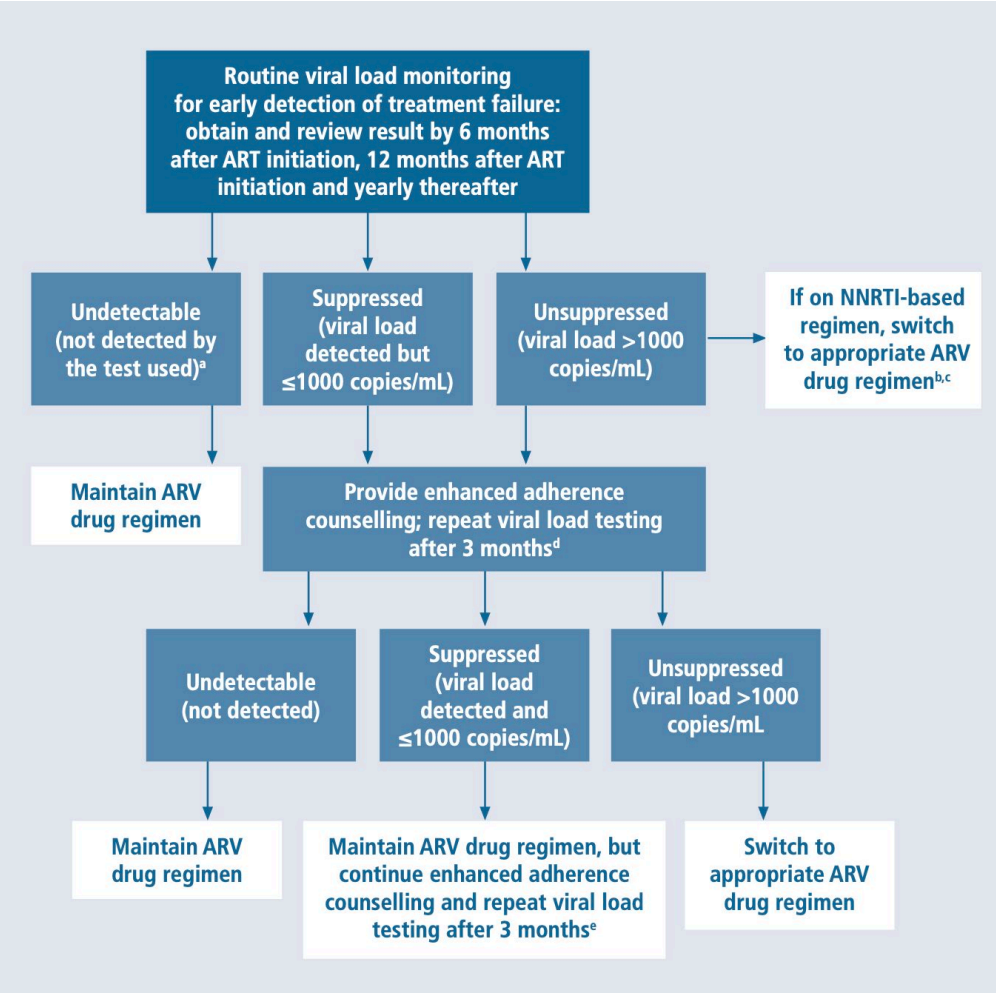


1. **Undetectable (not detected*):** no measurable virus. Zero risk of transmission to sexual partner(s); minimal risk of mother to child transmission.
2. **Suppressed (detected but ≤1000 copies/mL):** some virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Almost zero or negligible risk of transmission to sexual partner(s).
3. **Unsuppressed (>1000 copies/mL):** significant virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Increased risk of falling ill and/or passing virus on to sexual partner(s) or children.

The ultimate goal for all people living with HIV is to reach and sustain undetectable viral loads. Taking antiretroviral therapy as prescribed will support this goal, prevent transmission to their sexual partner(s) and/or children, and improve their own clinical well-being.

* Not detected by the test or sample type used.

2023 Updated WHO Treatment Monitoring Algorithm



Notes on Flowchart

a) Definition of undetectable has been updated from <50 copies/ml to not detectable by the test used

b) After a single unsuppressed viral load, therapy switch should be considered if treatment experience is likely

c) For those on NNRTI-based regimens with an unsuppressed viral load, a second viral load may be considered if DTG-based regimens are not available and the results of a viral load test can be returned and acted upon quickly

d) For repeat viral load testing, conduct same-day testing with point of care viral load where available. If not, the repeat viral load test should be given priority in the laboratory system

e) For individuals on NNRTI-based regimens with persistent detectable but suppressed viral loads, consider therapy switch based on clinical considerations and no adherence concerns

Further technical considerations

HIV viral load test results can be a motivation for adhering to treatment and achieving the ultimate goal of being undetectable.

Emphasizing and strengthening adherence counselling during antiretroviral therapy initiation and throughout treatment are essential, including communicating about the prevention benefits of viral load suppression to all people living with HIV.

Current WHO-prequalified tests, including point-of-care and alternative sample types such as dried blood spot samples, can support the goals of treatment programmes to accurately measure and report viral load results as unsuppressed, suppressed and undetectable.

2021 Point-of-care viral load recommendations

Recommendation

Point-of-care viral load may be used to monitor treatment among people living with HIV receiving ART.

(conditional recommendation; moderate-certainty evidence)

Box 2. Priorities for point-of-care viral load testing

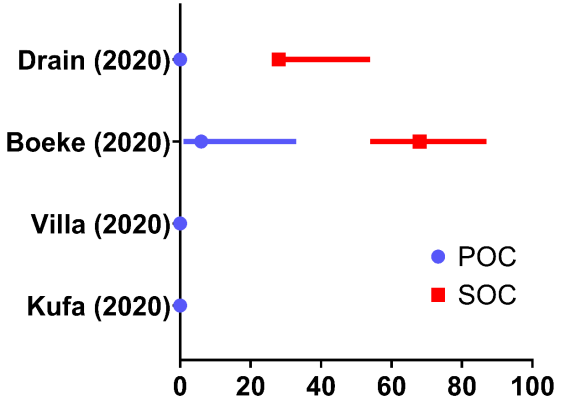
Point-of-care viral load testing should be given priority for the following populations:

- Pregnant and breastfeeding women
- Infants, children and adolescents
- People requiring a repeat viral load after a first elevated viral load
- People for whom treatment failure is suspected
- People presenting sick, living with advanced HIV disease or having a known opportunistic infection (TB, cryptococcal infection, etc.)
- First scheduled viral load test for people re-entering care

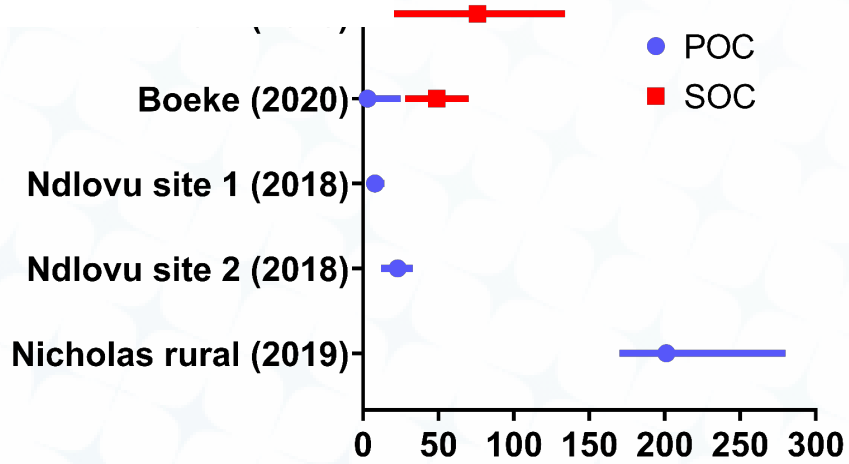
Point-of-care viral load systematic review

POC improves turnaround time for patient results

HR 17.7 (13.0-24.2)



- Improves turnaround time of results to clinician (HR 11.7)
- Increases probability of same-day results to patients
- Increases probability of and reduces time to differentiated care (RR 2.2 and HR 3.5, respectively)
- Increases retention in care and viral suppression at 18 months (RR 1.2)



POC reduces time to clinical action for elevated VL

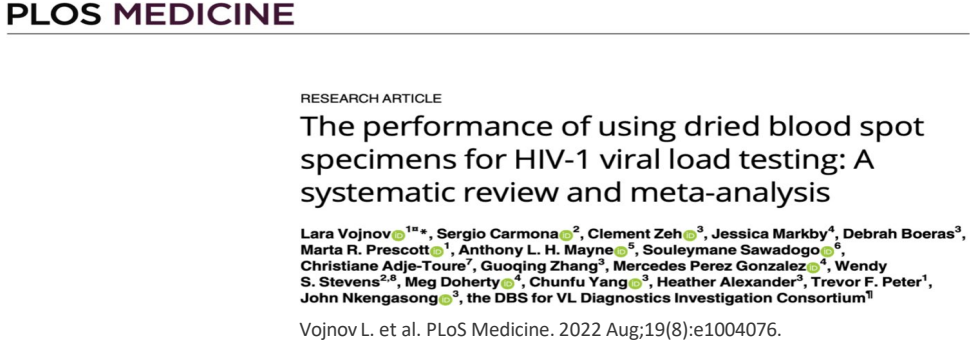
HR 10.9 (2.1-57.5)

How can dried blood spot samples be used?

Typical viral load technology reporting outputs

- Not detected = undetectable: the test could not detect any virus in the sample
- <LOD or <LLOQ = the test detected some virus but less than the limit of detection (<LOD) or lower limit of quantification (<LLOQ) (in nearly all cases these would be suppressed, ≤ 1000 copies/mL)
- Viral load copies/ml value = the quantified value of viral load detected
- >ULOQ = detectable viral load that is more than the upper limit of quantification (>ULOQ) (generally >1 million copies/mL or higher)

Current WHO-prequalified tests, including point-of-care and alternative sample types such as dried blood spot samples, can support the goals of treatment programmes to accurately measure and report viral load results as unsuppressed, suppressed and undetectable.


PLOS MEDICINE

RESEARCH ARTICLE

The performance of using dried blood spot specimens for HIV-1 viral load testing: A systematic review and meta-analysis

Lara Vojnov[1¤*], Sergio Carmona[2], Clement Zeh[3], Jessica Markby[4], Debrah Boeras[3], Marta R. Prescott[1], Anthony L. H. Mayne[5], Souleymane Sawadogo[6], Christiane Adje-Toure[7], Guoqing Zhang[3], Mercedes Perez Gonzalez[4], Wendy S. Stevens[2,8], Meg Doherty[4], Chunfu Yang[3], Heather Alexander[3], Trevor F. Peter[1], John Nkengasong[3], the DBS for VL Diagnostics Investigation Consortium[¶]

Vojnov L. et al. PLoS Medicine. 2022 Aug;19(8):e1004076.

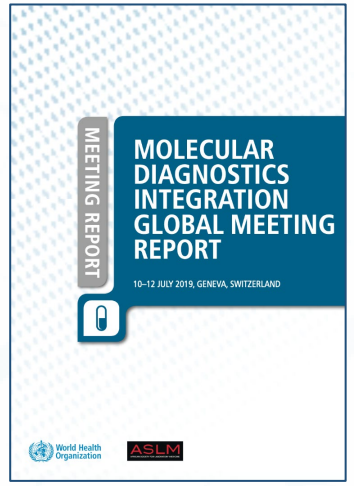
Diagnostic integration across programmes

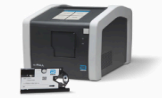
Disease programmes, especially HIV and TB, should actively work towards balanced integration of diagnostic services

- Integrated testing is operationally feasible with appropriate site selection to balance the expected demand

Near-POC testing can enable faster and increased rates of clinical action for HIV+ infants and PLHIV on ART experiencing viremia

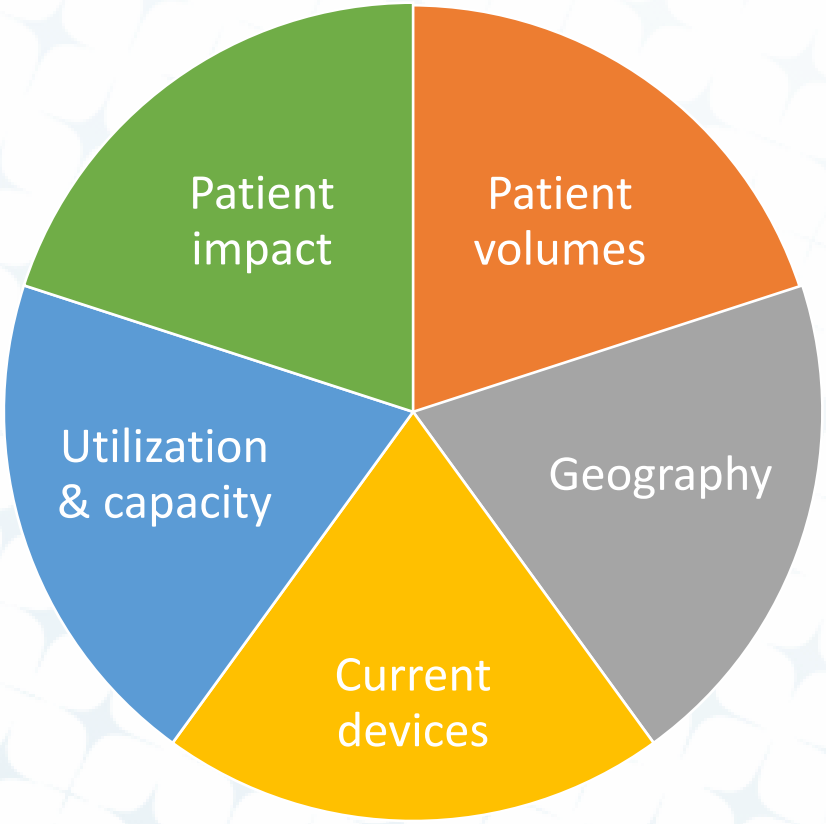
- Same-day result delivery was possible for EID with near-POC device
- Faster clinical action was achieved for both EID and VL improving outcome
- Integrated testing does not impact the potential benefit of near-POC testing and is viable option to scale-up near-POC testing



		Abbott m2000sp	Abbott m-PIMA	Cepheid GeneXpert GX-4, 16, 48, 80	Hologic Panther	Roche CAP/CTM 96	Roche 4800/ 6800/8800
							
Max daily throughput (incl. controls)		96 (8hrs) 288 (24hrs)	8 (8 hrs)	GX4: 16 (8hrs) GX16: 64 (8hrs)	320 (8hrs) 1,220 (24hrs)	168 (8hrs) 312 (24hrs)	384/960 (8hrs) 1,344/3,072 (24hrs)
Test menu	HCV VL	✔[a]	✘	✔[a]	✔	✔	✔[c]
	HBV VL	✔	✘	✔	✔	✔	✔
	HIV EID	✔[a]	✔[a]	✔[a]	✔	✔[a]	✔[c]
	HIV VL	✔[a]	✔[a]	✔[a]	✔[a]	✔[a]	✔[c]
	MTB	✔	✘	✔[b]	✘	✔	✔
	HPV	✔[a]	✘	✔[a]	✔	✔[c]	✔

[a] Technologies with WHO prequalification listing
[b] Technologies endorsed by WHO (Global Tuberculosis Program)
[c] Technologies currently undergoing WHO prequalification review
Information included as of December 20, 2019. Pictures are not to comparable scale.

Diagnostic Network Optimization



Several tools in development to support network optimization and mapping to ensure optimization and integration:

- USAID-FIND LabEquip
- CHAI integration tool
- Mozambique INS tool
- OptiDx

Diagnostic Network Optimization - Main Steps

1. Define Scope and Objectives of Optimization

2. Collect Data: Sites / Demand / Test Types / Costs / Sample Flow

3. Build Baseline Model

4. Adjust Data Inputs and Constraints (Geographic / Budgetary / System)

5. Build and Compare Scenarios

6. Select and Implement Plans

Viral suppression remains a key global, public health and individual goal

95

95% of HIV-positive people know their HIV status

95

95% of people diagnosed with HIV receive sustained ART

95

95% of people on ART have viral suppression

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