Evidence and rationale for using WHO HIV testing strategies and algorithms

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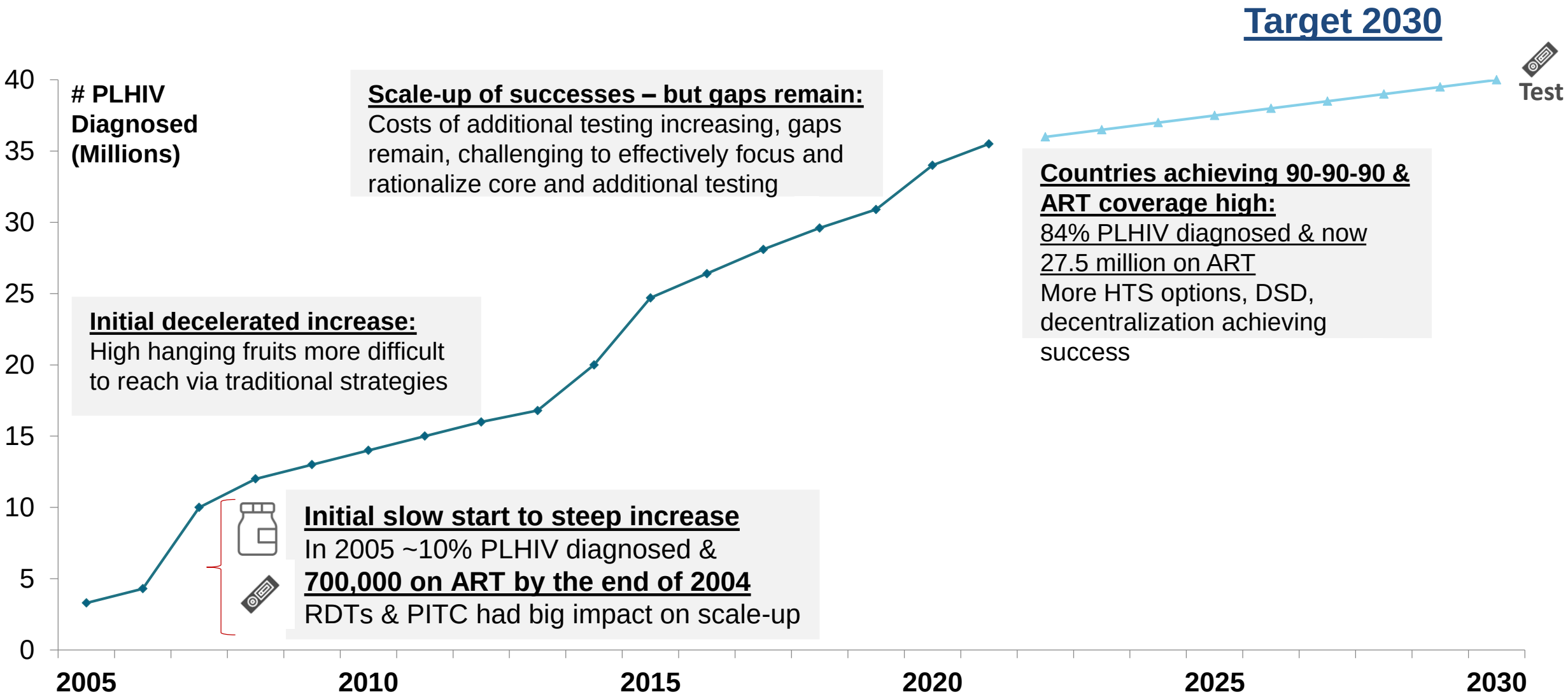
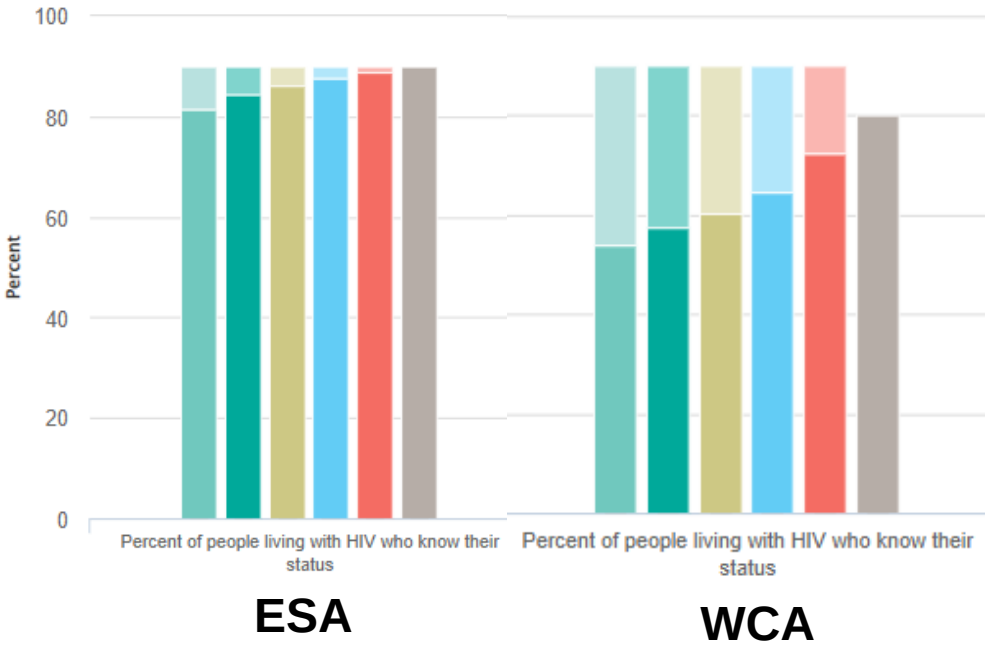
Progress toward global HIV testing targets



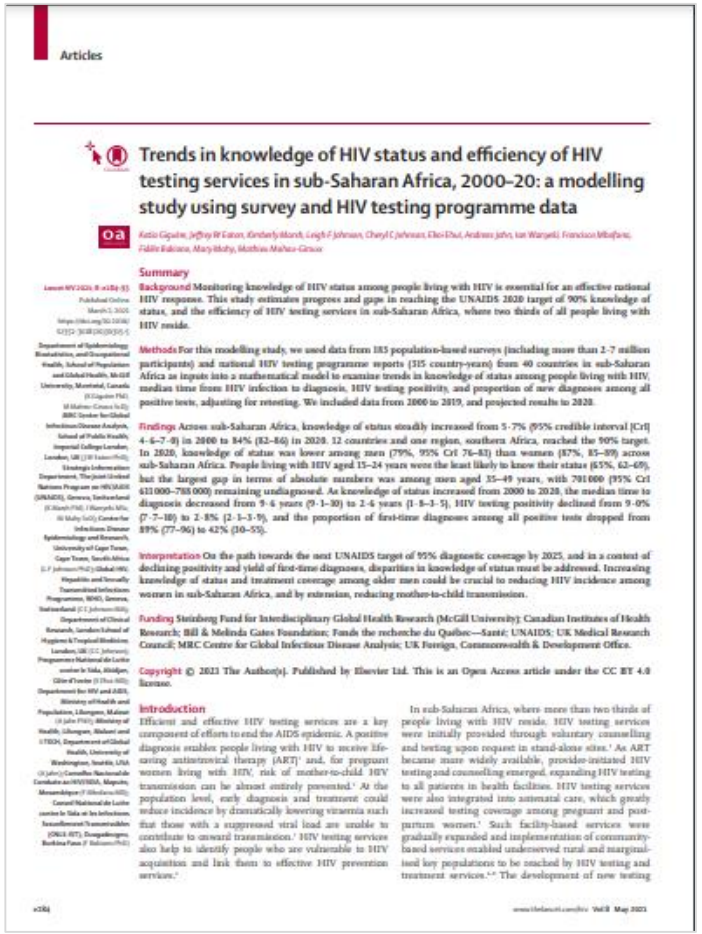
Source: WHO forecast 2020; UNAIDS 2022; WHO 2005; CHAI 2015; WHO, UNICEF, PEPFAR, GFTAM 2018

HIV positivity is declining and will continue to decline in sub-Saharan Africa

80-90% of all PLHIV diagnosed



ESA **WCA**



Articles

Trends in knowledge of HIV status and efficiency of HIV testing services in sub-Saharan Africa, 2000–20: a modelling study using survey and HIV testing programme data

Summary

Background Monitoring knowledge of HIV status among people living with HIV is essential for an effective national HIV response. This study estimates progress and gaps in reaching the UNAIDS 2020 target of 90% knowledge of status, and the efficiency of HIV testing services in sub-Saharan Africa, where two thirds of all people living with HIV reside.

Methods For this modelling study, we used data from 183 population-based surveys (including more than 2·7 million participants) and national HIV testing programme reports (315 country-years) from 40 countries in sub-Saharan Africa as inputs into a mathematical model to examine trends in knowledge of status among people living with HIV, median time from HIV infection to diagnosis, HIV testing positivity, and proportion of new diagnoses among all positive tests, adjusting for retesting. We included data from 2000 to 2019, and projected results to 2020.

Findings Across sub-Saharan Africa, knowledge of status steadily increased from 5·7% (95% credible interval [CrI] 4·6–7·0) in 2000 to 84% (82–86) in 2020. 12 countries and one region, southern Africa, reached the 90% target. In 2020, knowledge of status was lower among men (79%, 95% CrI 76–83) than women (87%, 85–89) across sub-Saharan Africa. People living with HIV aged 15–24 years were the least likely to know their status (65%, 62–69), but the largest gap in terms of absolute numbers was among men aged 35–49 years, with 701 000 (95% CrI 611 000–785 000) remaining undiagnosed. As knowledge of status increased from 2000 to 2020, the median time to diagnosis decreased from 9·4 years (9·1–10) to 2·4 years (1·8–3·5), HIV testing positivity declined from 9·0% (7·7–10) to 2·8% (2·1–3·9), and the proportion of first-time diagnoses among all positive tests dropped from 89% (77–96) to 42% (30–55).

Interpretation On the path towards the next UNAIDS target of 95% diagnostic coverage by 2025, and in a context of declining positivity and yield of first-time diagnoses, disparities in knowledge of status must be addressed. Increasing knowledge of status and treatment coverage among older men could be crucial to reducing HIV incidence among women in sub-Saharan Africa, and by extension, reducing mother-to-child transmission.

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Introduction

Efficient and effective HIV testing services are a key component of efforts to end the AIDS epidemic. A positive diagnosis enables people living with HIV to receive life-saving antiretroviral therapy (ART)[1] and, for pregnant women living with HIV, risk of mother-to-child HIV transmission can be almost entirely prevented.[2] At the population level, early diagnosis and treatment could reduce incidence by dramatically lowering viraemia such that those with a suppressed viral load are unable to contribute to onward transmission.[3] HIV testing services also help to identify people who are vulnerable to HIV acquisition and link them to effective HIV prevention services.[4]

In sub-Saharan Africa, where more than two thirds of people living with HIV reside, HIV testing services were initially provided through voluntary counselling and testing upon request in stand-alone sites.[5] As ART became more widely available, provider-initiated HIV testing and counselling emerged, expanding HIV testing to all patients in health facilities. HIV testing services were also integrated into antenatal care, which greatly increased testing coverage among pregnant and post-partum women.[5] Such facility-based services were gradually expanded and implementation of community-based services enabled underserved rural and marginalised key populations to be reached by HIV testing and treatment services.[6,7] The development of new testing

Key HTS trends

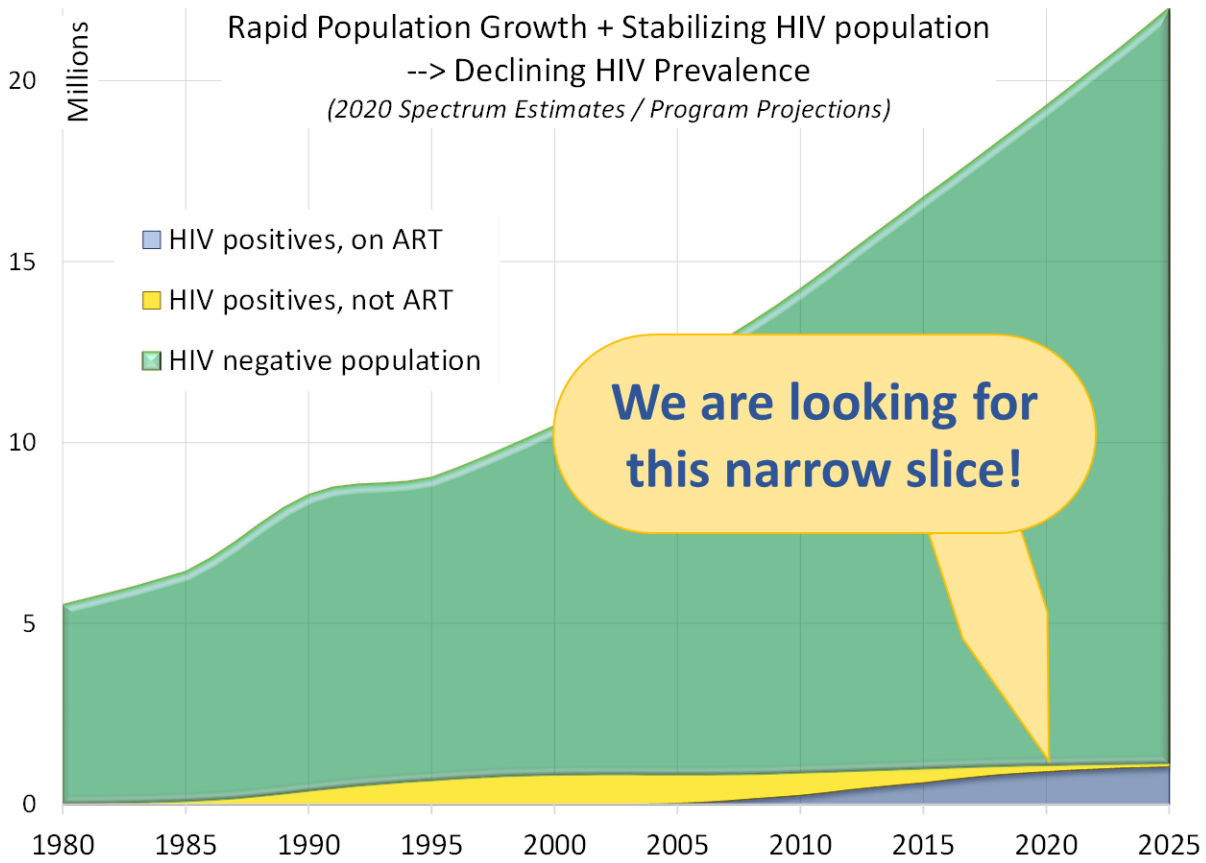
The number of people newly diagnosed with HIV declining rapidly due to ART scale-up

Between 2000-2020, HTS positivity declined from 9% to 2.8%; and will continue to decline

No country achieving HTS positivity at or above 5% nationally

UNAIDS 2022; WHO 2019, Maheu-Giroux 2021: https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30315-5/fulltext; Eaton AIDS 2022

Example in high HIV burden country: Malawi



In 2020, 3 million people tested
91,000 new positives identified

- Undiagnosed PLHIV declined from 78% in 2005 to 14% in 2017 and is projected to continue declining to around 6% in 2025.
- By 2025 national HTS positivity is expected to reach 1.5%.
  - Discounting those who already know their status, further reduces HTS positivity to 0.5% in 2025 nationally.

Source: Graphic courtesy MOH Malawi, CROI 2020 Eaton, WHO 2019

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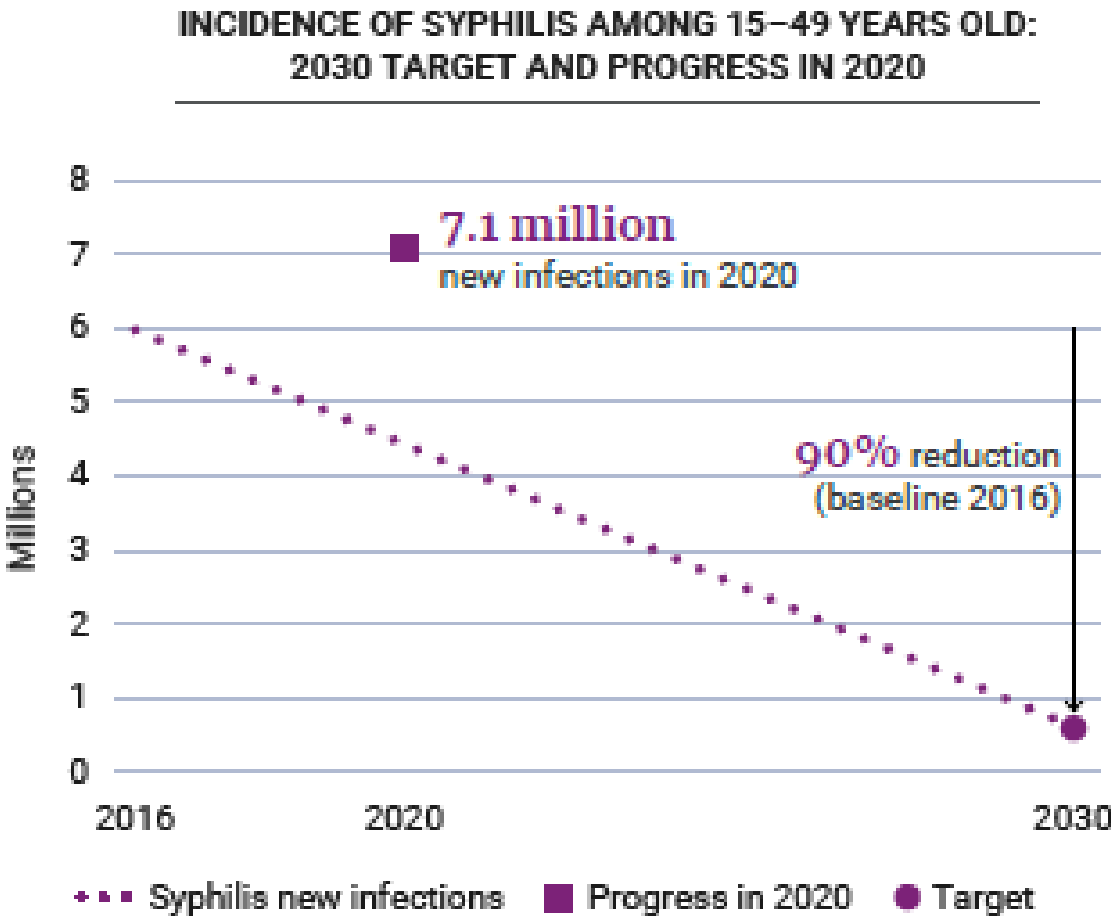
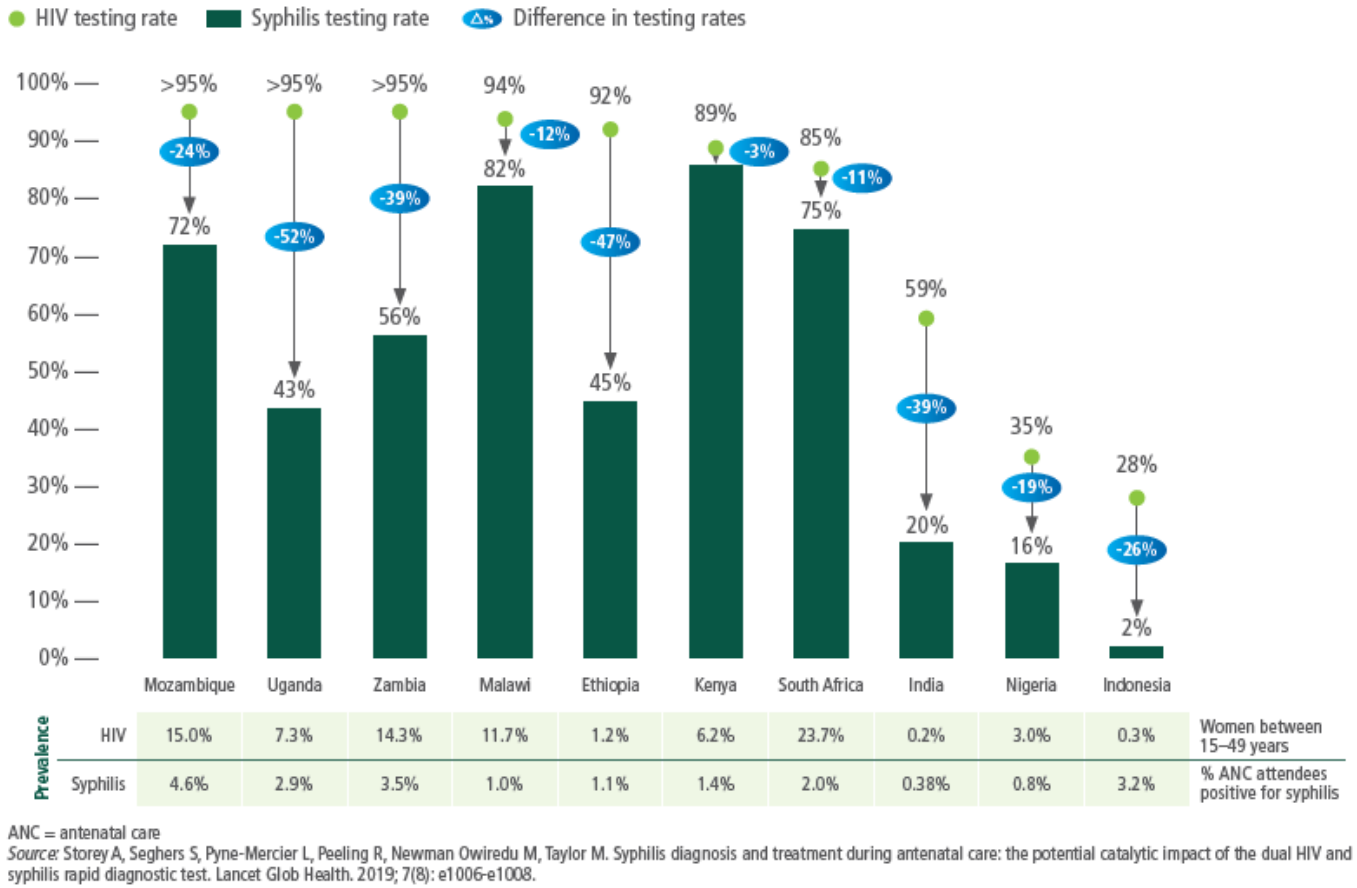
Important opportunities to address STIs

Particular focus on syphilis





ANC = antenatal care

Source: Storey A, Seghers S, Pyne-Mercier L, Peeling R, Newman Owiredu M, Taylor M. Syphilis diagnosis and treatment during antenatal care: the potential catalytic impact of the dual HIV and syphilis rapid diagnostic test. Lancet Glob Health. 2019; 7(8): e1006-e1008.

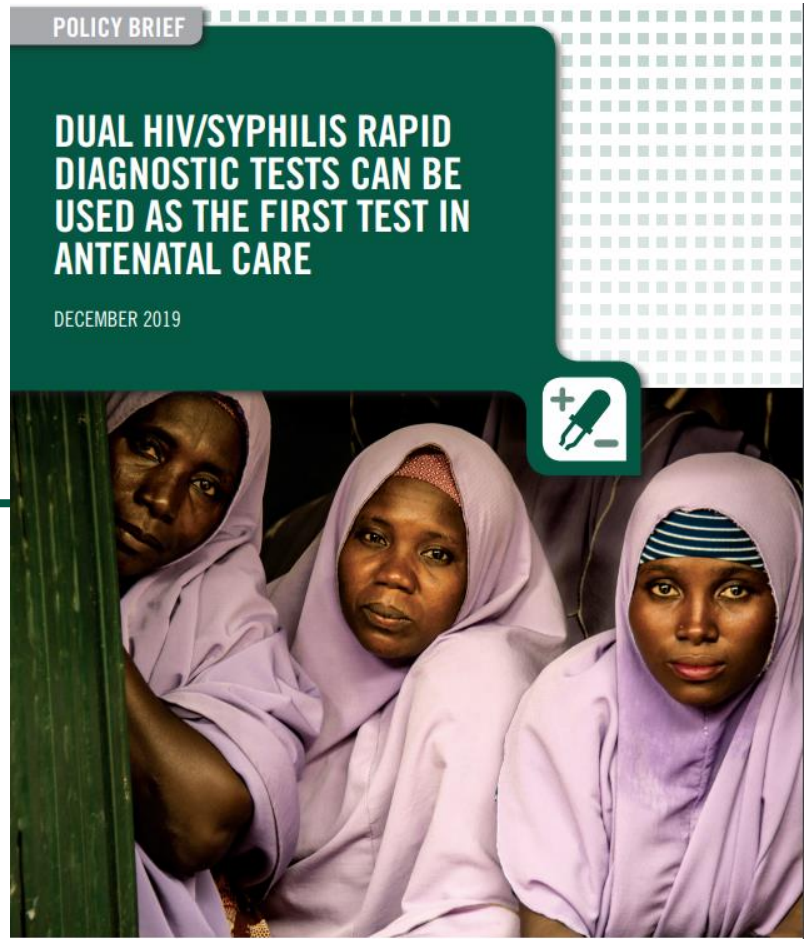
Source: WHO GHSS 2022; Storey 2019

Important opportunities to address STIs

Particular focus on syphilis

Recommends use of dual HIV/syphilis RDTs for pregnant women

Prioritize for first test in ANC



Recommends use of dual HIV/syphilis RDTs for key populations

Annual or bi-annual testing most cost-effective

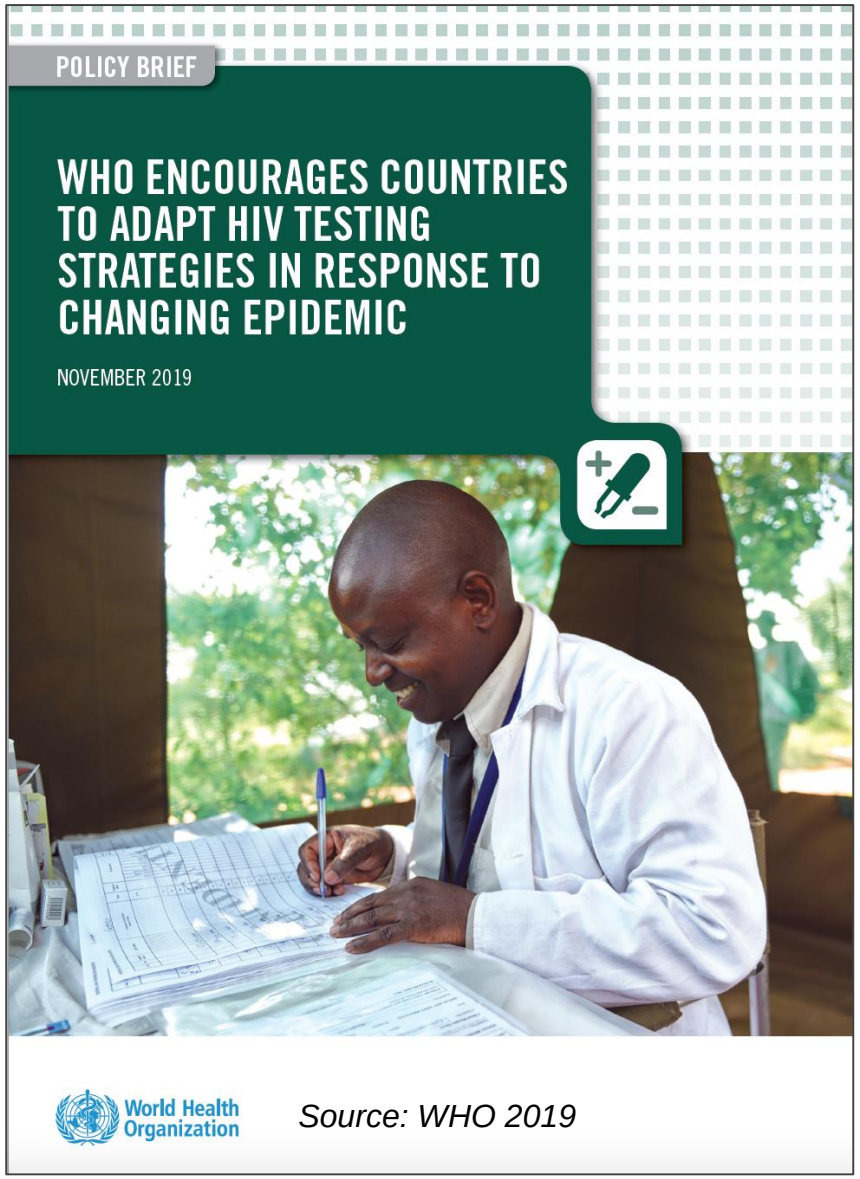
Source: WHO 2022; WHO 2019

High quality RDTs

- 23 different WHO PQed RDTs available for procurement
- HIV RDTs
  - All meet WHO's standards for at least 99% sensitivity and 98% specificity
- Dual HIV/Syphilis RDTs
  - 3 products available for procurement & low cost

Source: https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category_tid=58

Adapting national HIV testing strategies



Source: WHO 2019

WHO recommends all countries currently using two consecutive reactive tests for an HIV-positive diagnosis to move torward using three consecutive reactive tests for an HIV-positive diagnosis. This is increasingly important as treatment-adjusted HIV prevalence and national HTS positivity continue to decline over time.

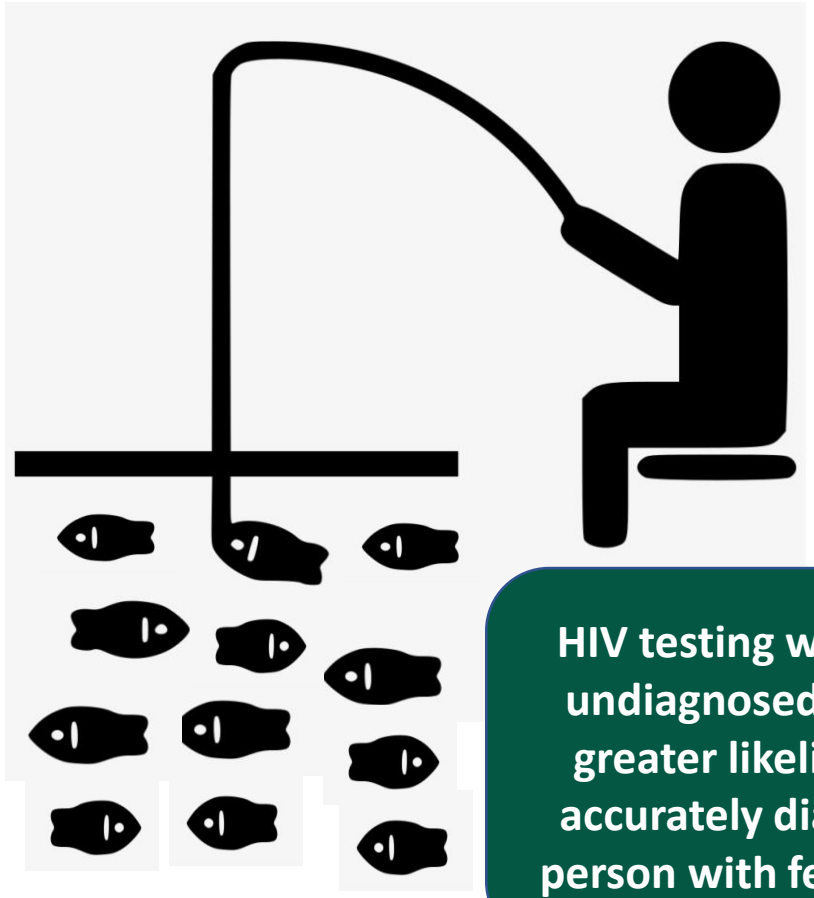
- **Ensure that the testing strategy has a positive predictive value ≥99% (PPV)**
  - Meaning of the persons classified as HIV+, ≥99% will truly be living with HIV
  - PPV depends on positivity rate among testing population

- **Quality assured assays, such as WHO prequalified, should be used:**
  - **≥99% sensitivity:** fewer than 1 *'false negative'* for 100 truly positive
  - **≥98% specificity:** fewer than 2 *'false positive'* for 100 truly negative
  - Either rapid diagnostic tests (RDTs) or enzyme immunoassay (EIA, CLIA, ECL)

Understanding positive predictive value (PPV)

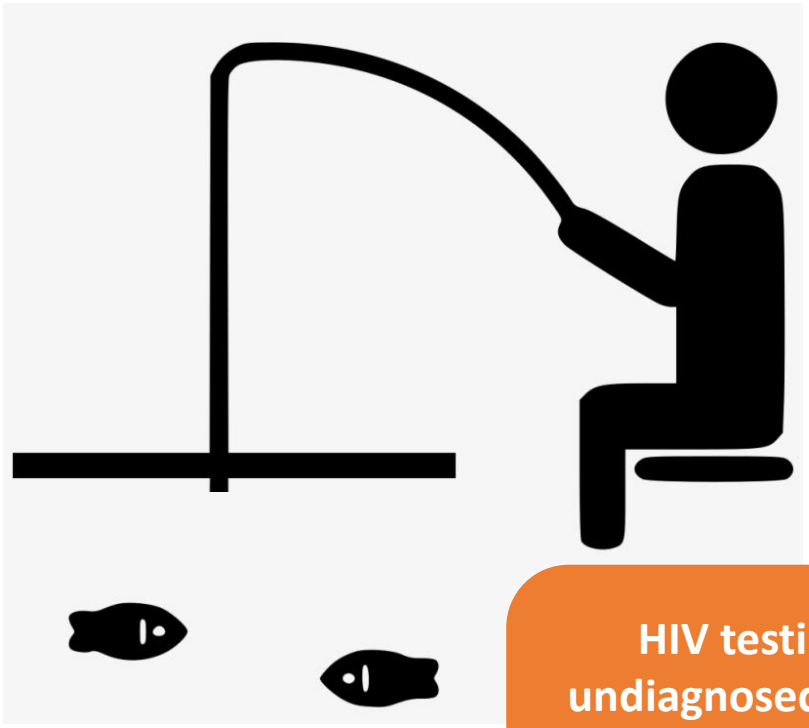
PPV= probability a person with a reactive HIV positive test result has HIV

High HIV prevalence



HIV testing with more undiagnosed PLHIV = greater likelihood of accurately diagnosing person with fewer tests

Low HIV prevalence



HIV testing with few undiagnosed PLHIV = lower likelihood of accurately diagnosing person with fewer tests

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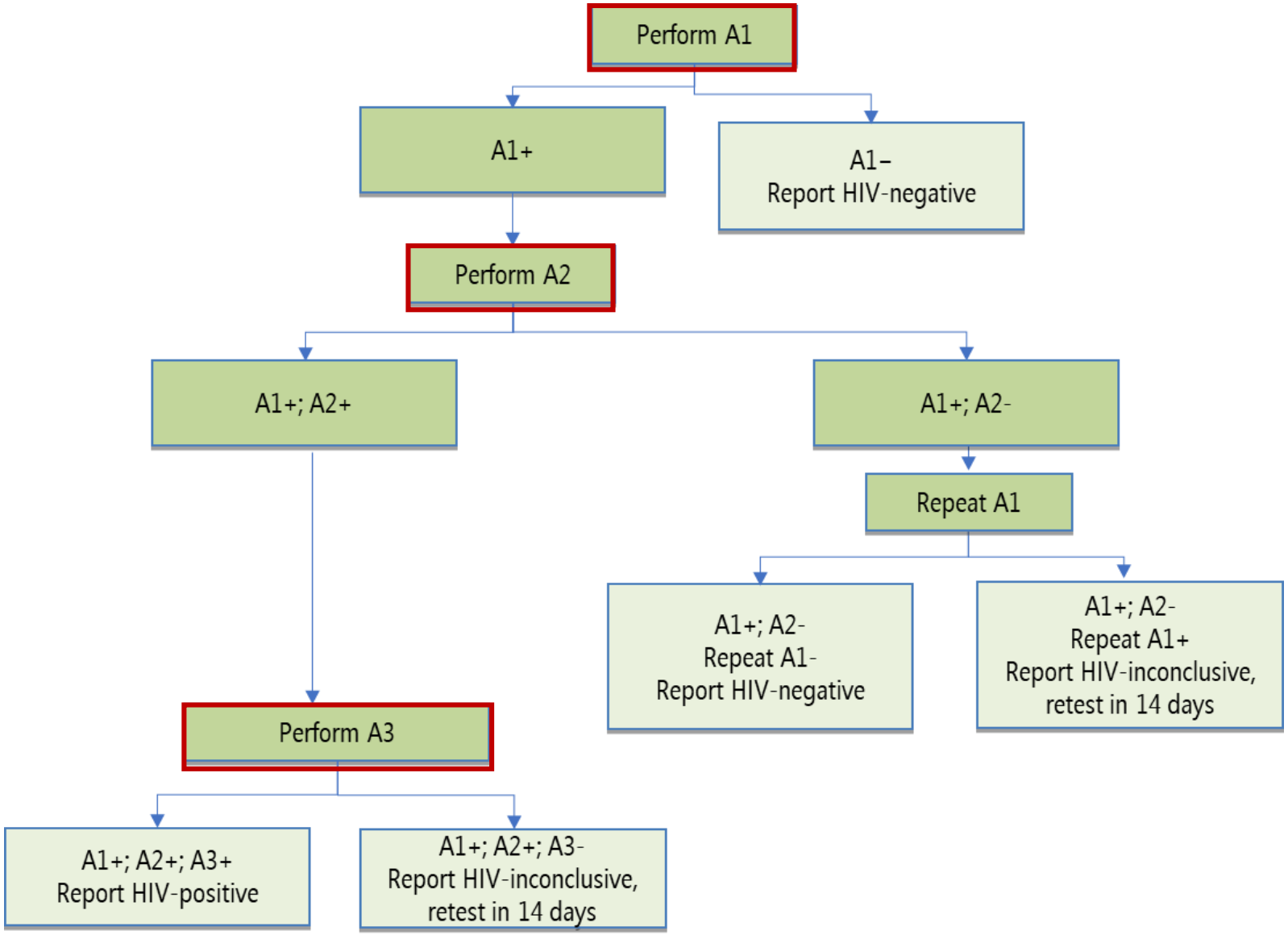
WHO recommended 3-test strategy

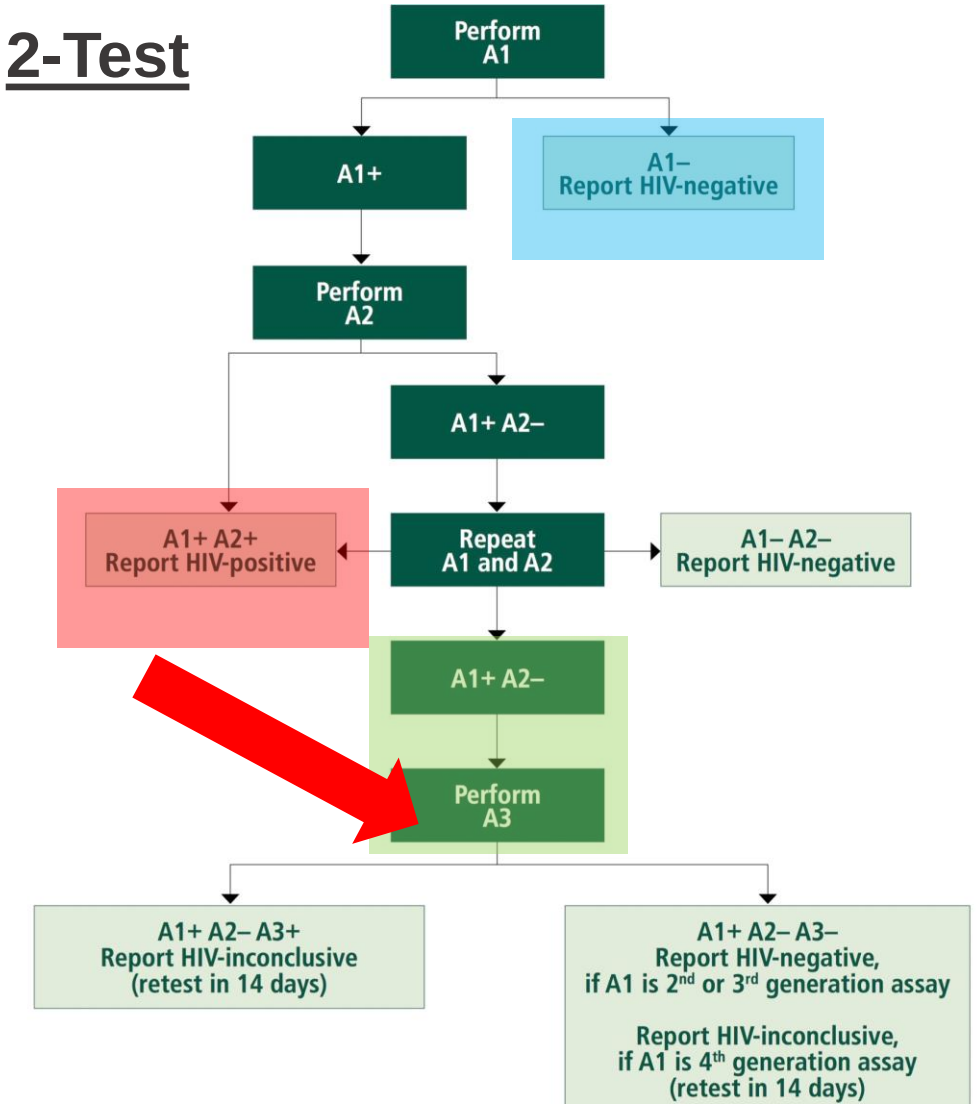


- All individuals are tested on Assay 1 (A1). Anyone with a non-reactive test result (A1–) is reported HIV-negative.
- Individuals who are reactive on Assay 1 (A1+) should then be tested on a separate and distinct Assay 2 (A2).
- Individuals who are reactive on both Assay 1 and Assay 2 (A1+; A2+) should then be tested on a separate and distinct Assay 3 (A3).
  - Report HIV-positive if Assay 3 is reactive (A1+; A2+; A3+)
  - Report HIV-inconclusive if Assay 3 is non-reactive (A1+; A2+; A3–). The individual should be asked to return in 14 days for additional testing.
- Individuals who are reactive on Assay 1 but non-reactive on Assay 2 (A1+; A2–) should be repeated on Assay 1
  - If repeat Assay 1 is non-reactive (A1+; A2–; repeat A1–), the status should be reported as **HIV-negative**;
  - If repeat Assay 1 is reactive (A1+; A2–; repeat A1+), the status should be reported as **HIV-inconclusive**, and the individual asked to return in 14 days for additional testing.

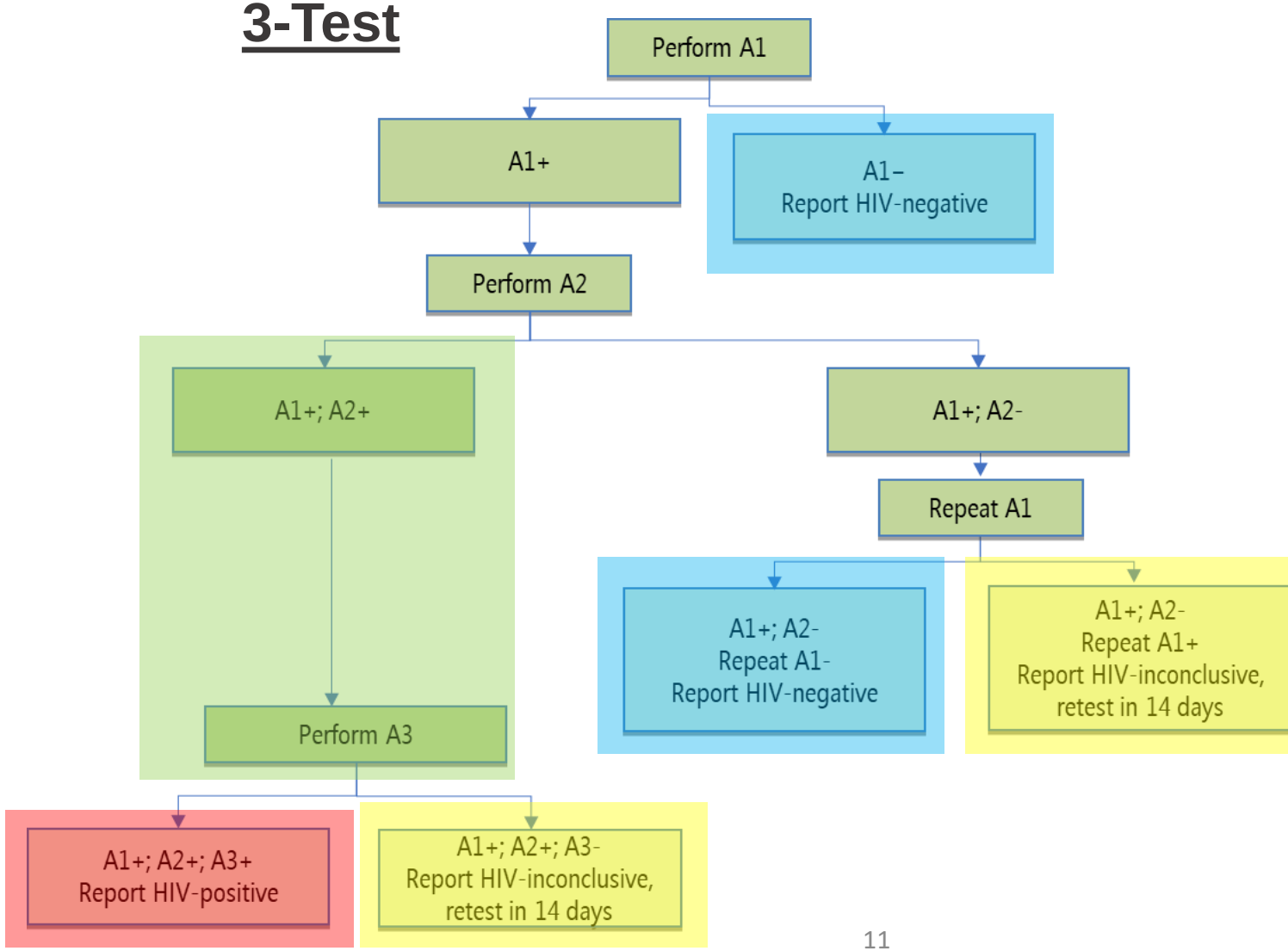
Source: WHO 2019

Difference between 2-test and 3-test strategy?

2-Test



3-Test



- *2- or 3-test strategy refer to number of consecutive reactive tests to diagnose HIV*
- *both strategies require 3 assays (A3) & neither uses any tiebreaker approaches*
- *3 test strategy recommended since 1997 & has been used in most settings outside Africa because of lower burden*

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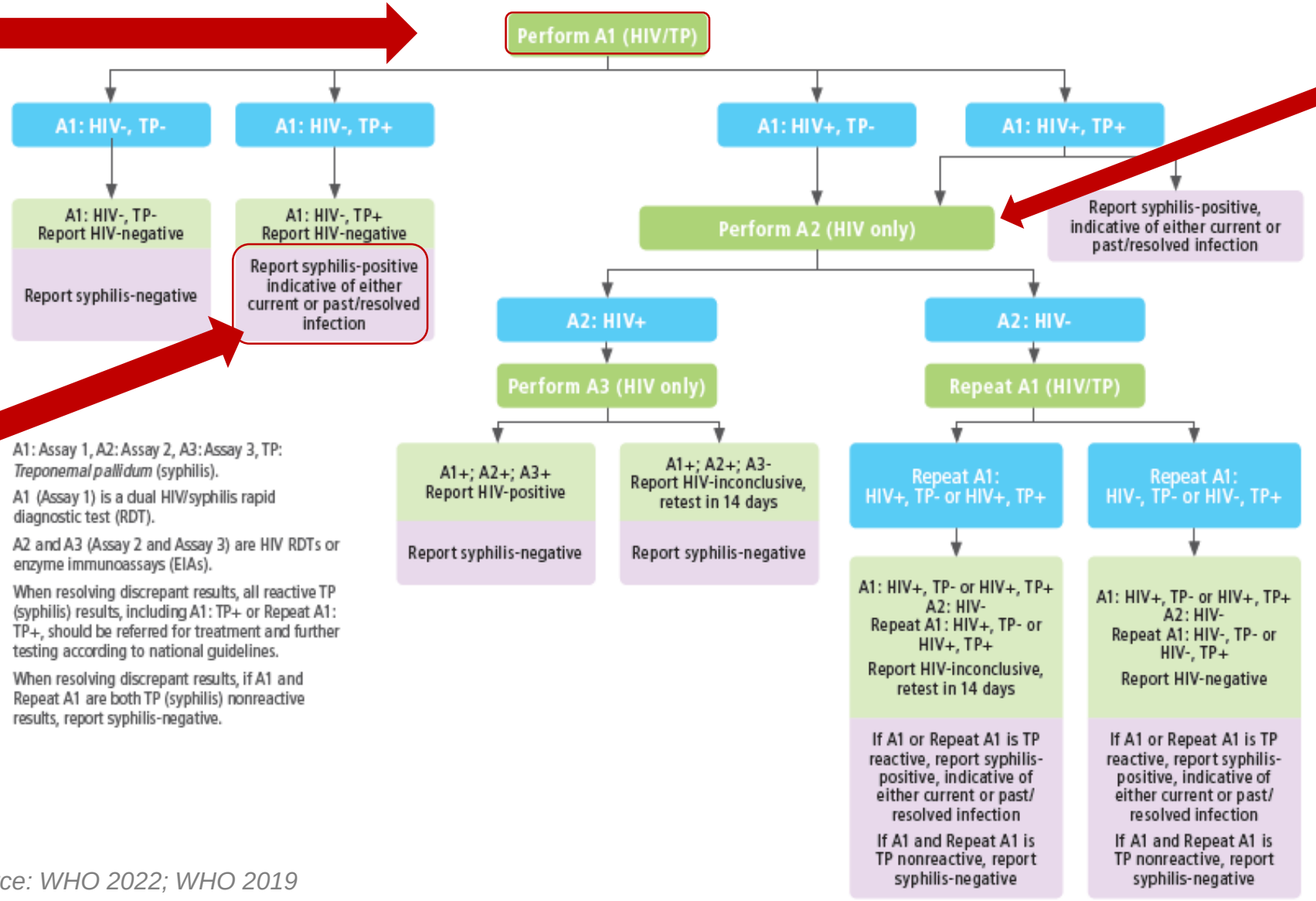
WHO recommended testing strategy for HIV/syphilis

Dual test used as the first test in strategy



HIV testing strategy is the same as standard of care

Treatment for any reactive syphilis result in pregnant women

A1: Assay 1, A2: Assay 2, A3: Assay 3, TP: *Treponemal pallidum* (syphilis).

A1 (Assay 1) is a dual HIV/syphilis rapid diagnostic test (RDT).

A2 and A3 (Assay 2 and Assay 3) are HIV RDTs or enzyme immunoassays (EIAs).

When resolving discrepant results, all reactive TP (syphilis) results, including A1: TP+ or Repeat A1: TP+, should be referred for treatment and further testing according to national guidelines.

When resolving discrepant results, if A1 and Repeat A1 are both TP (syphilis) nonreactive results, report syphilis-negative.

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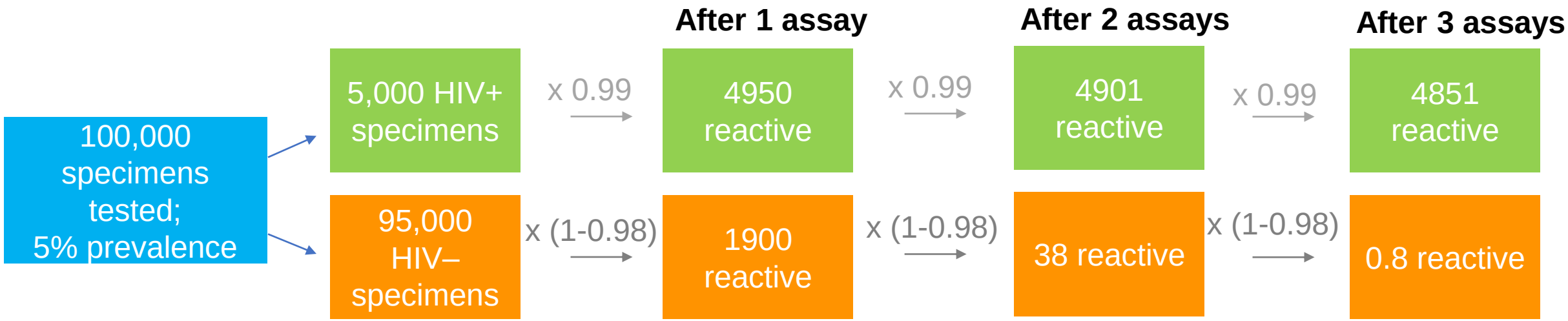
Source: WHO 2022; WHO 2019

PPV and number of tests

Probability of correctly being classified as HIV positive (assuming 99% sensitivity; 98% specificity)



$$PPV = \frac{4950}{4950+1900} = 72\%$$

$$PPV = \frac{4901}{4901+38} = 99.2\%$$

$$PPV = \frac{4851}{4851+0.8} > 99.9\%$$

***Simplified algorithm - consecutive reactive HIV tests only*

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Why a 3-test strategy for all settings?

No more settings have HTS positivity nationally at 5% or above, thus 99% PPV cannot be maintained
Without the 3-test strategy there will be increasing number of people misdiagnosed with HIV

Outcomes per 100,000 tested

Assuming 99% sensitivity; 98% specificity; simplified algorithm -- consecutive HIV+ tests only

True prevalence	Per 100,000 tested	After 1 assay
10%	10,000 HIV+ 90,000 HIV-	9900 true+ (99%) 1800 false+ (2%) **85% PPV**
5%	5000 HIV+ 95,000 HIV-	
1%	1000 HIV+ 99,000 HIV-	
0.1%	100 HIV+ 99,900 HIV-	

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Summary of WHO modelling analyses

Conducted modelling with country data to inform WHO the HIV testing guidelines

Modell compared 2-test vs 3-test strategy for varying positivity levels (5% to 0.1%):

- Number of misclassifications.
- PPV and NPV.
- Number of test kits used.
- Total HTS cost.

Source: Eaton et al 2021 https://www.medrxiv.org/content/10.1101/2021.03.31.21254700v1.full

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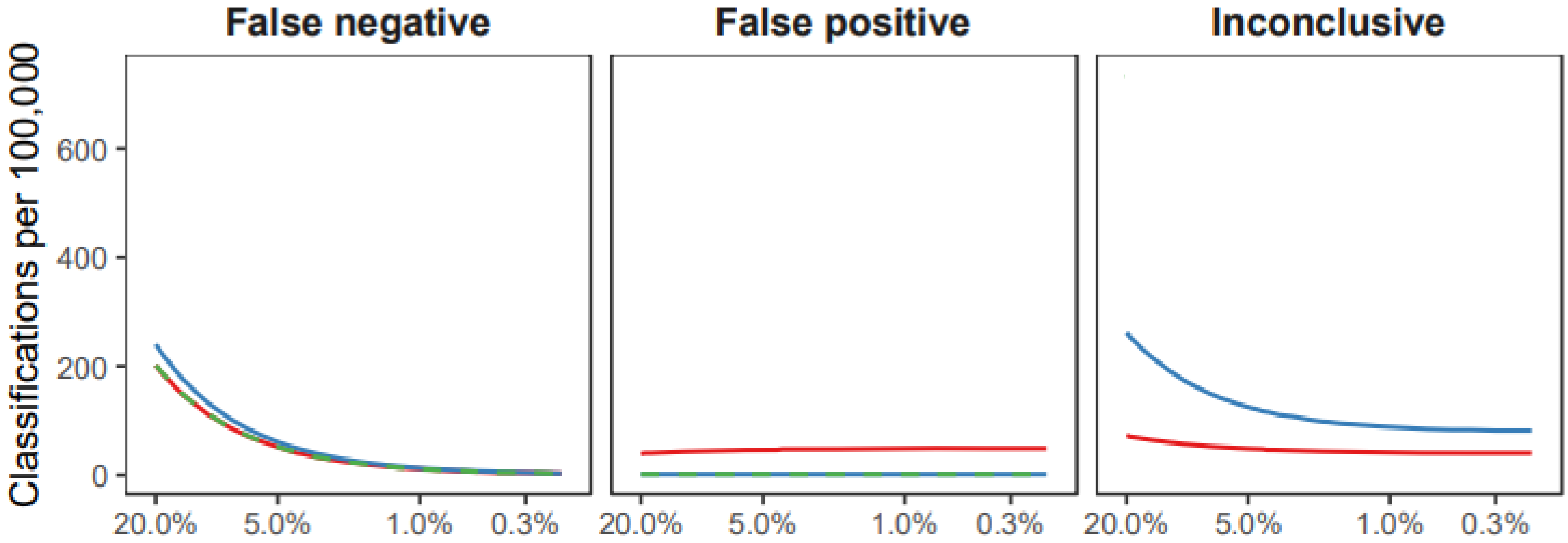
Expected number of false negative, false positive, and inconclusive classifications per 100,000 clients



Greater false positives diagnoses with 2-test strategy
Greater number of inconclusives with 3-test strategy (good tradeoff as would have been misdiagnosed HIV positive under 2-test strategy)

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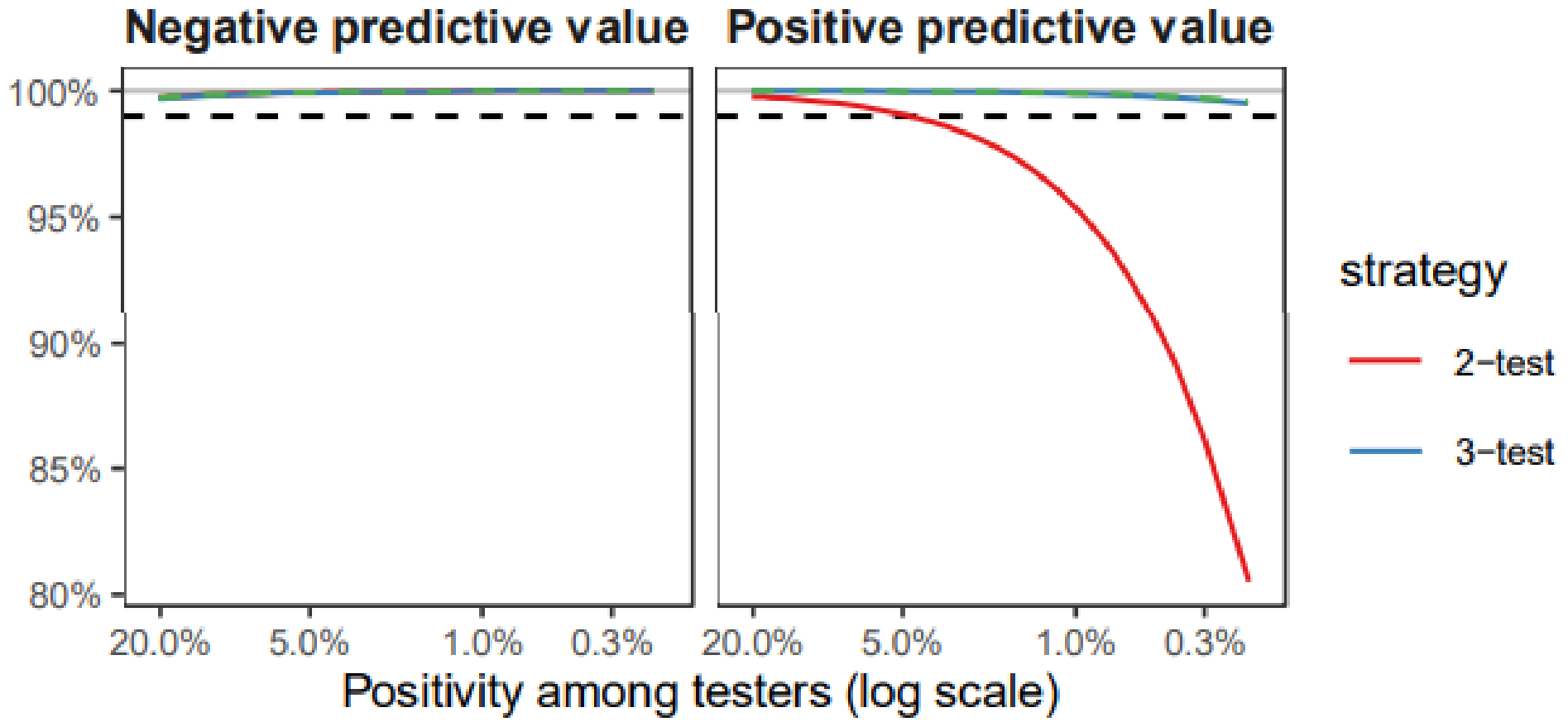
Negative predictive value and positive predictive value for 2 vs 3 test strategy



Positive predictive value drops off substantially as HIV positivity in population being tested drops

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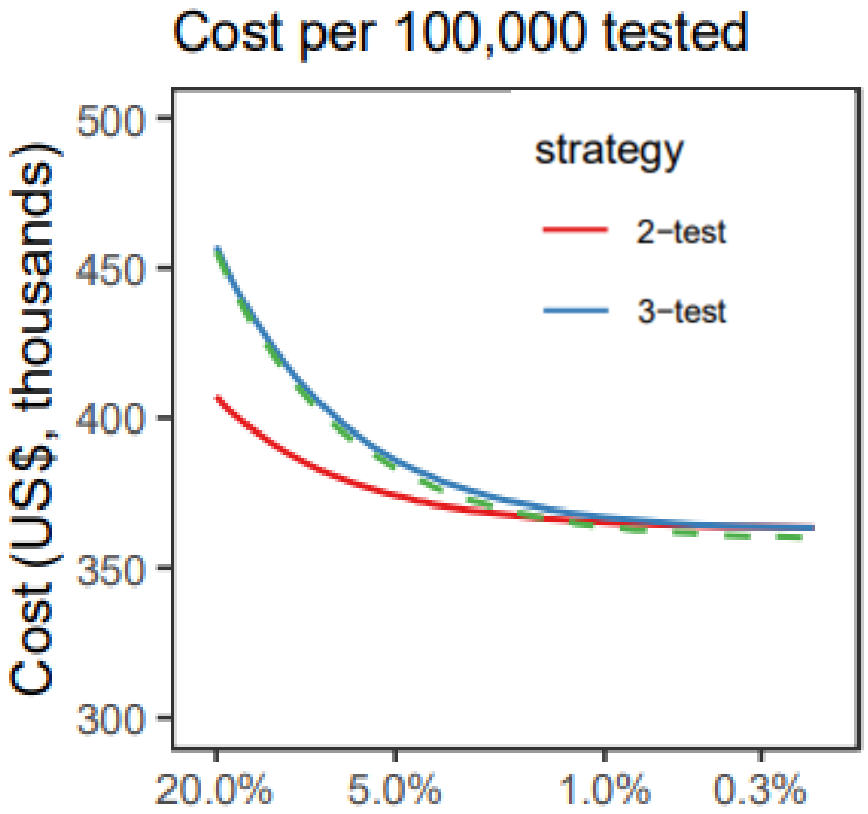
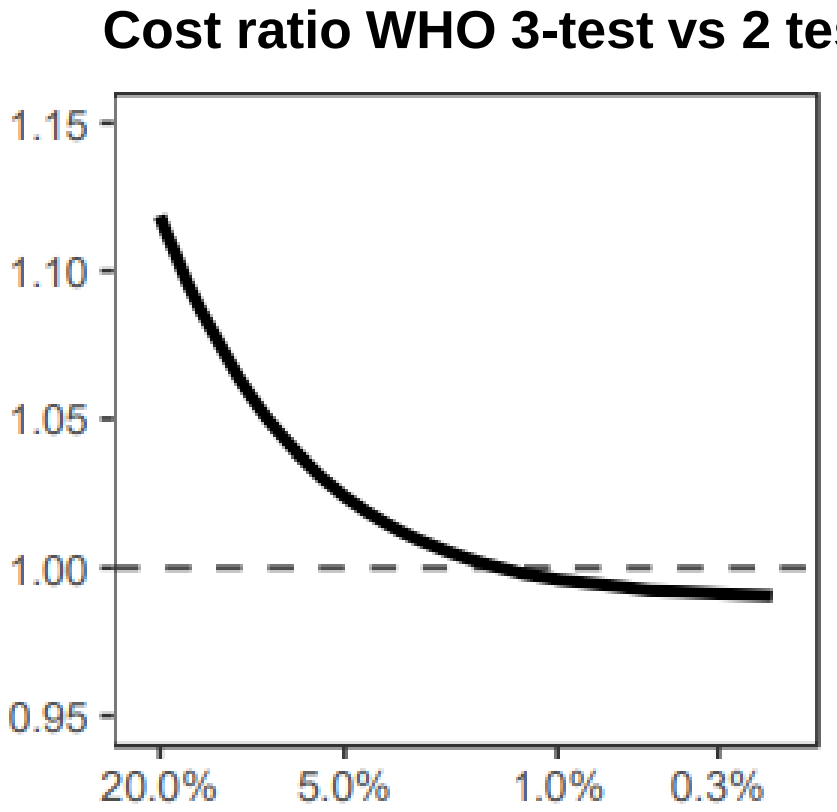
Test kits used

First test in national algorithm drives costs
Additional third test has limited impact

Cost differences





Additional third test does not increase testing programme costs

WHO retesting considerations

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Cost of retesting before ART initiation

	Low Prevalence Example	High Prevalence Example
HIV prevalence among testers	1.0%	10.0%
Serial testing strategy	3-test	2-test
Total testing cost[b]	$82 628	$87 020
Number of HIV–initiated on ART	9.2	38.9
Expected lifetime ART cost for HIV–[c]	$57 832	$243 399
Total retesting cost	$2011	$14020
HIV–initiated on ART with retesting	0.03	0.6
Expected lifetime ART cost for HIV–	$186	$3 628
Expected savings from retesting	$55 634	$225 751
Time to recover retesting costs by averted ART costs	0.5 y	0.8 y

Retesting prior to ART initiation recommended by WHO

- Strongly reinforced in 2014 as part of Treat All guidance when clinical assessment requirements were removed
- Highly cost-saving compared to even few cases of misdiagnosis and wrongful initiation of life-long treatment

What does retesting do?

- Provides quality assurance to prevent unnecessary lifelong ART initiation
- Primarily addresses human error that occurs in HIV testing services
- Does not replace need for 3-test strategy, as it has a completely different purpose

Source: Table, adapted from Eaton et al 2017 https://academic.oup.com/cid/article/65/3/522/3751368

Retesting on ARVs

Potential factors associated with false negative results

Assay-specific	Host-specific	Virus-specific
• Seronegativity associated with assays using only env antigen to detect HIV antibody • Among individuals diagnosed and treated during acute infection, 4th gen IA was less sensitive than 3rd gen IA regarding Ab seroconversion • Oral fluid assays performed poorly among adults and children infected with HIV	• Immunity: ○ ARVs (including PrEP) blunt antibody response ○ Antibody titer reduced over time among those virally supressed • Timing of ART initiation during infection: ○ In AHI, starting ART in Fiebig stage I-II produced greatest non-reactivity ○ Children started on ART<6 months of age had greatest non-reactivity ○ Starting ART based on CD_4 count (>350 vs. <350) appears to have no effect • Genetics: ○ Children genetically predisposed to seronegativity in presence of ART (HLA alleles)	• ARVs induce viral suppression ○ Low VL associated with nonreactivity • Clade, sub-type ○ HIVCRF01_AE developed reactive Oraquick results earlier • ARVs reduce size of viral reservoir

CONTINUUM (Often difficult to tease out specific causes)

Retesting on ARVs

Key considerations from WHO guidelines

Key guidance for addressing retesting on ARVs

- Most PLHIV who are on ART and who retest will continue to test positive
  - However, there are a few cases that can be missed, sometimes people diagnosed and started on ARV during the acute HIV infection period which is generally rare
  - Oral fluid HIV RDTs (i.e. often used for self-testing) were also slightly more affected when compared to other HIV assays (but remember overall cases were still very few)
- Programmes should not actively seek to retest PLHIV on ART
- PLHIV on ART who retest should be made aware of the possibility of false negative results
- Efforts to accurately establish HIV infection are important among individuals who may have acquired HIV while taking PrEP prior to initiating treatment

Source: https://www.who.int/publications/i/item/978-92-4-155058-1

Conclusions

Testing strategies should reflect changes in epidemiology:

- 3-test strategy substantially reduces false-positive misclassifications to ensure that 99% PPV target is achieve.
- Increases '*inconclusive*' results (A1+/A2+/A3-), but most will be confirmed negative at day 14 *(a good thing)*.
- Retesting on ARVs among PLHIV can result in false negative results, but is unlikely a key contributor to false negative results

Incremental budgetary impacts are low:

- Cost of 3- vs. 2-test algorithm are similar; switching to 3 test strategy doesn't substantially increase costs
- Lessons learned are that lowest cost first test has greatest impact
- Retesting prior to ART initiation remains cost-saving

Programmatic implications:

- Finding new ways to organize and restructure HTS is important (test for triage, HIV self-testing).
- Incorporate dual test into updates and roll-out of 3-test strategy
- Retesting prior to ART initiation still advised, but could be prioritized to increase feasibility in certain settings

For more information on HIV testing services

WHO HIV Testing Services Dashboard

WHO HIV Testing Services Info App

WHO HTS GL

Questions?

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