World Health Organization

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

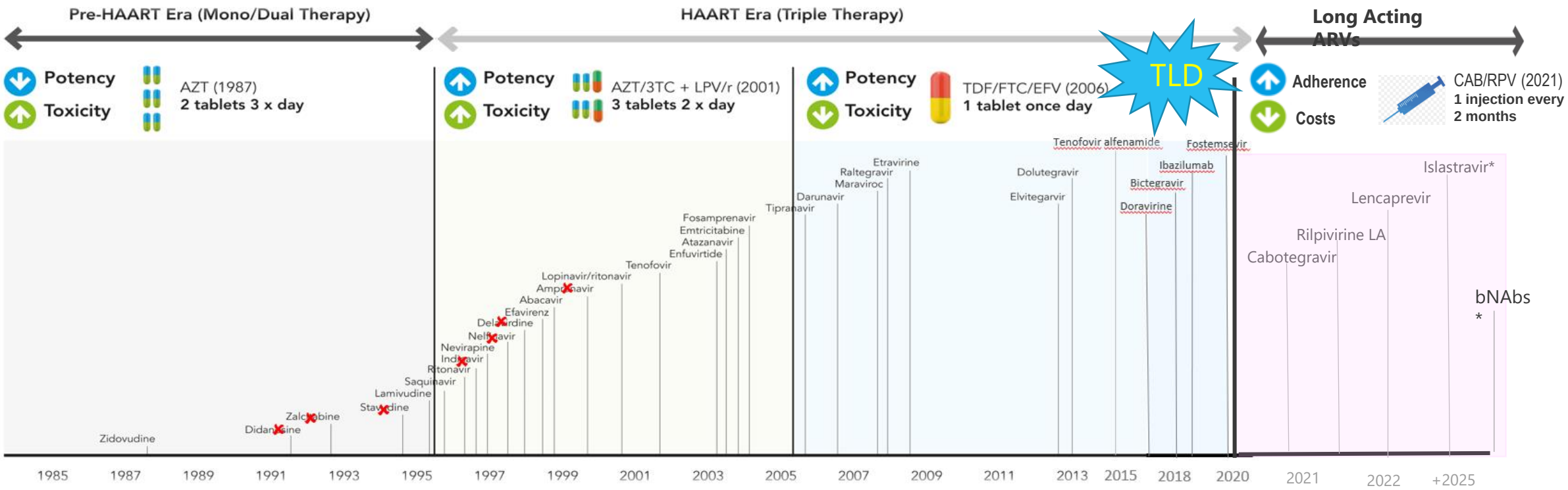
Department of Global HIV, viral hepatitis and sexually transmitted infections Programmes

12 October 2023

# The history of diagnostics within treatment monitoring

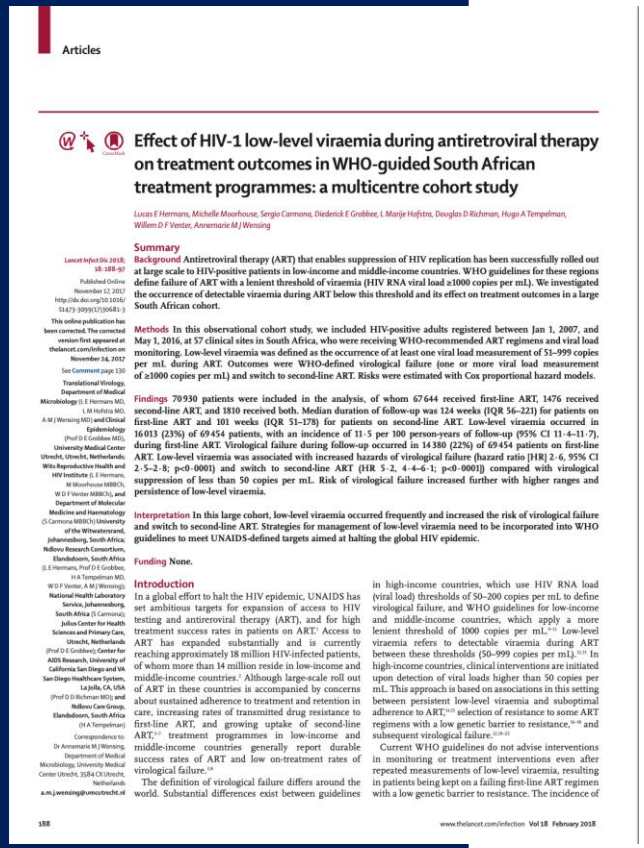
| | |
|---|---|
| 2006 | ART initiation of PLHIV with a CD4 ≤200 cells/ul |
| 2010 | ART initiation of PLHIV with a CD4 ≤350 cells/ul; viral load suggested |
| 2013 | Viral load as the preferred method to identify treatment failure |
| 2016 | ART should be initiated in ALL PLHIV, regardless as to CD4 cell count |
| 2017 | CD4 is critical to identifying people living with advanced HIV disease |

# The evolution of optimized ART: towards smarter and better treatment options




* expected

# Low-level viremia associated with poorer individual health



Articles

Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study

Lucas E Hermans, Michelle Moorhouse, Sergio Carmona, Diederick E Grobbee, L Marije Hofstra, Douglas D Richman, Hugo A Tempelman, Willem D F Venter, Annemarie M J Wensing

Summary

**Background** Antiretroviral therapy (ART) that enables suppression of HIV replication has been successfully rolled out at large scale to HIV-positive patients in low-income and middle-income countries. WHO guidelines for these regions define failure of ART with a lenient threshold of viraemia (HIV RNA viral load ≥1000 copies per mL). We investigated the occurrence of detectable viraemia during ART below this threshold and its effect on treatment outcomes in a large South African cohort.

**Methods** In this observational cohort study, we included HIV-positive adults registered between Jan 1, 2007, and May 1, 2016, at 57 clinical sites in South Africa, who were receiving WHO-recommended ART regimens and viral load monitoring. Low-level viraemia was defined as the occurrence of at least one viral load measurement of 51–999 copies per mL during ART. Outcomes were WHO-defined virological failure (one or more viral load measurement of ≥1000 copies per mL) and switch to second-line ART. Risks were estimated with Cox proportional hazard models.

**Findings** 70 930 patients were included in the analysis, of whom 67 644 received first-line ART, 1476 received second-line ART, and 1810 received both. Median duration of follow-up was 124 weeks (IQR 56–221) for patients on first-line ART and 101 weeks (IQR 51–178) for patients on second-line ART. Low-level viraemia occurred in 16 013 (23%) of 69 454 patients, with an incidence of 11·5 per 100 person-years of follow-up (95% CI 11·4–11·7), during first-line ART. Virological failure during follow-up occurred in 14 380 (22%) of 69 454 patients on first-line ART. Low-level viraemia was associated with increased hazards of virological failure (hazard ratio [HR] 2·6, 95% CI 2·5–2·8; p<0·0001) and switch to second-line ART (HR 5·2, 4·4–6·1; p<0·0001]) compared with virological suppression of less than 50 copies per mL. Risk of virological failure increased further with higher ranges and persistence of low-level viraemia.

**Interpretation** In this large cohort, low-level viraemia occurred frequently and increased the risk of virological failure and switch to second-line ART. Strategies for management of low-level viraemia need to be incorporated into WHO guidelines to meet UNAIDS-defined targets aimed at halting the global HIV epidemic.

**Funding** None.

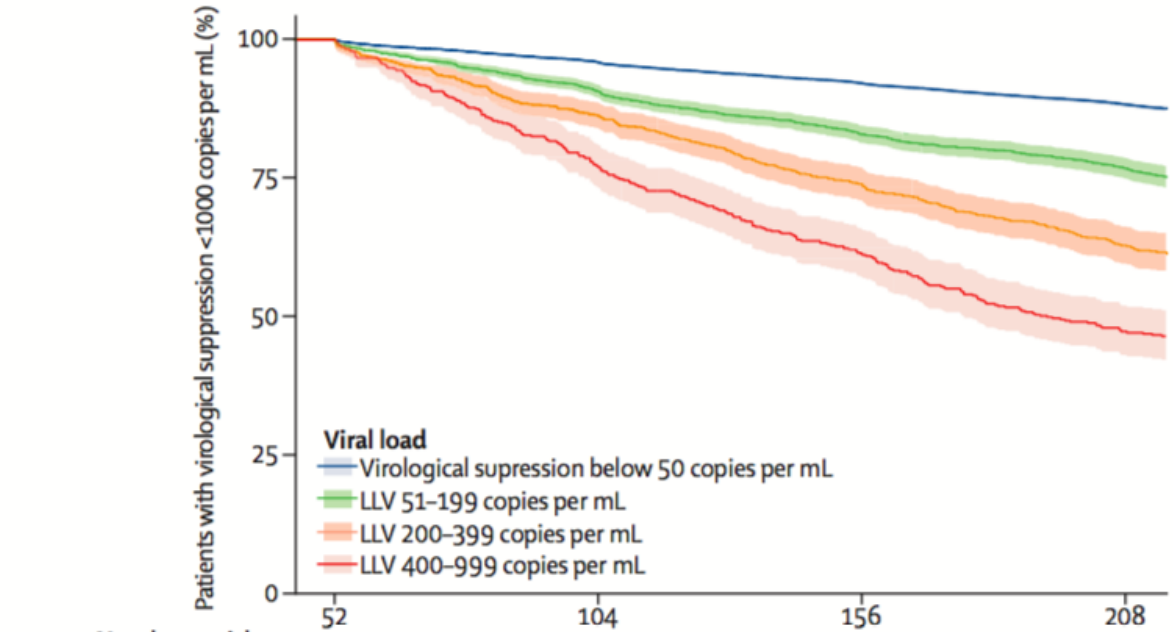
Introduction

In a global effort to halt the HIV epidemic, UNAIDS has set ambitious targets for expansion of access to HIV testing and antiretroviral therapy (ART), and for high treatment success rates in patients on ART.[1] Access to ART has expanded substantially and is currently reaching approximately 18 million HIV-infected patients, of whom more than 14 million reside in low-income and middle-income countries.[2] Although large-scale roll out of ART in these countries is accompanied by concerns about sustained adherence to treatment and retention in care, increasing rates of transmitted drug resistance to first-line ART, and growing uptake of second-line ART,[3–7] treatment programmes in low-income and middle-income countries generally report durable success rates of ART and low on-treatment rates of virological failure.[3–8]

The definition of virological failure differs around the world. Substantial differences exist between guidelines in high-income countries, which use HIV RNA load (viral load) thresholds of 50–200 copies per mL to define virological failure, and WHO guidelines for low-income and middle-income countries, which apply a more lenient threshold of 1000 copies per mL.[9–11] Low-level viraemia refers to detectable viraemia during ART between these thresholds (50–999 copies per mL).[12,13] In high-income countries, clinical interventions are initiated upon detection of viral loads higher than 50 copies per mL. This approach is based on associations in this setting between persistent low-level viraemia and suboptimal adherence to ART,[14,15] selection of resistance to some ART regimens with a low genetic barrier to resistance,[16–18] and subsequent virological failure.[12,19–21]

Current WHO guidelines do not advise interventions in monitoring or treatment interventions even after repeated measurements of low-level viraemia, resulting in patients being kept on a failing first-line ART regimen with a low genetic barrier to resistance. The incidence of



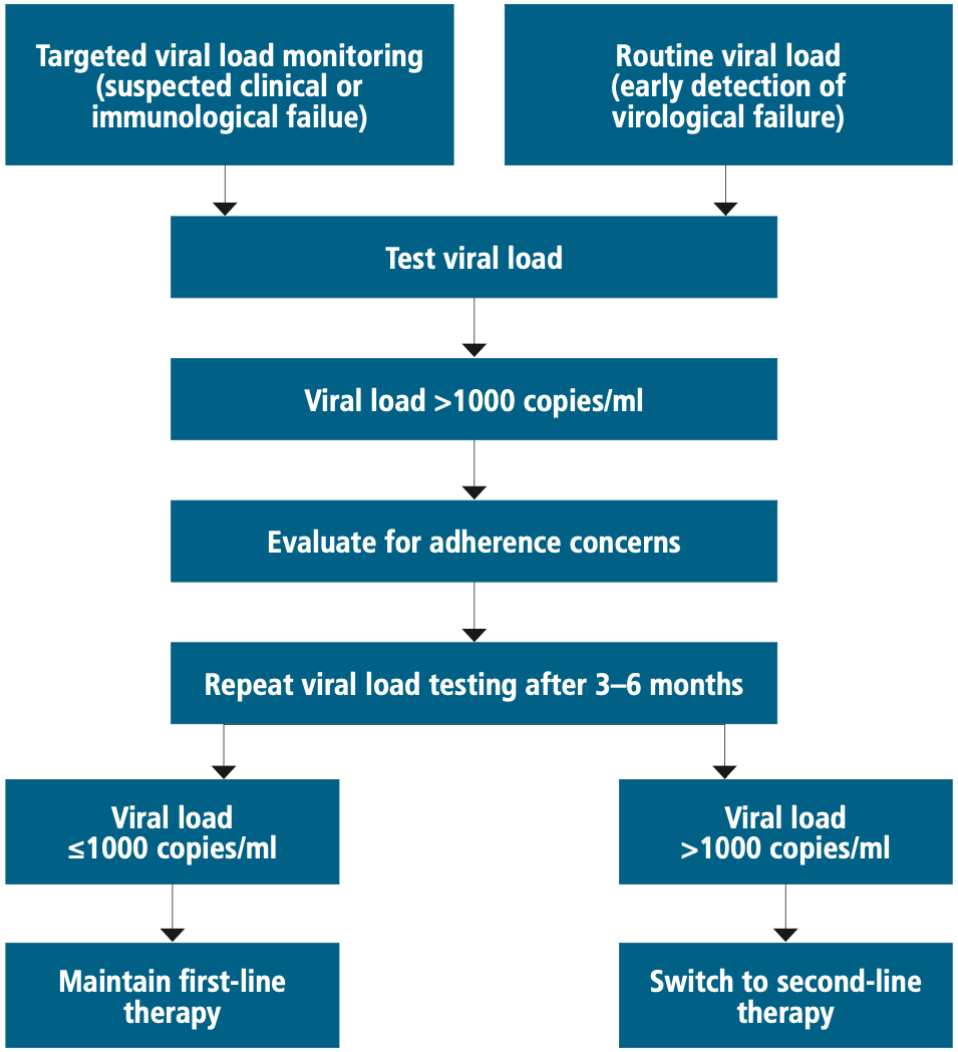


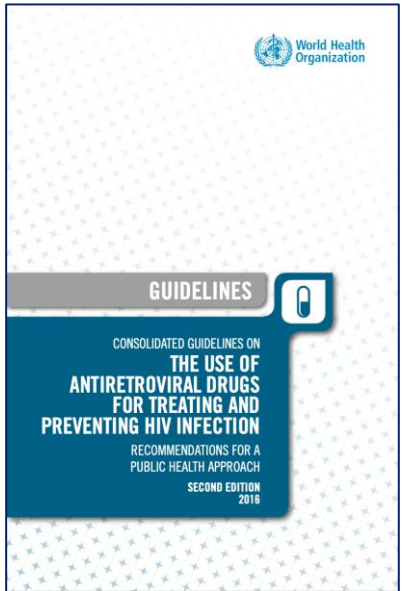

| Number at risk | | | | |
|---|---|---|---|---|
| <50 copies per mL | 18 844 | 21 842 | 18 508 | 13 431 |
| 51–199 copies per mL | 2274 | 2137 | 1581 | 1033 |
| 200–399 copies per mL | 800 | 756 | 575 | 429 |
| 400 –999 copies per mL | 401 | 379 | 310 | 216 |

Low-level viremia associated with:

- Virological failure
- Switch to 2nd line

# History of treatment monitoring algorithm: 2016 to 2020

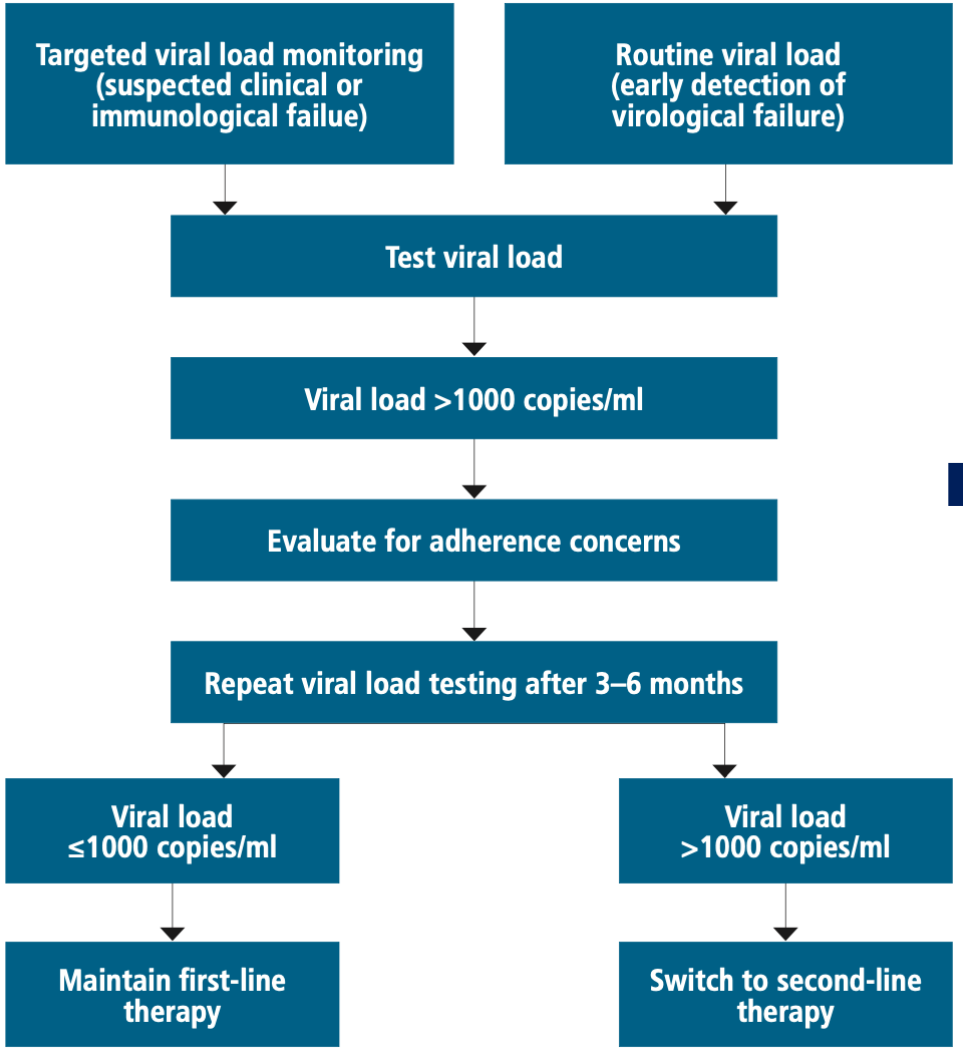


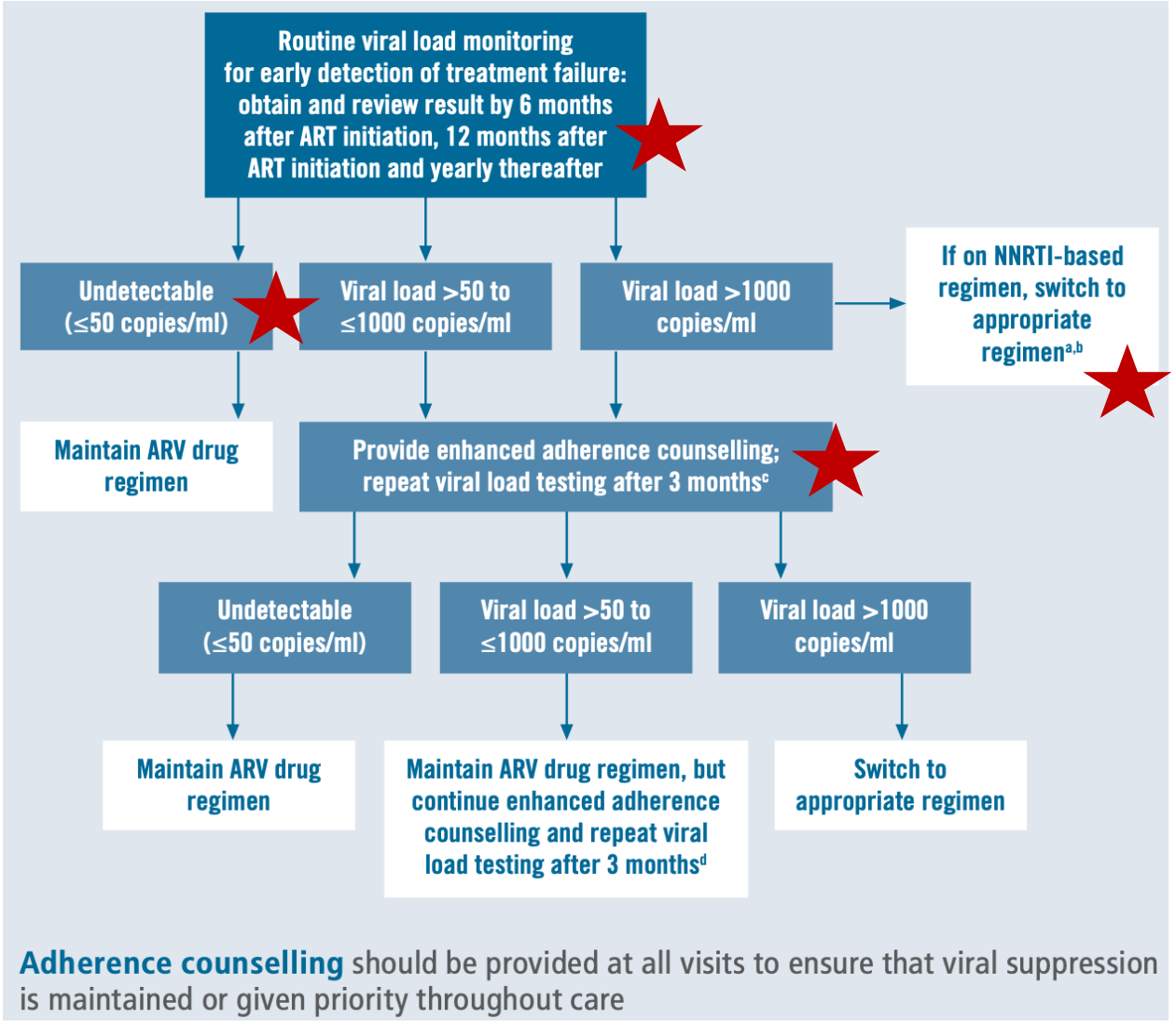



# Key goals for the 2021 treatment monitoring algorithm

- Appreciating the role and benefits of notifying PLHIV of an undetectable viral load
- Available evidence for optimal treatment monitoring algorithm considering DTG and TLD roll-out
- Impact of low-level viremia on HIV transmission
- Role of low-level viremia on individual health, and if possible within the context of DTG and TLD roll-out
- Timing of the first viral load
- Increasing rates of NNRTI-based drug resistance and quick switching to '2nd line'
- Clarifying timing of repeat viral load after an initial unsuppressed viral load

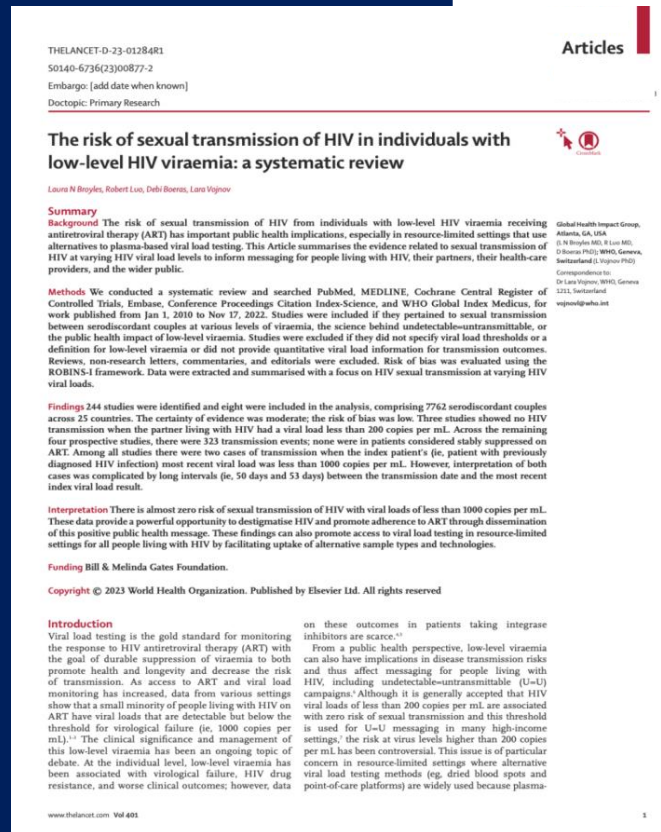
# History of treatment monitoring algorithm: 2016 to 2020




**Adherence counselling** should be provided at all visits to ensure that viral suppression is maintained or given priority throughout care

# Risk of sexual transmission when PLHIV have lower viral loads



THELANCET-D-23-01284R1
S0140-6736(23)00877-2
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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


**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.





Global Health Impact Group, Atlanta, GA, USA (L N Broyles MD, R Luo MD, D Boeras PhD); WHO, Geneva, Switzerland (L Vojnov PhD)

Correspondence to: Dr Lara Vojnov, WHO, Geneva 1211, Switzerland
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**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).[1,2] 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.[3,4]

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.[5] 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,[6] 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-



Three studies showed no HIV transmission when the person living with HIV had a viral load less than 200 copies/mL. Most transmission events occurred when the person living with HIV 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.

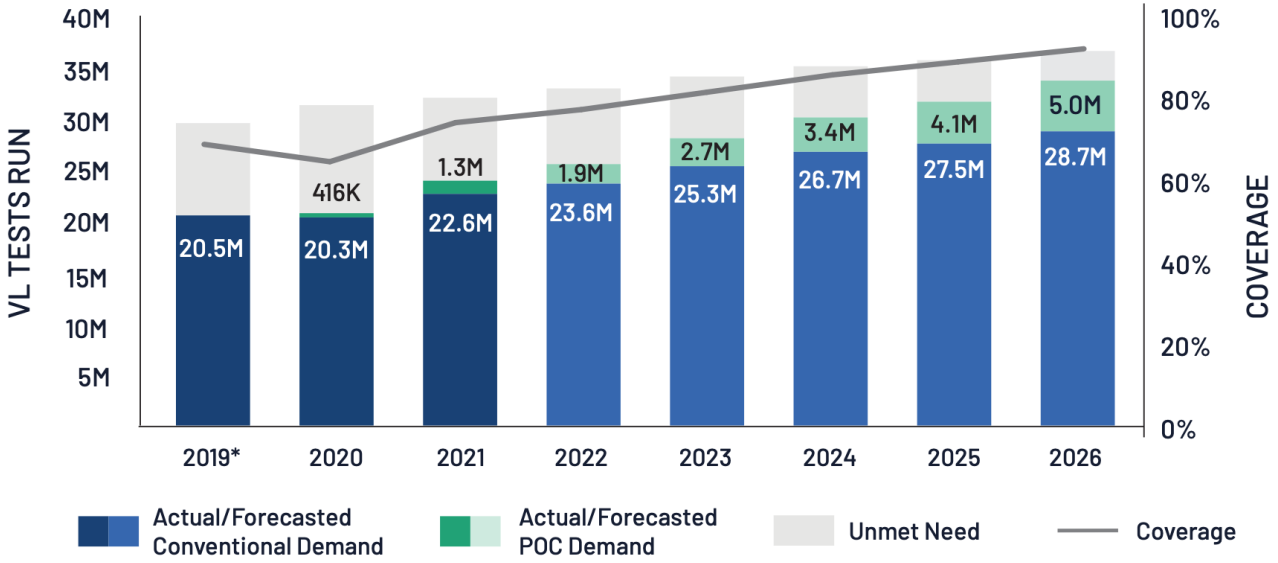
Among all studies, there were two cases of transmission when person living with HIV's most recent viral load was less than 1000 copies/mL (~700 and ~850 copies/mL). However, in both cases the viral load test was taken 50+ days prior to the transmission event.

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.

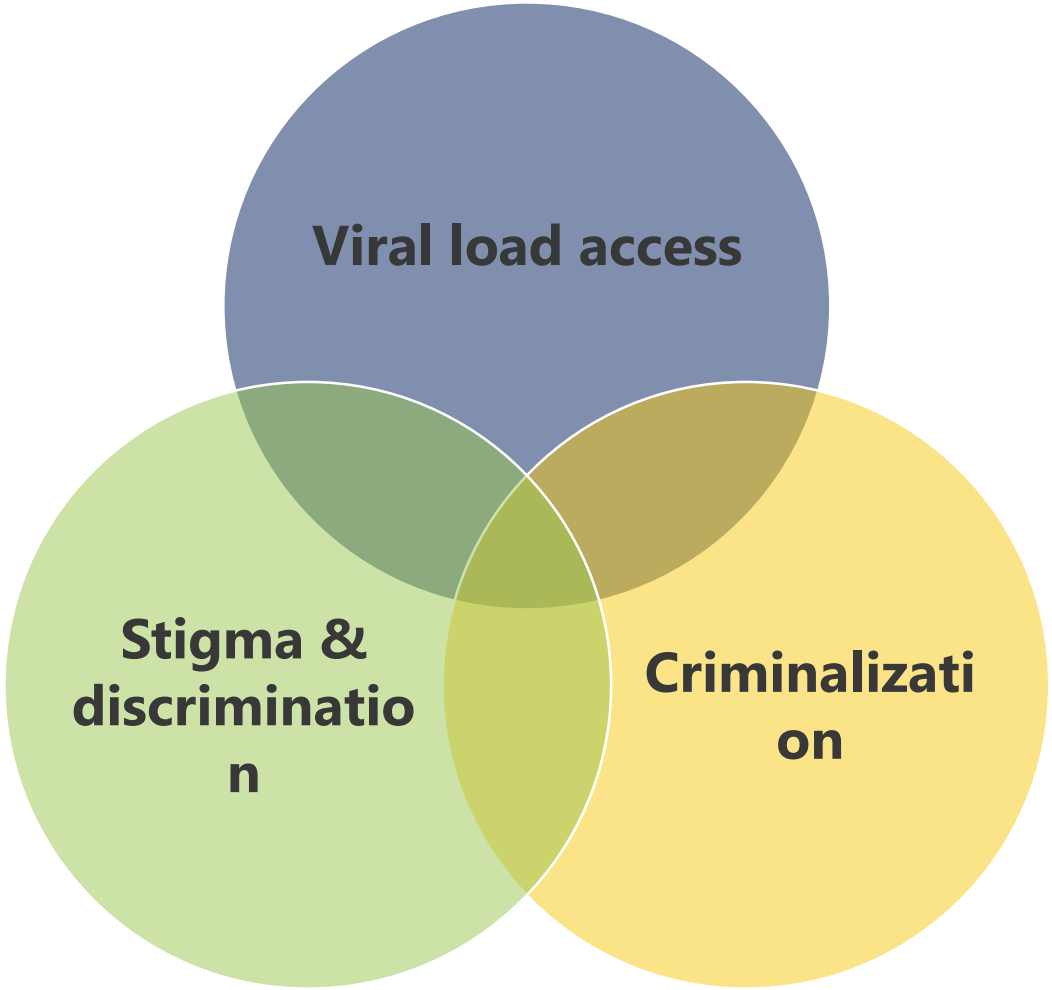


Broyles L. et al. Lancet 2023. https://doi.org/10.1016/S0140-

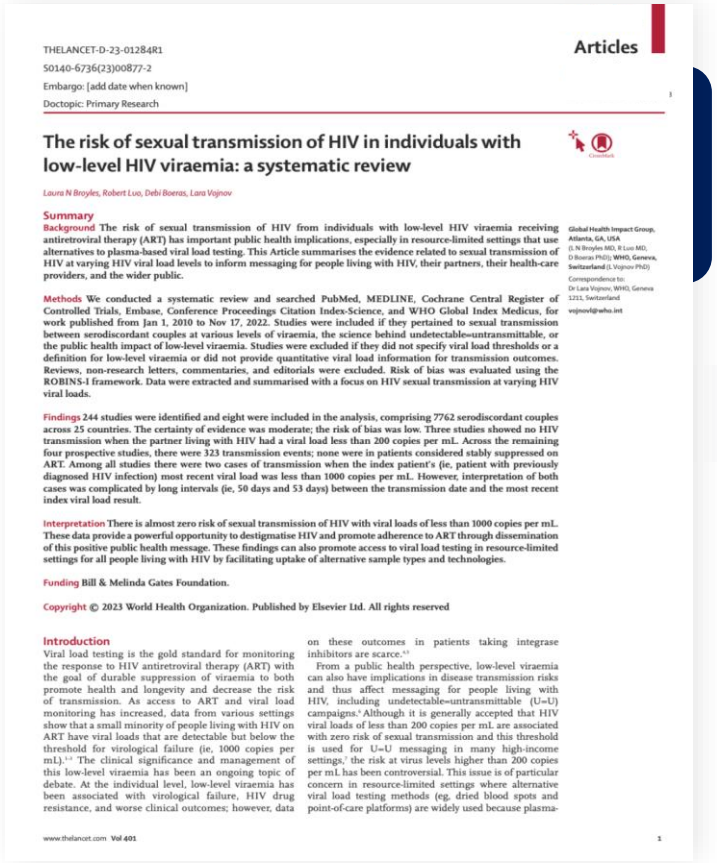
# Ongoing challenges for people living with HIV




- Continued and regular stigma and discrimination
  - Family
  - Friends
  - Health care providers
  - General public
- Punitive laws resulting in criminalization of PLHIV



# Evidence improving public health messaging



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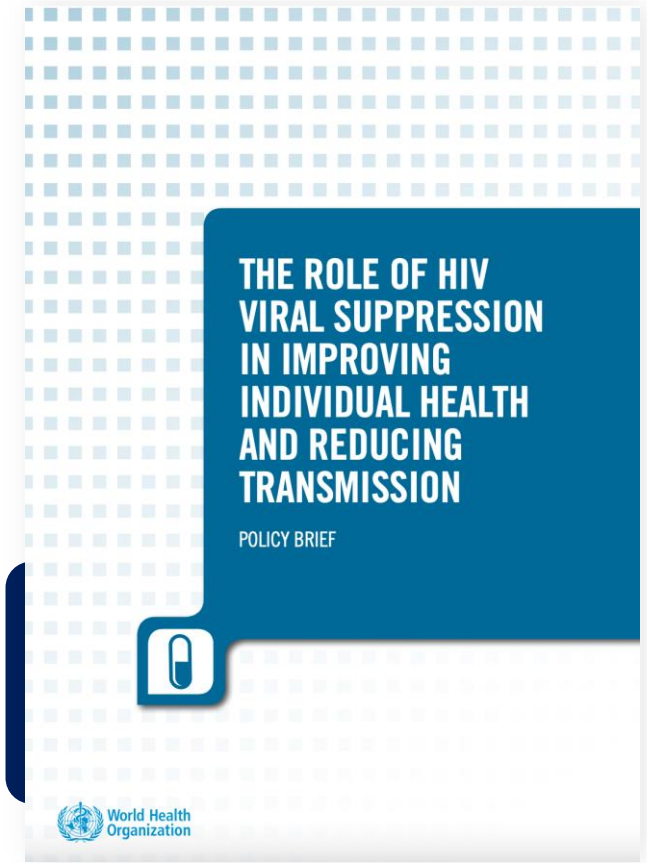
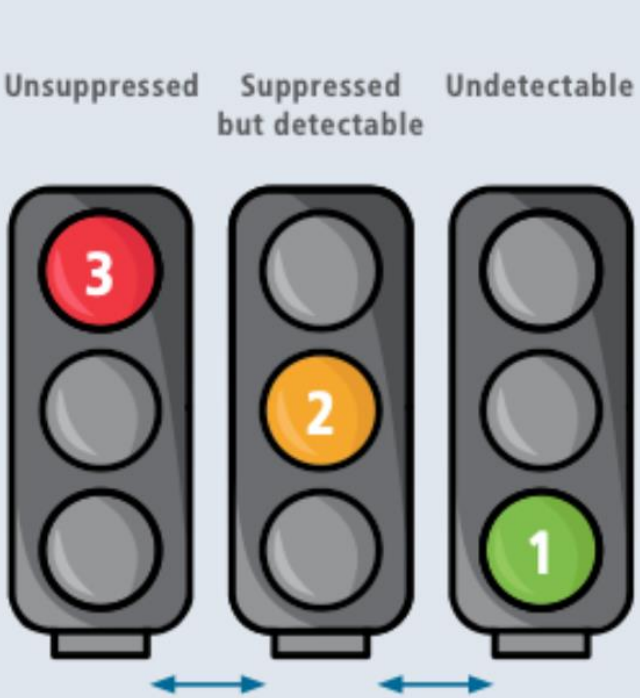
Evidence consolidation and review of the risks of sexual HIV transmission based on viral load levels

Reflecting on the benefits and harms of the evidence, impact of positive messaging, and challenges with stigma, discrimination, and criminalization



# Clear, celebratory messaging for people living with HIV

## 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.**

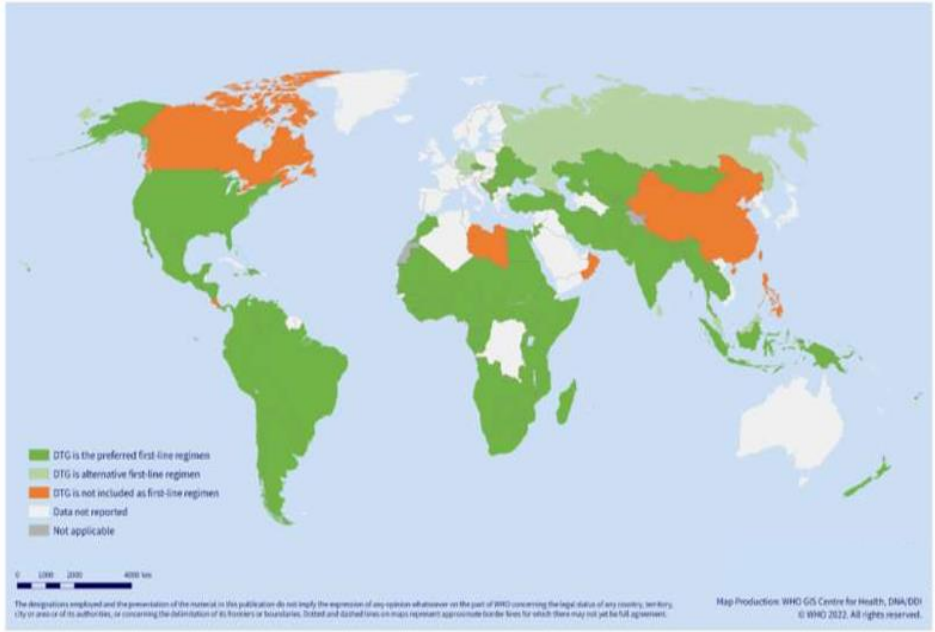
* Not detected by the test or sample type used.

# The evolution of optimized ART: towards smarter and better treatment options

- DTG/TLD have clinical and programmatic advantages over old regimens, including higher barrier to drug resistance
- Transition to TLD almost completed globally. The next action is to define what and how to monitor
- Some barriers to complete TLD transition: NTD concerns, local production of old drugs, BWG
- Concerns related to potential long-term toxicity (cardiometabolic issues) and resistance risk - WHO developed tools to monitor it

**Adoption of TDF+3TC (or FTC)+DTG as the preferred first-line antiretroviral combination for treatment iniation in national guidelines for adults and adolescents, July 2022**

By July 2022, 108 countries (88%) adopting DTG as part of the preferred first-line antiretroviral therapy for adults and adolescents, an 80% increase from 60 countries in 2020 when data for this indicator was first collected.

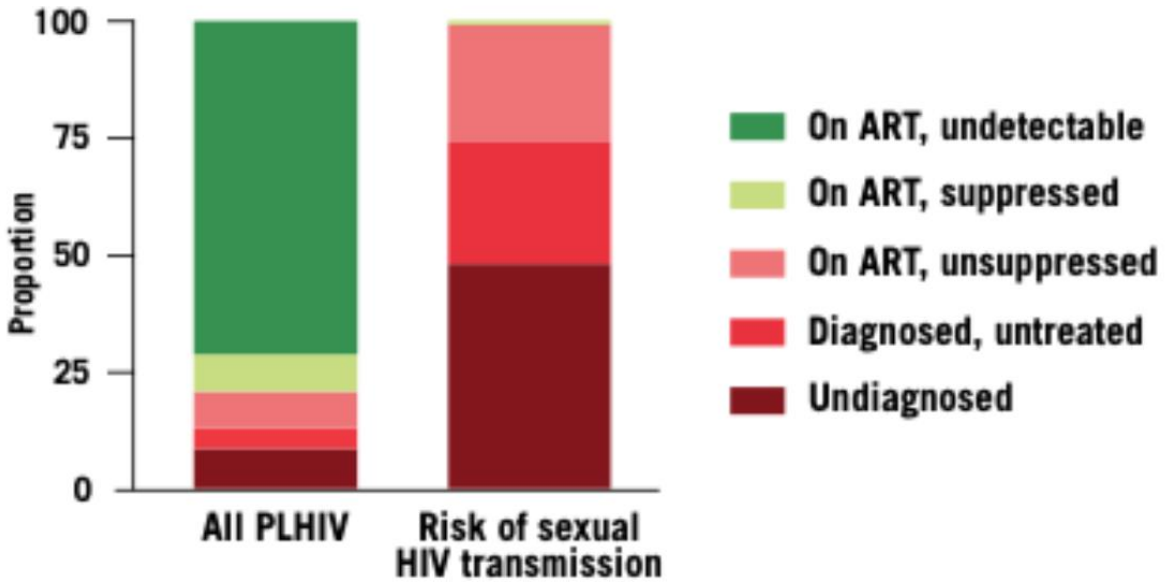



Source: Global AIDS Monitoring (UNAIDS/WHO/UNICEF) and Global HIV, Hepatitis and STIs Programmes (HHS), WHO, 2022

**Rapid global uptake of TLD: adopted in +100 LMICs and used by >80% of PLHIV on ART**

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

## 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).

# 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.

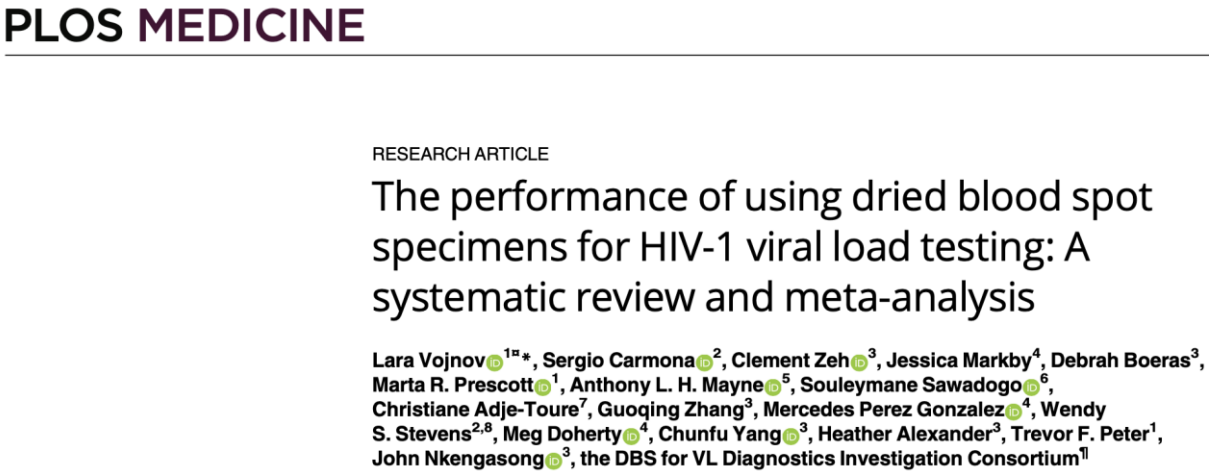
# How can dried blood spot samples be used?

World Health Organization

## 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

# Performance of dried blood spot samples for viral load testing

World Health Organization

| | | All technologies | Abbott RealTime HIV-1 two-spot | Abbott RealTime HIV-1 one-spot | Biocentric Generic HIV Charge Virale | bioMerieux NucliSENS EasyQ HIV-1 | Hologic Aptima | Roche COBAS TaqMan HIV-1 FVE | Roche COBAS TaqMan HIV-1 SPEX | Siemens VERSANT HIV-1 RNA |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | 10,831 | 2,004 | 700 | 531 | 1,062 | 124 | 3,076 | 3,190 | 144 |
| | **DBS:plasma threshold comparisons** | | | | | | | | | |
| **Sensitivity (UCL-LCL)** | 800:800 | 95.04 (91.45–97.17) | 92.59 (82.86–96.99) | 91.55 (4.60–99.96) | 98.64 (43.94–99.99) | 85.36 (80.27–89.32) | 93.47 (31.10–99.78) | 95.35 (87.11–98.42) | 99.70 (95.62–99.98) | 91.07 (74.87–97.22) |
| | 600:600 | 95.24 (92.21–97.12) | 92.71 (84.14–96.83) | 92.95 (0.04–100.00) | 98.55 (60.16–99.97) | 88.87 (83.99–92.40) | 94.54 (27.75–99.87) | 94.17 (83.85–98.05) | 99.26 (96.03–99.87) | 93.45 (84.10–97.47) |
| | 500:500 | 95.43 (92.38–97.30) | 93.11 (84.49–97.11) | 92.96 (0.00–100.00) | 98.40 (66.61–99.95) | 89.04 (84.76–92.22) | 94.50 (29.45–99.86) | 93.37 (81.99–97.75) | 99.22 (95.81–99.86) | 97.21 (66.06–99.84) |
| | 400:400 | 95.51 (92.35–97.41) | 92.48 (84.11–96.61) | 94.36 (0.00–100.00) | 97.79 (60.28–99.92) | 90.17 (85.52–93.44) | 94.69 (28.03–99.88) | 92.26 (80.79–97.13) | 99.36 (95.26–99.92) | 97.18 (62.91–99.86) |
| | 200:200 | 94.78 (91.11–96.99) | 90.80 (82.55–95.37) | 97.18 (0.00–100.00) | 98.09 (65.21–99.93) | 89.42 (83.74–93.28) | 95.01 (22.04–99.92) | 89.86 (76.26–96.07) | 99.16 (94.75–99.87) | 97.67 (71.68–99.86) |
| | Detectable | 95.39 (90.12–97.91) | 92.81 (76.47–98.09) | 93.13 (62.76–99.09) | 97.98 (59.94–99.94) | 88.59 (75.29–95.18) | 75.42 (51.82–89.75) | 97.10 (58.02–99.88) | 99.76 (94.64–99.99) | 90.08 (83.66–94.15) |



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# Performance of dried blood spot samples for viral load testing

| | | All technologies | Abbott RealTime HIV-1 two-spot | Abbott RealTime HIV-1 one-spot | Biocentric Generic HIV Charge Virale | bioMerieux NucliSENS EasyQ HIV-1 | Hologic Aptima | Roche COBAS TaqMan HIV-1 FVE | Roche COBAS TaqMan HIV-1 SPEX | Siemens VERSANT HIV-1 RNA |
|---|---|---|---|---|---|---|---|---|---|---|
| **Specificity (UCL-LCL)** | 800:800 | 83.56 (71.57–91.12) | 92.01 (83.14–96.41) | 99.77 (23.66–100.00) | 38.14 (10.78–75.88) | 95.99 (91.31–98.20) | 72.16 (41.80–90.34) | 92.86 (64.86–98.92) | 37.59 (13.30–70.28) | 86.62 (68.28–95.11) |
| | 600:600 | 82.52 (69.82–90.60) | 92.54 (81.42–97.23) | 99.77 (12.38–100.00) | 28.13 (5.97–70.70) | 95.21 (91.29–97.42) | 89.34 (50.48–98.57) | 92.95 (68.03–98.79) | 32.98 (11.54–64.98) | 78.77 (60.95–89.82) |
| | 500:500 | 80.41 (66.80–89.33) | 93.16 (81.96–97.61) | 99.77 (9.33–100.00) | 23.72 (4.28–68.41) | 95.27 (91.10–97.54) | 89.06 (50.38–98.49) | 91.71 (67.71–98.32) | 29.63 (9.78–62.04) | 65.63 (30.99–89.04) |
| | 400:400 | 79.81 (65.43–89.20) | 93.15 (80.02–97.88) | 99.77 (8.20–100.00) | 11.35 (0.61–72.77) | 95.61 (90.73–97.98) | 88.44 (47.82–98.46) | 92.04 (67.80–98.45) | 27.71 (9.04–59.65) | 64.91 (24.64–91.28) |
| | 200:200 | 81.57 (67.54–90.40) | 97.22 (91.66–99.11) | 99.78 (5.34–100.00) | 15.09 (1.30–70.49) | 92.94 (89.26–95.43) | 81.48 (71.52–88.52) | 91.60 (71.21–97.96) | 25.31 (7.60–58.26) | 64.68 (26.23–90.41) |
| | Detectable | 60.98 (34.29–82.40) | 78.79 (8.46–99.33) | 93.16 (66.40–98.94) | 18.62 (4.87–50.58) | 93.46 (90.43–95.59) | 87.18 (66.58–95.87) | 58.09 (6.37–96.58) | 4.25 (0.17–53.54) | 69.23 (40.93–87.96) |



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# Performance of near point-of-care viral load testing

**Performance of Cepheid Xpert HIV-1 viral load plasma assay to accurately detect treatment failure**

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**Background:** Coverage of viral load testing remains low with only half of the patients in need having adequate access. Alternative technologies to high throughput centralized machines can be used to support viral load scale-up; however, clinical performance data are lacking. We conducted a meta-analysis comparing the Cepheid Xpert HIV-1 viral load plasma assay to traditional laboratory-based technologies.

**Methods:** Cepheid Xpert HIV-1 and comparator laboratory technology plasma viral load results were provided from 13 of the 19 eligible studies, which accounted for a total of 3790 paired data points. We used random effects models to determine the accuracy and misclassification at various treatment failure thresholds (detectable, 200, 400, 500, 600, 800 and 1000 copies/ml).

**Results:** Thirty percent of viral load test results were undetectable, while 45% were between detectable and 10 000 copies/ml and the remaining 25% were above 10 000 copies/ml. The median Xpert viral load was 119 copies/ml and the median comparator viral load was 157 copies/ml, while the $\log_{10}$ bias was 0.04 (0.02–0.07). The sensitivity and specificity to detect treatment failure were above 95% at all treatment failure thresholds, except for detectable, at which the sensitivity was 93.33% (95% confidence interval: 88.2–96.3) and specificity was 80.56% (95% CI: 64.6–90.4).

**Conclusion:** The Cepheid Xpert HIV-1 viral load plasma assay results were highly comparable to laboratory-based technologies with limited bias and high sensitivity and specificity to detect treatment failure. Alternative specimen types and technologies that enable decentralized testing services can be considered to expand access to viral load.



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| n | 3790 |
|---|---|
| Cepheid Xpert | |
| Median viral load (copies/ml) | 119 |
| Comparator | |
| Median viral load (copies/ml) | 157 |
| Difference in medians (copies/ml) | −38 |
| Mean bias (log copies/ml) | 0.04 (0.02–0.07) |
| Threshold comparisons | |
| Sensitivity (UCL-LCL) | |
| 1000 : 1000 | 96.47 (95.10–97.47) |
| 800 : 800 | 96.92 (95.80–97.75) |
| 600 : 600 | 96.86 (95.74–97.69) |
| 500 : 500 | 96.74 (95.60–97.59) |
| 400 : 400 | 96.04 (94.80–96.98) |
| 200 : 200 | 95.36 (93.37–96.77) |
| Detectable | 93.33 (88.24–96.31) |
| Specificity (UCL-LCL) | |
| 1000 : 1000 | 96.59 (92.90–98.39) |
| 800 : 800 | 96.75 (92.58–98.61) |
| 600 : 600 | 95.88 (91.86–97.96) |
| 500 : 500 | 95.35 (90.22–97.85) |
| 400 : 400 | 96.00 (92.66–97.86) |
| 200 : 200 | 97.69 (94.56–99.04) |
| Detectable | 80.56 (64.63–90.39) |



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# 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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