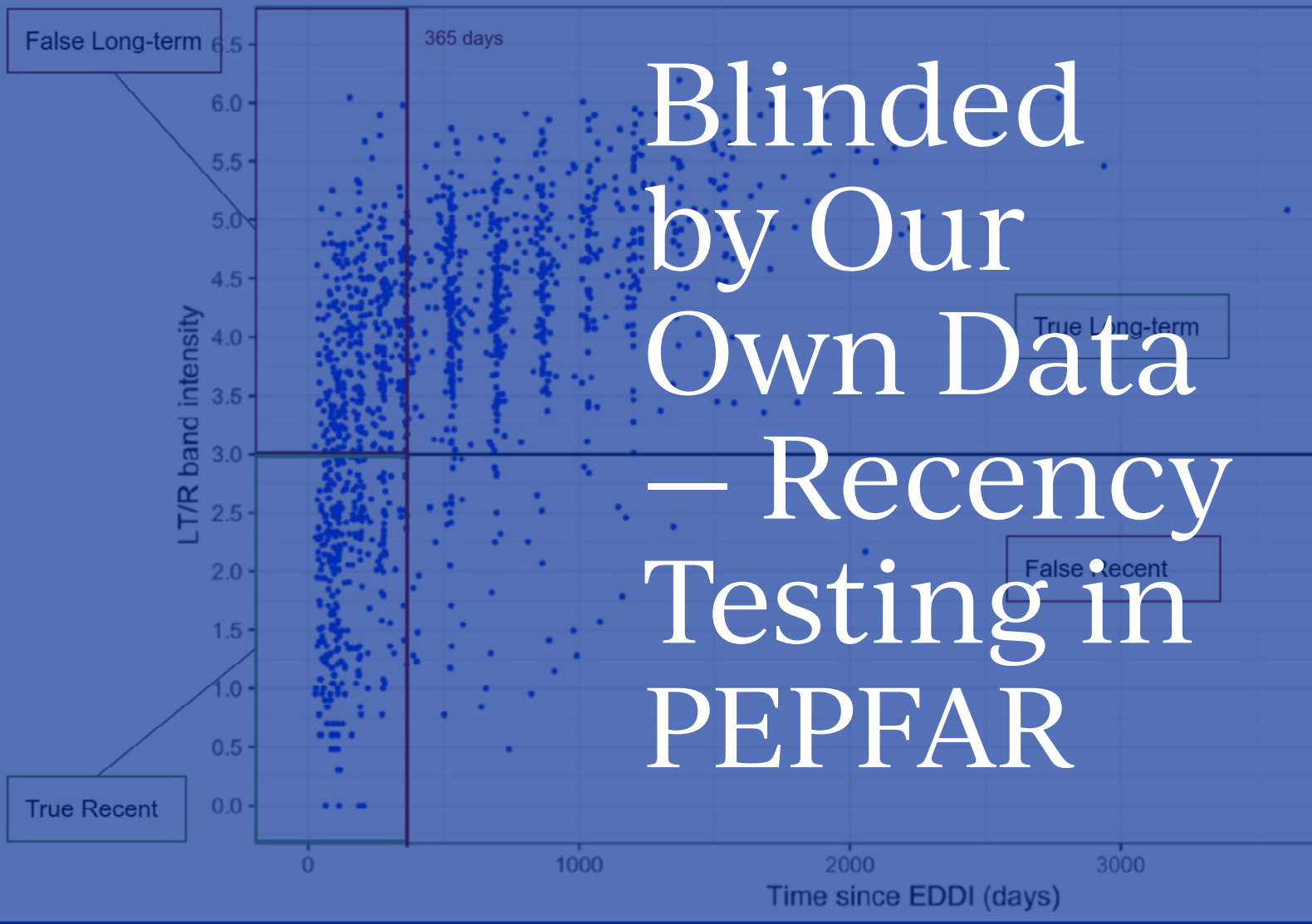
MAY 2022



Blinded by Our Own Data — Recency Testing in PEPFAR

amfAR
MAKING AIDS HISTORY

EXECUTIVE SUMMARY

HIV recency testing was introduced into PEPFAR programming in 2019 as a means to update PEPFAR's strategic surveillance systems and ultimately improve the targeting of resources in the changing landscape of HIV. Countries have made remarkable progress in advancing towards UNAIDS 95-95-95 targets and the goal of ending the HIV epidemic as a public health threat by 2030. That progress in many countries is leading to declining new HIV infections and numbers of people who have never been diagnosed needing to access an HIV diagnosis for the first time. These changing dynamics have led PEPFAR to change its approach to HIV testing to attempt to focus testing resources towards areas and populations with the highest transmission rates.

Recency testing is a cornerstone of this evolution of PEPFAR's strategy for HIV testing. Recency testing attempts to assess for individuals newly diagnosed with HIV how recently they contracted HIV—"recent" being generally understood to be within the last 6–12 months. Recency testing has already been deployed by PEPFAR as part of the population-based HIV impact assessments (PHIAs) and by other researchers as the basis for estimating HIV incidence. PEPFAR, however, is proposing a new use of recency testing: to serve as the basis of a real-time HIV surveillance system to identify small geographic areas and sub-populations that are most at risk to acquire HIV and to re-allocate resources to those areas in rapid fashion to stop any onward transmission.

Using recency testing for this purpose is unprecedented and unproven. Recency testing-based surveillance systems have begun implementation in at least 24 countries with PEPFAR support with large scale-up of these programs planned in 2022 and 2023. Unfortunately, recency-based surveillance is unable to perform at the levels required for the real-time surveillance system that PEPFAR has envisaged and brings with it high costs, human rights concerns, and other issues that are likely to make the program a futile waste of resources for both PEPFAR and ministries of health.

The challenges faced by a recency-based surveillance system implemented as part of routine HIV programming stem from at least five pathways that make the data unsuitable for PEPFAR's objectives:

1. **Recency testing has poor sensitivity for recent infections:** Studies routinely find that recency testing fails to diagnose individuals with true recent infections (infected less than six months) between 35% and 68% of the time. This is inherent to the methodology applied to detect recent infections and not an issue of implementation that can be resolved by improved training.[1]
2. **Recency testing has poor specificity for recent infections:** Recency testing alone in the field returns false positive results between 15% and 90% of the time as individuals currently on treatment, people who have advanced HIV disease, and other factors affect the accuracy of the test. Even when recency tests are combined with viral load testing—as PEPFAR recommends—results are still inaccurate between 5% and 30% of the time.[2]

[1] Kassanjee R, Pilcher CD, Keating SM, et al., 2014, finding LAg-avidity correctly identified samples from individuals infected <6 months ~65% of the time, with variation by HIV subtype and individuals infected 6-12 months ~15% of the time, available at: https://doi.org/10.1097/QAD.0000000000000429; Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013, finding LAg-avidity failed to identify 57% of samples from individuals infected <6 months and 69% <12 months based on an ODn<1.5 threshold, available at: https://doi.org/10.1371/journal.pone.0082772; CEPHIA (Grebe E, Facente SN, Hampton D, Cheng C, Owen R, Keating SM, Pilcher CD, Welte A, Busch M, Murphy G & Consortium for the Evaluation and Performance of HIV Incidence Assays), 2019, assessing the Asanté HIV-1 Rapid Recency® Assay at a band intensity of 3.0 failed to diagnosed many samples as recent, available at: https://doi.org/10.5281/zenodo.3509834; Galiwango RM, Ssuuna C, Kaleebu P, et al., December 2021, finding that RTRI failed to diagnose 30% and 50% of samples from individuals infected <6 months at different laboratories, available at: https://doi.org/10.1089/AID.2020.0279.

[2] Zhu Q, Wang Y, Liu J, Duan X, et al., 2020, finding 16.7% of "recent" results were misclassified based on LAg+viral load <1000 alone, available at: https://doi.org/10.1016/j.ijid.2020.09.1421; Voetsch A, Duong Y, Stupp P, et al., 2021, using ARV detection to find 15.7% of "recent" results misclassified based on LAg+viral load<1000 alone, available at: https://doi.org/10.1097/QAI.0000000000002707; Rice BD et al., 2020, using clinical records searches and ARV detection (separately) to identify recent mis-classifications 9.1% and 4.2% of the time respectively in Kenya, available at: https://doi.org/10.1002/jia2.25513; HSE Health Protection Surveillance Centre, 2020, finding 62.5% of recent results were misclassified after LAg+viral load<1000 based on clinical records, CD4 count <200, AIDS-defining illness, or prior PEP use, available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2018reports/HIV_2018_recentinfection.pdf.

3. **Inter-reliability of recency testing is suspect:** Recency testing results must be read carefully to deliver consistent results across different sites. Inconsistency in the reading of results undermines the comparability of the results. However, research has shown that even at a laboratory level using the point-of-care tests PEPFAR is deploying, the inter-reliability of results was only around 70%. PEPFAR's planned program intends for recency testing to be deployed at all testing sites in all PEPFAR program countries rather than being based out of labs, creating enormous opportunity for inconsistencies in the reading of results to go undetected.[3]
4. **Routine program data are likely to bias results in unpredictable ways:** When published studies include recency testing to assess incidence, there are attempts to control for biases in the population and geographic regions that are included in the study. By contrast, such controls are not possible in routine program data. Because of this, high-performing HIV testing programs with good testing uptake among specific populations at greater risk of HIV (e.g., youth, key populations) may appear to be higher transmission areas than similar geographic regions that have poor HIV testing uptake among these populations.
5. **Recency testing doesn't provide real-time information:** Recency-based incidence estimation is not a real-time incidence estimation. Because of high false-recent results and the demography of individuals who will initially test recent, recency-based surveillance is more indicative of transmission patterns that were active nearly two years ago, rather than real time. While incidence studies can reflect these realities, a real-time surveillance system premised on the idea of real-time or near-time response is actually operating well behind when transmission was taking place.[4] Additionally, the geographic location where individuals are diagnosed does not necessarily align with where they contracted HIV.

These errors compound each other leading to the reality that when evaluating recency results—especially at the small geographic or small sub-population level required for PEPFAR's vision of a responsive real-time surveillance network—the data are not even an accurate reflection of true recent infections even among the tested population, let alone as a basis to generalize to the untested population. Responding to such noise diverts scarce resources away from direct delivery of core HIV prevention and treatment services to chase statistical blips or long transpired transmission patterns that run counter to PEPFAR's self-proclaimed data-driven approach to HIV programming.

Additionally, routine recency testing carries with it a host of ethical and human rights concerns including, 1) whether patients should be subjected to testing that has no clinical benefit to them; 2) whether the results of recency tests should be provided to patients; and 3) implications of sharing results on HIV criminalization generally, outing, and subsequent criminalization of key populations, or the potential to provoke intimate partner violence. While many of these concerns are currently minimized through informed-consent protocols and not providing patients with the results of their tests, there has been movement in PEPFAR's guidance towards allowing for results to be returned without any of the pre-work necessary to mitigate these concerns.

Finally, the costs of the recency testing program are as of yet unknown. PEPFAR has not released any official costing estimates. The commodities costs for the recency tests themselves are increasing and the addition of viral load confirmation testing increases the commodities and laboratory costs involved. However, much greater resources—both human and financial—are consumed by healthcare workers (HCWs) implementing the programming, the training requirements, data systems, surveillance staff, and outbreak investigation teams necessary to make use of the data. Many of those costs are not borne by PEPFAR alone, but are being absorbed by ministries of health who employ most of the healthcare workforce in each country. These costs are likely to become permanent entrenched costs to produce data of extremely limited to no value as a programmatic surveillance system.

This report elaborates on the scientific underpinnings for this proposed use of recency testing in detail. A cheap and reliable surveillance system of the type that PEPFAR envisions could be a useful tool to target limited HIV testing and prevention resources. **However, for that system to function properly, it must be based on solid evidence that such a surveillance system will produce reliable results that can be acted upon. Recency testing is not that system and cannot realistically become that system based on currently available technologies and methodologies. Instead, recency-based surveillance systems are likely to undermine client care, and waste resources and healthcare worker time that would be better used improving client HIV testing, prevention, and treatment services.**

Based on this, we make the following recommendations to PEPFAR:

1. PEPFAR should immediately suspend its recency testing program (including HCW trainings) until an independent evaluation can be completed of how a LAg-avidity-based surveillance system—especially one premised on informing site or small geographic region differences in real time—can overcome the inherent accuracy and implementation challenges of current recency testing.
2. PEPFAR must release a transparent accounting of the money that has been spent for COPs 2019–2021 on rolling out recency testing, including commodities, training costs, surveillance staff, data systems, and an estimate of the costs of healthcare workers implementing recency testing whether those costs are borne by PEPFAR or not. Additionally, PEPFAR should develop cost expectations for the program over the next five years if expansion of the program were to continue as envisaged—scaling to all

[3] Galiwango RM, Ssuuna C, Kaleebu P, et al., December 2021.

[4] Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013, describing the "shadow" for HIV recency testing as "a measure of how far back in time incidence is being estimated" based on test characteristics, available at: https://doi.org/10.1371/journal.pone.0082772.

facilities whether PEPFAR supported or not in all countries approaching epidemic control.

3. PEPFAR should fund a rigorous and independent evaluation of the programmatic utility of recency testing to date, including how resources have been re-allocated in response to recency findings and hotspots, how programs have programmatically responded to those results, and what programmatic impact those responses have had on new HIV infections.
4. PEPFAR should conduct a full cost-benefit analysis of point-of-care recency testing systems compared with lab-based systems that includes assessments of sustainability and ability to adopt new recency surveillance methods should they be developed, the training costs required (including on-going quality-assurance and quality-improvement requirements), impact on healthcare worker time, and effect on client experience and access to care.
5. PEPFAR should fully evaluate alternative approaches to measuring HIV incidence in countries and regions where HIV epidemic control has been achieved.

These errors compound each other leading to the reality that when evaluating recency results—especially at the small geographic or small sub-population level required for PEPFAR's vision of a responsive real-time surveillance network—the data are not even an accurate reflection of true recent infections even among the tested population, let alone as a basis to generalize to the untested population.

INTRODUCTION

Recency Terms

RTRI: Rapid Test for Recent Infection

RITA: Recent Infection Testing Algorithm

HTS: HIV Testing Services

LAg: Limiting Antigen

PPV: Positive Predictive Value

NPV: Negative Predictive Value

FRR: False Recency Rate

HIV recency testing is a relatively new tool that attempts to determine whether an individual acquired HIV recently or not. What it means for an individual to be "recently" infected depends on the methodology used, but is generally defined as someone having contracted HIV within the past 12 months. In 2019, the President's Emergency Plan for AIDS Relief (PEPFAR) began promoting recency testing as a tool for HIV epidemic surveillance and to help better target HIV prevention and testing resources by geography and population.[5]

Recency testing has now been rolled out to various degrees in at least 24 PEPFAR program countries, with several others in planning phases.[6] PEPFAR has driven adoption of recency testing as a strategy through its annual Country Operational Planning (COP) process and relationships with partner ministries of health. Beginning in COP 2019, PEPFAR included language in their COP Guidance stating that "PEPFAR-supported countries should include recency testing in their standardized HTS national algorithm," effectively asking that ministries adopt recency testing as an inherent part of HIV testing programs.[7]

Despite delays due to the COVID-19 pandemic, there has been an aggressive pace of adoption of recency testing. The pace is particularly aggressive given the reality that there is—as of yet—no documentation that the routine implementation of recency testing leads to improved service delivery. Additionally, several concerns—including some that were already published when recency testing was first proposed in COP 2019—have been raised regarding the accuracy and quality of the data being generated, the practicality of responding to the data, the human rights implications that the recency testing program has for people living with HIV, and the costs of the program.[8]

This report evaluates the state of the PEPFAR HIV recency testing program, its rationale, the science behind it, the utility of the data, and the implications for PEPFAR in light of competing priorities for PEPFAR's limited resources.

[5] PEPFAR, *PEPFAR 2019 Country Operational Plan Guidance for all PEPFAR Countries*, p. 58, available at: https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf, stating that "[r]ecency testing should be incorporated as surveillance and for early detection of transmitting networks, not as research. All countries approaching epidemic control (Burundi, Ethiopia, Eswatini, Kenya, Namibia, Rwanda, and Zimbabwe) must fund recency testing and have a policy for recency testing for all newly diagnosed PLHIV."

[6] PEPFAR, *PEPFAR 2022 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries*, p. 562, available at: https://www.state.gov/wp-content/uploads/2022/02/COP22-Guidance-Final_508-Compliant-3.pdf. Implementing countries: Cambodia, DRC, El Salvador, Eswatini, Ethiopia, Guatemala, Honduras, Kenya, Laos, Lesotho, Malawi, Namibia, Nicaragua, Nigeria, Panama, Rwanda, South Africa, Tanzania, Thailand, Ukraine, Uganda, Vietnam, Zambia, Zimbabwe. Planning and training: Botswana, Brazil, Burundi, Dominican Republic, Jamaica, Kyrgyzstan, Tajikistan.

[7] PEPFAR, COP19 Guidance, p. 58, available at: https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf.

[8] See, e.g., amfAR, AVAC, CHANGE, *New HIV Testing Strategies in PEPFAR COP19: Rollout and Human Rights Concerns*, February, 2019; Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013; Kassanjee R, Pilcher, CD, Keating, SM, et al., 2014.

THE NEED FOR HIV SURVEILLANCE SYSTEMS

Twenty years after PEPFAR was established, the investments made by domestic governments and donors —including the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and PEPFAR—have brought many countries to the verge of achieving the UNAIDS 95-95-95 targets.[9] When sustained across all populations and sub-populations, new HIV infections should be reduced below the all-cause mortality rate among people living with HIV (PLHIV), therefore reducing the overall prevalence of HIV in a country or geographic region. This is the state of "epidemic control," as PEPFAR has defined it.

However, achieving a state of epidemic control and maintaining epidemic control are two different things. HIV as a chronic infection without a currently viable cure can rebound within populations if HIV testing, prevention, and treatment programs fail to identify newly infected individuals, support them enrolling and remaining engaged in care and—for those already on treatment—ensure people enrolled have sustained viral suppression. In locations with declining new infections and more stable national epidemics, strategies for HIV programming must adapt to this new phase of the epidemic. For example, as the majority of PLHIV know their HIV status, HIV testing programs are attempting to evolve to target testing resources to communities most vulnerable to HIV acquisition and de-prioritize broad-based general testing programs.

The PEPFAR COP 2022 guidance outlines this approach as the primary goal:

> ***Goal 1 is to Accomplish the Mission—that is, to achieve and sustain epidemic control using Evidence-based, Equitable, Person-Centered HIV Prevention and Treatment Services.*** *As countries approach and attain the 95-95-95 goals, it is important to adapt the program from one focused on rapid scaling of ART coverage and other services to one that consistently and effectively supports continuity of treatment and person-centered services for all people living with HIV. This takes a public health approach to identify and specifically support populations falling short of the benchmarks or populations where new transmission is occurring by utilizing public health systems aligned with national or subnational public health entities for case surveillance and recency [testing].*[10] *[emphasis original]*

The COP 2022 Guidance also outlines that PEPFAR's *programmatic* intent with recency surveillance data is to use those data to identify the specific populations and geographic regions that require intervention:

> *Routine analysis of [recency] data is used to monitor epidemiological trends in recent infections and signal recent HIV transmission among subgroups and geographic locations. Programmatically, these signals of potential hotspots of recent transmission can be investigated further to identify and address missed opportunities within routine HIV testing, treatment, and prevention services in order to prevent ongoing transmission; these missed opportunities may be limited to a cluster or also exist at a district, regional, or national level and/or may be limited to specific sub-groups (e.g., AGYW or key populations).*[11]

[9] UNAIDS, *Understanding Fast-Track: accelerating action to end the AIDS epidemic by 2030*, available at: https://unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf.

[10] COP22 Guidance, p. 54. See also, p. 33 stating: "As countries reach 95/95/95 goals and achieve epidemic control, they must adapt their plans and design their activities and policies to sustain epidemic control for the long term. Epidemic control maintenance will require disease-specific surveillance, the capability to detect and investigate outbreaks using relevant tools, including recency infection surveillance, treatment literacy of patients, and continued excellence in ART services to achieve continuous treatment, durable viral load suppression, and rapid return to treatment of those whose treatment is interrupted."; p. 54, stating: "Recency surveillance provides information about new and chronic infection patterns (cutting edge of the epidemic), insights on where recent infections may be diagnosed, and demographic patterns—including age, sex, and geography. These data can also help identify where there are gaps in the clinical cascade from diagnosis to viral suppression, population, and geography. Recency data are even more needed in light of COVID-19 to identify patterns in recent infections." Available at: https://www.state.gov/wp-content/uploads/2022/02/COP22-Guidance-Final_508-Compliant-3.pdf.

[11] COP22 Guidance, p. 567.

PEPFAR puts great emphasis on the strategic importance of a surveillance system based on HIV recency testing to drive programmatic evolution. COP guidance between 2019 and 2022 has consistently talked about using the results of real-time recency testing surveillance[12] to target testing programs[13] and PrEP programming,[14] determine eligibility for DREAMS program expansion,[15] and for other services. The strategy is logically sound and follows PEPFAR's vision of being driven by data. However, this strategy is premised on three key assumptions:

1. the data from a recency-based surveillance system is of high enough quality to provide a reliable evidence base for programmatic evolution;
2. the programmatic capacity to respond to the data exists or can be efficiently built; and
3. the costs of the recency testing program will justify diverting resources away from direct service delivery to implement the recency program in the immediate term.

Unfortunately, even as a long-term investment into domestic public health surveillance capacity, the current formulation of the recency testing strategy is unlikely to succeed because it fails each of these assumptions, which we turn to below.

Unfortunately, even as a long-term investment into domestic public health surveillance capacity, the current formulation of the recency testing strategy is unlikely to succeed...

[12] COP22 Guidance, pp. 566-567; See also, COP22 Guidance pp. 53, stating: "Establishing triangulation of routine data from surveillance, program, laboratory, pharmacy, and recency surveillance provide essential real-time guidance for changing program direction, which survey data can only provide periodically."; pp. 562-563, stating: "While initiating or bringing recency testing to scale as a part of surveillance, PEPFAR teams should consider: [...] 5) using standardized site-level data collection tools (both electronic and paper-based) and a central dashboard to monitor quality and analyze aggregate data in real-time; and 6) routine monitoring and use of data, in as close to real-time as possible, to assess quality of testing and for public health response."; p. 565, stating: "National HIV recency dashboards, developed and managed by Ministries of Health, allow for an overview and stratified view of RTRI testing, service coverage, kit performance, QC specimen performance, and testing quality at reporting sites. Ongoing review of real-time data can quickly identify quality related issues, trigger root cause analyses, and help take corrective actions in a timely manner to strengthen program performance."; p. 567, stating: "In COP22, country teams should consider the following elements in building and maintaining a real-time surveillance system of new infections: [...] 2) collaboration with Ministry of Health officials to develop and implement policies that endorse the use of RTRI testing among persons diagnosed in routine HIV testing services; [...] 6) development or configuration of health information systems for data capture, management, and automated analysis and data visualization at national and sub-national levels on a dashboard (including availability of user-friendly visualization tools); [...] 9) use of recent infection surveillance data to monitor trends in recent infections and identify, investigate, and respond to potential relative hotspots of recent infection transmission. [...] Country teams should work with HQ, ISMEs, and IPs to maximize real-time-data use for public health response."; pp. 568-569, stating: "Role of site level staff and implementing partners in recent HIV infection surveillance and response [...] Collect, report, and visualize recent infection surveillance data through appropriate data systems (electronic or paper) in real-time." Available at: https://www.state.gov/wp-content/uploads/2022/02/COP22-Guidance-Final_508-Compliant-3.pdf. COP19 Guidance, p. 58, stating: "All countries approaching epidemic control (Burundi, Ethiopia, Eswatini, Kenya, Namibia, Rwanda, and Zimbabwe) must fund recency testing and have a policy for recency testing for all newly diagnosed PLHIV. This will help countries detect recent HIV infections among all newly diagnosed individuals in real-time; linking this activity to case finding modalities will help increase HIV-positive yield. By characterizing recent HIV infections with respect to person, place, and time, countries are able to mount a rapid public health and programmatic response to prevent further transmission from all newly diagnosed persons including recently infected individuals." Available at: https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf.

[13] COP19 Guidance, p. 358, stating, "Recency testing should be used to identify geographic and demographic hot-spots (areas or groups with recent transmission), and those hot-spots should be targeted for testing campaigns, with timely and intensive index-testing performed for all who test positive." *PEPFAR, PEPFAR 2020 Country Operational Plan Guidance for all PEPFAR Countries*, p. 201, available at: https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance_Final-1-15-2020.pdf, stating: "As countries approach epidemic control, case-finding must be increasingly guided by the PHIAs, program data and recency testing. The costs in unnecessary testing extend well beyond the expense of the testing kits; HRH resources are wasted on unnecessary efforts that lack impact."; COP22 Guidance, pp. 309-10, stating: "Where available, programs should use recency testing data to identify geographic and demographic areas or groups with high rates of recent transmission, and target index testing and other HIV services to these areas."

[14] COP20 Guidance, p. 154, stating: "PrEP cannot be considered outside of the above risk groups unless recency testing or other specific data such as PHIA are available and indicative of a high risk of HIV acquisition."; COP20 Guidance, p. 158, stating: "Again, to optimize PrEP, teams should have recency testing available and being implemented in the country."; *PEPFAR, PEPFAR 2021 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries*, p. 199, available at: https://www.state.gov/wp-content/uploads/2020/12/PEPFAR-COP21-Guidance-Final.pdf, p. 199, stating: "Prioritization of risk groups for scaling up PrEP should be evidence-based and, in addition to HIV incidence rates, can be informed by coverage estimates, recency testing, PHIAs, or other survey data."

[15] COP21 Guidance, p. 213, available at: https://www.state.gov/wp-content/uploads/2020/12/PEPFAR-COP21-Guidance-Final.pdf, stating: "Expansion decisions will be approved based on epidemiological need, not solely on the existence of saturated current DREAMS SNUs. Recent data from PHIAs, recency-based surveillance, demographic and health surveys, implementing partners, and other current sources should be used to determine areas for expansion."

RECENCY TESTING

Recency Test Methodologies

BED HIV-1 Assays: BED tests measure the proportion of HIV-1 specific immunoglobulin (IgG) in the blood compared to total IgG. Lab-based and can be done on plasma, serum, or dried blood spots.[16]

LAg-Avidity Assays: Measures the binding strength of HIV-1 antibodies in the blood. Lab- or point-of-care-based and can be done on plasma, serum, or dried blood spots.

Less-sensitive Vitros (LS-Vitros) and Vitros Avidity Assays: Quantify the levels of HIV-1 and HIV-2 antibodies in the blood. Lab-based and done on plasma.

BioRad Avidity: Similar to LAg-avidity, measures the binding strength of antibodies to an antigen. Lab-based and done on serum.

The recency testing platform that PEPFAR uses is based on HIV-1 Limiting Antigen Avidity (LAg-Avidity). LAg-avidity assesses the binding strength of HIV antibodies as a biomarker for the duration of HIV infection.[17] Tests for LAg-avidity were initially developed by the U.S. Centers for Disease Control and Prevention (CDC) and are currently commercialized by two vendors, Sedia Biosciences (PEPFAR's primary supplier) and Maxim Biomedical.[18] Both Sedia and Maxim offer lab-based kits [Enzyme Immunoassays (EIA)] as well as well as point-of-care (POC) or rapid test for recent infection (RTRI) test kits that have been on the market since 2018 [Sedia: Asanté HIV-1 Rapid Recency Assay (Asanté);[19] Maxim: HIV Swift Recent Infection Assay (Swift)[20]]. The RTRI was also initially developed at the CDC and is distributed under a licensing agreement with the CDC.[21]

Lab-based EIA utilizes spectrophotometry to read the results after preparing serum, plasma, or dried-blood spot samples.[22] The process requires laboratory staff and equipment, but provides flexibility as the threshold point for determining recent from long-term infections can be set at different levels. This flexibility allows for potentially optimizing LAg recency testing as part of a sequential testing series to increase the accuracy of the results.[23] RTRI tests utilize finger-prick blood akin to standard point-of-care HIV testing and use similar test strip formats. RTRIs are calibrated to a specific LAg threshold value (discussed more below) and are generally read visually, offering less flexibility when used as part of a multi-assay surveillance strategy.

LAg-avidity is not the only method of recency testing available (see inset), but it is one of the most prominently deployed and is the basis of PEPFAR's strategy on recency testing. Therefore, this brief will focus exclusively on LAg-avidity. However, other recency assays face many of the same issues that are discussed throughout this brief.[24]

Importantly, no LAg-avidity recency assay (LAg)—or any other recency assay—has been approved by the U.S. Food and Drug Administration (FDA), nor have they been reviewed or approved for WHO prequalification. Rather, they have been authorized by the U.S. CDC for research purposes.[25] As stated on the Sedia webpage for Asanté, the test kit is "[n]ot for use in diagnostic procedures, [research use-only] products are not to be used for diagnostic purposes, patient management, clinical purposes, or for investigational use within the U.S."[26]

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[16] Sedia Biosciences Corporation, Sedia Biosciences launches the SEDIA BED HIV-1 Incidence EIA, available at: https://www.sediabio.com/sedia-biosciences-launches-the-sedia-bed-hiv-1-incidence-eia/.

[17] Longosz A, Mehta S, Kirk ., et al., 2014.

[18] Maxim Biomedical, Products, available at: https://www.maximbio.com/products.

[19] Sedia, Asanté™ HIV-1 Rapid Recency, available at: https://www.sediabio.com/asante-hiv-1-rapid-recency/.

[20] Maxim, Swift™ HIV Recent Infection Assay (RIA) Controls Kit, available at: https://www.maximbio.com/swift-hiv-recent-infection-assay-controls-kit.

[21] Agyemang E, Kim A, Dobbs T, et al., 2022, available at: https://doi.org/10.1371/journal.pone.0262071. See competing interests statement.

[22] Sedia, Sedia® HIV-1 LAg-Avidity EIA Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf. Note that processing for dried blood spots requires additional steps and preparation materials.

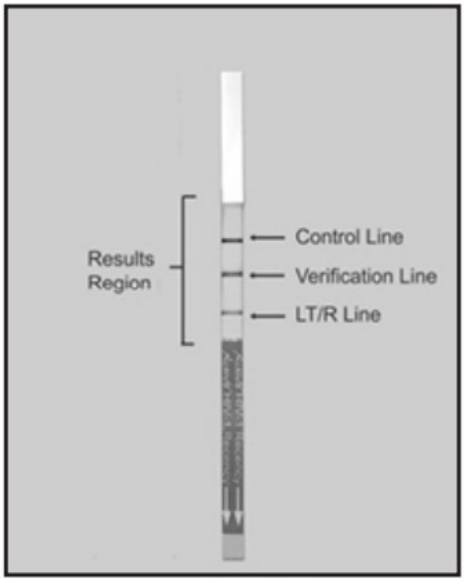
[23] Konikoff J, Brookmeyer R, Longosz AF, Cousins, MM, Celum, C, et al., 2013, available at: https://doi.org/10.1371/journal.pone.0082772. See Table 2.

[24] Kassanjee R, Pilcher CD, Keating SM, et al., 2014.

[25] See Sedia, Asanté™ HIV-1 Rapid Recency ® Assay Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/06/LN-6122-05-Product-Insert-Asante-HIV-1-Rapid-Recency-Assay.pdf, stating: "This product is for Research Use Only and is not intended for use in procedures or for determining clinical outcome or treatment." See also, Sedia® HIV-1 LAg-Avidity EIA Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf, stating: "The Sedia® HIV-1 LAg-Avidity EIA is solely intended for research use only such as estimating HIV-1 incidence in a population, monitoring and evaluating intervention programs, and identifying high-incidence populations so that prevention research, vaccine trials, and resources are most appropriately utilized. This product is not intended for use in diagnostic procedures or for determining clinical outcome or treatment."

[26] Sedia, Asanté™ HIV-1 Rapid Recency, available at: https://www.sediabio.com/asante-hiv-1-rapid-recency/.

Image 1. Asanté HIV-1 Rapid Recency Assay



An example of the Asanté HIV-1 Rapid Recency Assay. The "Control Line" is a quality assurance control and will appear on all valid tests. The "Verification Line" confirms detection of HIV akin to a standard HIV rapid test. The "LT/R Line" is the primary line of interest for recency testing and appears when a client is diagnosed as "long-term." For recently infected individuals, the control line and verification line with appear, but not the LT/R line.[27]

Additionally, as recognized by PEPFAR in the COP Guidance,[28] **a recency test result has no clinical benefit to the individual being tested and has no impact on their clinical management or service eligibility.**

LAg-based testing has been used substantially within research to estimate national and population HIV incidence in different contexts. But utilizing recency testing as part of a research study to estimate incidence is very different from using it as real-time (or near-term) surveillance and to inform programmatic targeting as PEPFAR is proposing. Programmatic applications require a higher standard of performance to avoid phantom investigations and diversion of resources based on inaccurate and misleading data.

The challenges with recency testing as a tool for real-time surveillance and programmatic targeting stem from the basic fundamentals of any diagnostic test: the sensitivity and specificity and the positive and negative predictive values of the results that it produces (see inset on page 11). LAg-based testing falls short on both measures for the populations in which the test is being deployed.

How LAg-Avidity Works

As noted above, LAg-avidity is based on the binding strength (avidity) of HIV-1 antibodies produced by the immune system.

> *The principle of the test is based on the observation that in response to exposure to the HIV-1 virus, the immune system produces low avidity HIV-1 antibodies early in the infection, and as time progresses, the immune system matures and produces high avidity HIV-1 antibodies. The amount of high avidity HIV-1 antibody present in the blood can therefore be used as an indication that the infection is a long-term one, instead of a recent one.*[29] *[internal citations removed]*

As with most biomarkers, there is considerable variability in how quickly the immune system starts producing the high avidity antibodies used to differentiate long-term from recent infections. Avidity is scored based on the normalized optical density (ODn) of antibodies that remain bound at the end of the test. ODn values are generally compared to a threshold value: below the threshold an infection is considered "recent," above the threshold, long-term. The original recommended threshold ODn for the lab-based EIAs was <1.0, but has subsequently been revised up to <1.5. Other thresholds that have been evaluated go up to <2.0 and <3.0. At each level, a greater proportion of truly recent HIV infections will be correctly diagnosed as "recent" (i.e., the test becomes more sensitive), but at the cost of misidentifying more long-term infections as recent (the test becomes less specific). The Asanté RTRI performs roughly equivalent to an ODn of <2.0,[30] while lab-based platforms can use any threshold value.

LAg-based tests do not specify exactly how recently an infection took place. Rather, "recent" itself is simply a defined variable in a study that can range anywhere from four months to two years. The definition of "recent" that is used also creates trade-offs between the specificity and sensitivity of the test and how it will perform. In most cases, the definition of "recent" used aligns with the mean duration of recent infection (MDRI), the average number of days a person who is diagnosed as "recent" will have been infected. MDRI is a function of the performance of the test at a specific ODn threshold and characteristics of the tested population. In practice, there is no way to know the characteristics of the specific population in which the test is applied, so MDRIs are based on lab-based studies of well-characterized sample populations instead. Therefore, there is an implicit assumption that the population in which the test is being deployed is similar to that of the well-studied population. For LAg-avidity utilizing an ODn of <1.5, the MDRI has been estimated between 130 for EIA and 180 days for RTRI.[31] But for an individual test, the only result is "recent" or "not recent," rather than information about the specific amount of time since infection.

Beyond normal human variation, LAg-avidity results are affected greatly by additional factors including whether

[27] Sedia, Asanté HIV-1 Rapid Recency Assay Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/06/LN-6122-05-Product-Insert-Asante-HIV-1-Rapid-Recency-Assay.pdf.

[28] COP22 Guidance, p. 563, stating: "Recency testing (RTRI or RITA) has no impact on clinical case management of an individual nor on that individual's health. As such, it is recommended that results not be returned to individuals in any setting, but countries should defer to the ethical guidelines or processes established by local MOH or IRBs to inform such a decision." Available at: https://www.state.gov/wp-content/uploads/2022/02/COP22-Guidance-Final_508-Compliant-3.pdf.

[29] Sedia, Sedia® HIV-1 LAg-Avidity EIA Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf .

[30] CEPHIA, *Asanté HIV-1 Rapid Recency® Assay Evaluation Report*, available at: https://zenodo.org/record/3509834#.Ymr5jBzMJhE, stating: "There was a high correlation (Spearman rank correlation r=0.785) between ODn of LAg-Avidity EIA and the LT/R Line intensity of the Asanté™ HIV-1 Rapid Recency® Assay for 570 HIV-1 specimens with cutoff of 3.0 matching with LAg ODn of 2.0 corresponding to a Mean Duration of Recent Infection of about 180 days". See also, Trace-Recency, FAQs, available at: https://trace-recency.org/ufaqs/how-does-the-rtri-compare-to-the-hiv-1-lag-avidity-eia/, stating: "The performance of RTRIs in distinguishing recent from long-term infection are similar to the LAg assay at normalized optical density (ODn) cutoff of 2.0 corresponding to the mean duration of recent infection (MDRI) of 6 months for the Asante RTRI), or LAg ODn cutoff of 1.5 corresponding to an MDRI of 4 months for the Maxim Swift."

[31] See Sedia, Asanté™ HIV-1 Rapid Recency ® Assay Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/06/LN-6122-05-Product-Insert-Asante-HIV-1-Rapid-Recency-Assay.pdf; See also, CEPHIA, Asanté HIV-1 Rapid Recency® Assay Evaluation Report, available at: https://zenodo.org/record/3509834#.Ymr5jBzMJhE, finding that the MDRI for the Asanté recency assay differs greatly depending on whether it is read visually or electronically. Assessed MDRIs were 105 days (95% CI: 86-124) and 197 days (95% CI: 171-224) for visual reading and electronic reading of results respectively.

individuals have low CD4 counts (<200), have an AIDS-defining illness, are or have previously been on antiretroviral (ARV) treatment, or are elite controllers of HIV—all of which are more likely to be misclassified as "recent" by LAg-avidity despite being long-term infected.[32] Additionally, individuals living with HIV-2 are likely to be always classified as "recent" infections.[33]

Because of this variability, it is recommended that individuals with the above characteristics are screened out or not included in the recency testing population when using LAg-avidity assays for incidence estimation. In a real-world environment, such exclusions are impossible and thus it is recommended that recency assays be combined with additional tests to attempt to exclude individuals most likely to be misclassified as recent. Using multiple tests sequentially to better classify individuals as recently infected or not is referred to as a recent infection testing algorithm (RITA).

Specificity and Positive Predictive Value of LAg-Avidity for Detecting Recent HIV Infections

The specificity of LAg-avidity-based testing for recent infection is how accurately the test distinguishes recent infections from long-term infections. Specificity is measured as the proportion of individuals with long-term infections that are incorrectly classified as "recent."[34] This is also called the False Recency Rate (FRR). The related concept of the positive predictive value (PPV) of LAg is that for an individual who tests "recent," what proportion of those results are accurate.

A number of studies have evaluated the FRR or PPV of LAg-avidity-based testing methodology (see Table 1). An independent assessment of five recency assay methodologies from 2014 identified the FRR of LAg-avidity to be only 1.3%,[35] but is based on restricting the testing population and excluding individuals on ARV treatment and elite controllers. Additionally, the researchers extended the definition of "recent" for purposes of the study to two years to—in the words of the paper—"better capture the tails of persisting 'recent' results and thus reduce the FRRs."[36] For people with long-term HIV on ART (again using two years as the definition of "recent") the observed FRR was 58.8%—meaning they would be misclassified as "recent" more often than not. For individuals with a low viral load (<75 copies), the FRR was 47.1%.

A 2019 evaluation of the Asanté RTRI found similar results, though differing somewhat based on whether the results were read visually or using an electronic reader. Again, utilizing a two-year definition of "recent," the FRR was found to be 1.6% using visual reading and 3.6% for electronic reading when treated patients and elite controllers were excluded. For elite controllers, the FRR was 11.5% and 16.0% and for treated patients 53.5% and 58.1% respectively for visual reading and electronic reading.[37]

Utilizing LAg for surveillance purposes requires that the chosen test, or RITA, performs well in a real-world testing population that includes treatment-naive, treatment-experienced, and individuals who present for testing with advanced HIV disease. PLHIV who have previously been diagnosed presenting for HIV testing is increasingly common for a wide variety of reasons and motivations[38]—and not just in PEPFAR programs or countries.[39]

A number of studies have been published utilizing data from the field that document the high FRR/low PPV experienced in utilizing LAg or even a RITA, including from the PEPFAR-funded Population-Based HIV Impact Assessments (PHIAs).[40] Table 1 summarizes these results. **The experienced FRR in the field when compared to a RITA consisting of LAg ODn<1.5 and viral load of >1,000 (RITA-1) confirmation varies from 15.1% to 89.6%. Effectively, LAg testing alone provides no usable indication of actual recent infections.**

Confirming recent test results with VL is the most common recommendation for RITA, including by the WHO and PEPFAR. However, studies that have used more intensive RITAs that include VL as well as other criteria (clinical records review, CD4 count, ARV testing, and AIDS-defining illness) have found that even with VL confirmation, RITA-1 still misclassifies individuals testing "recent" between 4.2% and 27.3% of the time—but these are not directly comparable percentages due to the different methodologies of the various RITAs and whether the populations have been pre-screened to exclude individuals with prior ART use.[41]

These misclassification proportions are not likely to be equally distributed such that they can be ignored as generalized noise in the data. Different programs and geographic regions may have different testing behaviors and practices among the population that would differentially impact on the PPV. If program resources are going to be diverted to different geographic "hotspots" and outbreak investigation teams are going to be deployed, high misclassification proportions or low PPVs and low overall "recent" results in any specific geographic

[32] Sedia, Sedia® HIV-1 LAg-Avidity EIA Product Insert, available at: https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf.

[33] Ibid.

[34] It's worth noting that specificity for LAg tests could also be accurately defined as the proportion of truly long-term infected individuals that are correctly classified as "long-term." However, the primary goal of the recency testing program is to identify "recent" infections, not long-term infections and so we focus here on the specificity with regard to truly recent HIV infections.

[35] Kassanjee R, Pilcher CD, Keating SM, et al., 2014.

[36] Ibid, p. 2445.

[37] CEPHIA, *Asanté™ HIV-1 Rapid Recency® Assay Evaluation Report*, available at: https://zenodo.org/record/3509834#.Ym_pGnXMJhE.

[38] Giguère K, Eaton J, Marsh K, et al., 2021.

[39] HSE Health Protection Surveillance Centre, 2020, available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2018reports/HIV_2018_recentinfection.pdf, finding that 63% (80/128) of recent infections in Ireland identified through LAg were previously diagnosed individuals.

[40] PHIA Project, available at: https://phia.icap.columbia.edu/.

[41] An additional paper, excluded from Table 1 as it didn't follow the same methodologies, found that LAg-avidity continued to misclassify 2.34% of patients (8/342) two to four years after seroconversion with VL>10,000 as "recent" and 3.1% of patients (8/258) four to eight years after seroconversion with VL>10,000. For patients with VL between >400 and <10,000, LAg did not misclassify any individuals suggesting higher VL can cause issues for LAg. Longosz, A., Mehta, S., Kirk, G., et al., 2014, available at: https://doi.org/10.1097/QAD.0000000000000221.

Sensitivity, specificity, positive and negative predictive values

Sensitivity and specificity are properties of a test or diagnostic tools—and are measures of how well the tool correctly classifies those who are truly positive as positive (sensitivity) and those who are truly negative as negative (specificity) (Figure 1). For diagnostic tests reliant on patient biomarkers the accuracy of the diagnostic is dependent on how consistent the biomarker is across individuals. Beyond that, the sensitivity and specificity of tests are trade-offs of one another, meaning that as you increase one, the other will decrease. Therefore, discussions about what is a priority—minimizing false-negatives or minimizing false-positives—are critical when determining where to set threshold points.

Predictive values are how likely the result is to be true at the individual level. For example, if someone is classified as positive, the positive predictive value is the probability the person truly is positive. Conversely, the negative predictive value is the likelihood someone is negative if they are classified as negative by the test. While sensitivity and specificity are properties of the test or tool, the predictive values change depending on the prevalence in the population. In populations with a higher prevalence of the condition being tested, the positive predictive value increases while the negative predictive value decreases. Similarly, when the prevalence is low, the negative predictive value is higher and the positive predictive value is lower.

Figure 1. Sensitivity, specificity, positive and negative predictive values and false recency rates

	True positives	True negatives	
Test positive	**A** **True positives**	**B** **False positives** *False recency rate (FRR)*	Positive predictive value = A/(A+B)
Test negative	**C** **False negatives** *False long-term*	**D** **True negatives**	Negative predictive value = D/(C+D)
	Sensitivity = A/(A+C) Total positive	Specificity = D/(B+D) Total negative	TOTAL Prevalence = (A+C)/(A+B+C+D)

Recent Infection Testing Algorithms (RITAs)

RITAs were developed to reduce the false positives (people who are misclassified as recent when in fact they are long-term infected) that recency assays produce when used in an environment where the HIV testing patient pool is not clearly defined or controlled. RITAs are generally sequential steps and each criterion must be met in order to confirm a recency positive assay result.

RITAs are not uniform in their application. Different studies, countries, and projects have used different algorithms with varying results. The most common RITA that is recommended by both PEPFAR and WHO is to confirm recency results with a viral load test as a single additional confirmatory criterion.[42] More rigorous studies often combine several additional criteria in more complex algorithms.

Tests used in RITAs include:

VL Testing: Individuals on ART and elite controllers are more likely to screen recent. In most RITAs utilizing VL testing after a recency test, a VL>1000 will confirm a likely recent infection.

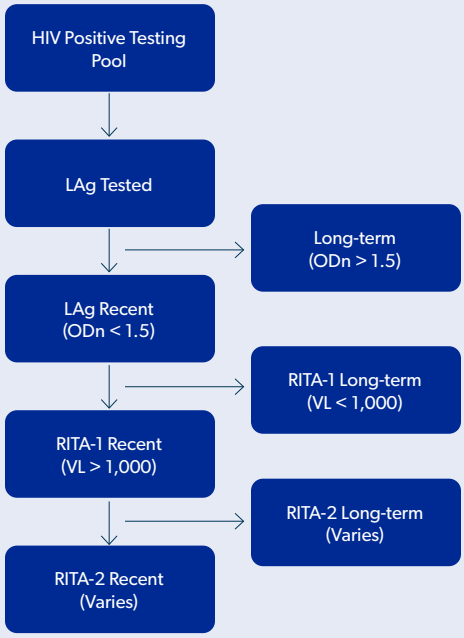
CD4 Count: Individuals with low CD4 counts are likely to be long-term infections but are also more likely to screen recent on avidity assays. RITAs use CD4 counts >200 after a recency test to confirm a recent infection.

Clinical Records: Where possible, searches of clinical records can be used to determine whether a patient presenting as a new HIV diagnosis has been previously documented to be on ART. If so, the patient is re-classified as long-term.

ARV Testing: Laboratory assays can screen blood for the presence of ARVs. If ARVs are found, the patient is presumed to be on treatment and re-classified as long-term. Worth noting is that there's no way to understand whether the ARVs identified in a person's blood were the result of treatment, or from PrEP or PEP use.

AIDS-Defining Illness: Individuals with an AIDS-defining illness are also more likely to screen recent despite having long-term infections. RITAs using AIDS-defining illness exclusion criteria will treat any individual with such an illness as long-term.

Figure 2. Recent Infection Testing Algorithm (RITA) Typical Sequence



RITA-1: RITA consisting of LAg (EIA or RTRI) + viral load confirmation; RITA-2: RITA consisting of RITA-1 + any additional RITA confirmatory testing or verification.

[42] Of note, PEPFAR's recommendation of confirmatory VL is voluntary for its programs. So different PEPFAR-funded recency projects are implementing recency testing utilizing different standards. Importantly, WHO's recommendation here is limited to using recency for the purposes of incidence estimation. WHO does not have guidance on utilizing recency testing for surveillance or program targeting.

region are highly likely to mislead rather than inform program efforts.

Sensitivity of LAg-Avidity for Detecting Recent HIV Infections

Sensitivity of LAg testing is the opposite of specificity—it is the test's ability to correctly identify indviduals with truly recent HIV infections as "recent." Incorrectly identifying a recently infected individual as long-term infected is a false long-term result. The related negative predictive value (NPV) of LAg is the proportion of individuals who test "long-term" for whom those results are accurate.

Few studies have characterized the false long-term rate of LAg or other recency assays. The independent evaluation of recency assays published in 2014 did not specifically address false long-term results experienced, but did provide some data on the sensitivity of the different recency assays assessed.[43] For LAg using an ODn<1.5 threshold for individuals infected <6 months, LAg correctly identified them only ~65% of the time, with some variation by HIV subtype. For individuals infected 6 months to <12 months, LAg identified them as recent ~15% of the time. Further six-month increments had declining rates of being identified as a recent infection.

Another study of RITA algorithm optimization assessed LAg performance on well characterized blood samples in the U.S. that included a mixed treatment-experienced/treatment-naive population also raises concerns about the sensitivity of LAg.[44] Table 2 shows the results of LAg in 1,780 samples and the proportion of recent results correctly identified at each ODn threshold. Using the standard threshold of ODn<1.5, LAg failed to identify 57% of infections that were <6 months as recent and 69% of infections <12 months, while having an FRR of 56% and 72%, respectively. At the higher ODn threshold the sensitivity improved, but at the cost of increasing the FRR.

Table 1. Studies with Published False Recency Rates or Positive Predictive Values of LAg

COUNTRIES INCLUDED IN STUDY	RECENCY ASSAY	RITA-2 ALGORITHM	LAg TESTED	LAg RECENT POSITIVE	RITA-1 POSITIVE (VL ONLY)	RITA-2 POSITIVE	LAg FRR (RITA-1)	RITA-1 FRR	LAg FRR (RITA-2)	SOURCE
Cameroon, Cote d'Ivoire, Eswatini, Ethiopia, Kenya, Lesotho, Malawi, Namibia, Rwanda, Tanzania, Uganda, Zambia, Zimbabwe	HIV-1 LAg-Avidity EIA (plasma) Maxim HIV-1 LAg DBS EIA (DBS)	RITA-2: RITA-1+ARV spetronomy	23,887	2,450	357	301	85.4%	15.7%	87.71%	Voetsch, et. al. (*JAIDS*)
Kenya	Maxim HIV-1 LAg-Avidity EIA	RITA-2: RITA-1 + Clinical Records Search	426	106	11	10	89.6%	9.1%	90.57%	Rice, et. al. (*JIAS*)
		RITA-2: RITA-2 + ARV metabolite testing	530	60	48	46	20.0%	4.2%	23.33%	
Zimbabwe	Maxim HIV-1 LAg-Avidity EIA	NA	313	49	33		32.7%			
China	Beijing Kinghawk LAg-EIA (DBS)	RITA-2: RITA-1 + CD4 > 200	1,152	205	174	145	15.1%	16.7%	29.27%	Zhu, et. al. (*IJID*)
Ireland	Sedia HIV-1 LAg-Avidity EIA	RITA-2: RITA-1 + Clinical records, CD4 > 200, AIDS defining illness, PEP use	508	128	66	48	48.4%	27.3%	62.50%	HSE Health Protection Surveillance Centre
Malawi	Asanté HIV-1 Rapid Recency Assay	NA	9,162	556	304	NA	45.3%			Telford, et. al. (*MMWR*)
Rwanda	Asanté HIV-1 Rapid Recency Assay	NA	7,919*	753	479	NA	36.4%			RWIbasira, et. al. (*PLoS One*)

* Excludes 26% of patients who self-reported prior ART use.

DBS: dried blood spot; EIA: Enzyme Immunoassay; RITA: Recent infection testing algorithm; RITA-1: RITA testing algorithm of LAg-avidity + viral load <>1,000 copies; RITA-2: RITA testing algorithm of RITA-1 + additional criteria as shown; FRR: False recency rate; PPV: Positive Predictive Value.

[43] Kassanjee R, Pilcher CD, Keating SM, et al., 2014, available at: https://doi.org/10.1097/QAD.0000000000000429. See Figure 3.

[44] Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013.

Data from the CEPHIA evaluation report of the Asanté RTRI found similar challenges based on 1,431 samples from 431 patients with treated patients and elite controllers excluded. Figure 3 shows the scatterplot of results from these patients.[45] Each dot represents a single sample with number of days since estimated infection on the bottom. The horizontal line in the middle shows the standard threshold for categorizing recent vs long-term (recent below the line, long-term above it) for the Asanté RTRI. The four quadrants: 1) Lower left; 2) Upper left; 3) Upper right; and 4) Lower right correspond to the four possible outcomes of the test: 1) True recent infection correctly identified as recent (true recent); 2) True recent infection incorrectly classified as long-term (false long-term); 3) True long-term infection correctly classified as long-term (true long-term); and 4) True long-term infection incorrectly classified as recent (false recent). As can be seen, while the trend for long-term infections is strong, for true recent infections, LAg-avidity does not strongly identify recent infections (<12 months). A recent study in Uganda utilizing the Asanté RTRI also demonstrated poor sensitivity of LAg with an additional challenge of interpretation of the test strips.[46] The study assessed samples of individuals with known dates of seroconversion, 85 of which were <6 months, for testing at two labs. They found RTRI only identified 27 (32%) and 42 (49%) of the samples as recent at the two labs respectively. Overall, there was only 72% concordance between the laboratories. As the authors state:

> ***The Asanté recency assay had a low sensitivity of between 30% and 50% for identifying samples from individuals infected <6 months.*** *[...] We found substantial interlaboratory variability in test strip scoring, which is also likely to be a problem in field settings with suboptimal lighting that may further limit the programmatic utility of the test. [...]* ***Given the low sensitivity for recent infections, this assay using visual assessment of bands may be of limited utility for HIV-1 recency screening and cross-sectional incidence estimation*** *in this or similar settings, but may be of some value in identifying recent infections within high incidence subgroups or populations. [emphasis added]*

Table 2. Number of Samples Classified as Assay Positive Using the LAg-Avidity Assay Alone

Duration of infection		LAg-Avidity assay cutoff			
(years)	N	<0.5	<1.0	<1.5	<3.0
0.0 to <0.5	142	18 (13%)	46 (32%)	61 (43%)	105 (74%)
0.5 to <1.0	167	8 (5%))	17 (10%)	36 (22%)	75 (45%)
1.0 to <2.0	262	20% (8%)	25 (%)	35 (13%)	90 (34%)
2.0 to <3.0	301	21 (%)	28 (%)	34 (%)	69 (%)
3.0 to <4.0	440	10 (%)	17 (%)	23 (%)	64 (%)
4.0 to <5.0	125	1 (%)	5 (%)	11 (%)	15 (%)
>0.5	343	7 (%)	10 (%)	18 (%)	51 (%)

Reproduced from Konikoff J, Performance of a limiting-antigen acidity enzyme immunoassay for cross-sectional estimation of HIV incidence in the United States (2013).

Critically, false long-term results are harder to detect in the field and can't be corrected for through the use of RITAs. The recency assay is the entry point to a RITA. If an individual initially screens long-term on LAg, no further inquiry or confirmation is used to confirm the long-term result. Moreover, applying additional RITA criteria actually worsens the false long-term performance of LAg. In the U.S. study above, defining recent as LAg<1.5 and VL >1,000, VL confirmation increased the proportion of false long-term results to 68% at <6 months and 81% at <12 months.[47]

Importantly, in incidence studies, false long-term results are less critical because they can be somewhat accounted for in the formulas and adjustments for producing the incidence estimates. The unknowns in these calculations explain why incidence estimates generally require large sample sizes and produce results with wide confidence intervals at geographic levels below the country level.

However, for real-time surveillance and programmatic response—in which both financial and human resources are going to be redirected based on recency testing data as proposed by PEPFAR—false long-term results are absolutely critical to ensuring that resources are not misdirected away from sites with ongoing transmission because of the inherent NPV of LAg. Sample sizes at the sub-population and small geographic region or facility level are unlikely to be high enough to overcome the estimated levels of both false long-term rates and FRR for LAg-based testing.

Conclusion on LAg-Avidity for Programmatic Surveillance

Being a data-driven program requires data, but it does not require bad data. Being data-driven requires an understanding of the nuances within the data available and utilizing those data with the humility necessary given the quality and characteristics of the processes and tools that produce those data. Utilizing LAg surveillance to identify and target geographic hot spots and populations at greatest risk violates those principles.

The accuracy of the recency testing data that PEPFAR is or will be working with cannot reliably indicate the locations and populations that are seeing the highest transmission rates. If 35%–68% (or more) of truly recent infections are missing due to false long-term results inherent to LAg and approximately 15–20% of "recent" positive results are misclassifications even after viral load confirmation, our underlying data are so inaccurate *due to the nature of the performance of LAg as a biomarker* that it has been exceptionally limited to no programmatic value. It cannot realistically be used to understand where infections are happening for the purposes of programmatic targeting, and certainly

[45] CEPHIA, *Asanté™ HIV-1 Rapid Recency® Assay Evaluation Report*, available at: https://zenodo.org/record/3509834#.Ym_pGnXMJhE.

[46] Galiwango RM, Ssuuna C, Kaleebu P, et al., 2021.

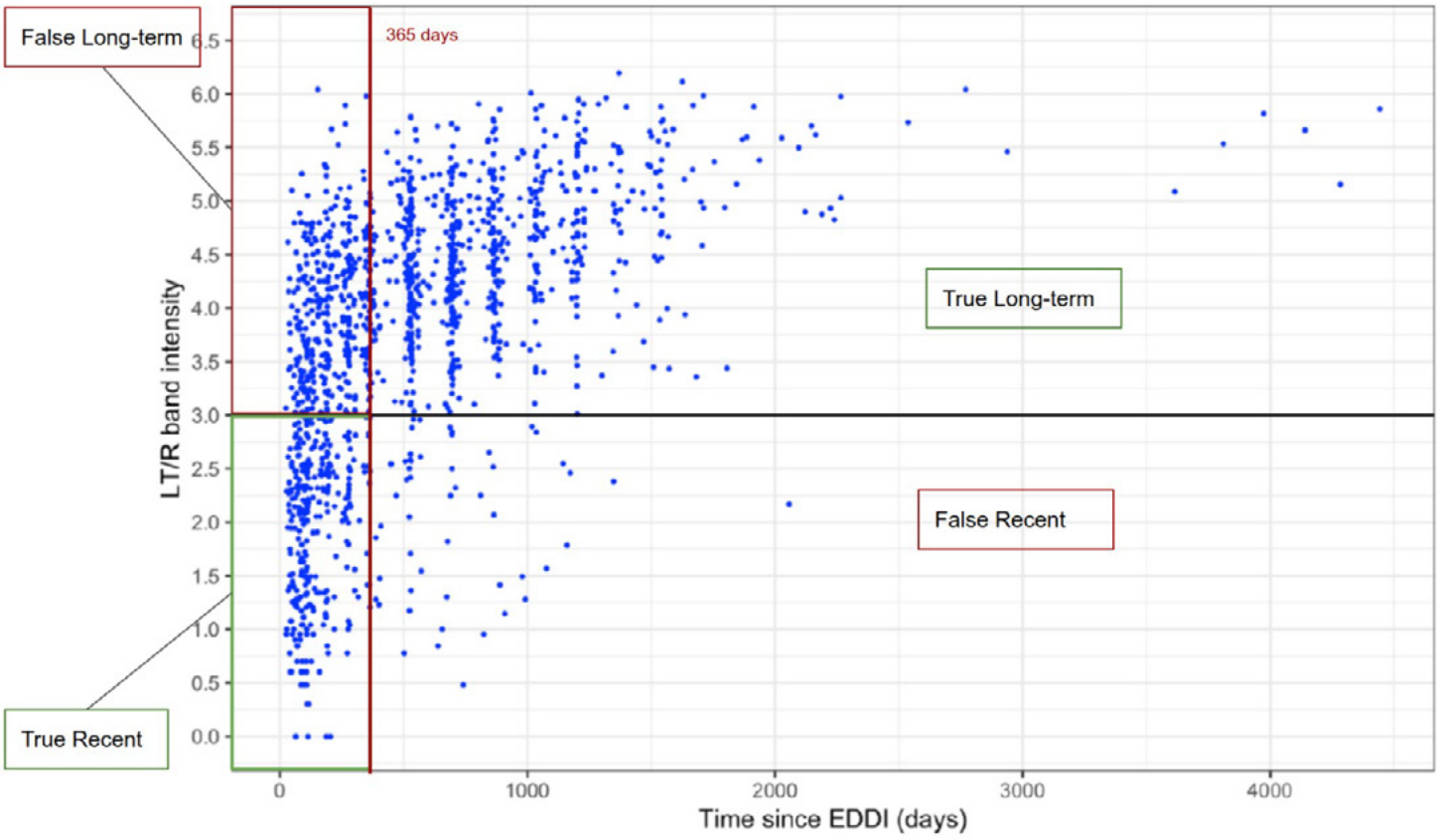
[47] Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013, available at https://doi.org/10.1371/journal.pone.0082772. See Table 2.

not at the facility or neighborhood level being proposed by PEPFAR. This problem is compounded by the simplistic manner PEPFAR is proposing of looking just at the proportion of people being diagnosed as "recent" on LAg in different geographies and populations.[48] While there is no doubt that recency data may appear to be accurate, it is a trap that results in "garbage in, garbage out" programmatic decision-making.

The PEPFAR-funded Trace-Recency Initiative[49] that is frequently referenced in the COP guidance as the repository of training materials and other information on recency testing does not provide any of this important information on the performance characteristics of LAg-based recency testing. The training module, "Overview of RTRI: Assay Principle and Test Performance"[50] only provides data on the performance of the Asanté POC test as a diagnostic test for HIV (for which it is not FDA-approved nor WHO-prequalified) and concordance of the Asanté RTRI test with lab-based EIA recency testing systems. No discussion of the sensitivity, specificity, positive or negative predictive values of LAg as it relates to actual recent infections is offered, nor any discussion on the statistical methods and sample sizes needed to use results correctly.

Again, this is a separate agenda and utilization profile than using LAg for the purposes of incidence estimation on large-scale studies and populations. In such studies, the algorithms applied are designed, and the sample sizes large enough, to accurately estimate population incidence with reasonable (if wide) confidence intervals. No algorithms or "fixes" are possible to clean up, correct, or adjust the small geographic or facility-level results with the accuracy necessary to inform geographic targeting.

Figure 3. Scatterplot of Asanté™ HIV-1 Rapid Recency® Assay results of 1,431 samples from 431 subjects, excluding treated patients and SCOPE elite controllers



Source: Modified from CEPHIA Asanté HIV-1 Rapid Recency Assay Evaluation Report

This chart is modified from the CEPHIA Asanté™ HIV-1 Rapid Recency Assay Evaluation Report using an intensity read of 3.0. EDDI: Estimated Days since Detectable Infection; LT/R: Long-term/Recent. One-year line and labels of quadrants added to original figure.

[48] Trace-Recency, *Example Dashboard—Cluster Detection and Response*, available at: https://trace-recency.org/example-dashboard/.

[49] Trace-Recency, available at: https://trace-recency.org/.

[50] Trace-Recency, *Overview of RTRI: Assay Principle and Test Performance*, available at: https://trace-recency.org/wp-content/uploads/tools/training-materials/modules/01.-Overview-of-RTRI-Principle-and-Performance_April2021.pptx.

PROGRAMMATIC UTILITY OF THE DATA

Aside from the performance characteristics of LAg, basing the surveillance system off program data creates a number of additional challenges. Necessary assumptions about the population being tested are not met in many program settings, and ignoring this may further call the trustworthiness of the data into question. Real-time programmatic responses to the data being generated are therefore more difficult to justify and may not be worth doing given the levels of uncertainty.

We look at a number of these issues here. This list is unlikely to be a comprehensive assessment of all the problems.

The problem with being wrong in our identification of hotspots due to biases such as these is that they may direct attention and resources away from the locations of greatest need towards locations that may have the best testing programs already in place.

Testing and Selection Bias in Routine Program Data

Data from large surveys like PHIAs[51] and Demographic and Health Surveys (DHS) must be approached differently than data from routine programs. In the PHIAs and other incidence estimation exercises, the population of participants is carefully selected in order to control for dynamics in the population that might bias the results and the testing protocols are standardized for all participants. Likewise, the PHIAs and other incidence studies are cross-sectional assessments based on single testing moments with the program, which creates consistency across all populations included in the study.

In recency testing with routine programmatic data collection as currently envisioned by PEPFAR, no such sampling controls are in place. This creates inherent biases in the population providing data into the surveillance system which—if not able to be accounted for—affects the validity of the results. At least two different sources of biases are introduced: testing bias and selection bias. Testing biases are introduced based on different testing practices among the population. People in different areas of the country or different sub-populations—like key populations—may present for testing more frequently than others. Doing so will result in those regions and populations being more likely to detect recent infections *even if transmission rates are the same as other regions and populations with lower frequency of testing.*

[51] PHIA Project, available at: https://phia.icap.columbia.edu/.

Selection bias is introduced based on differences in the implementation of testing programs in different regions or for different sub-populations. For instance, regions with strong youth outreach testing programs, targeted outreach programs to men, or high coverage of assisted partner notification services/index testing will look different to regions that rely more exclusively on passive voluntary counseling and testing services. Implementing different recruitment strategies for identifying people to test affects whether the results from one region can be accurately compared to others.

Because of these biases, a real risk exists that areas will be flagged as hotspots of comparatively high transmission rates worthy of investigation not because of truly high rates of ongoing transmission but because of high-performing testing programs or different testing practices among the population. **The problem with being wrong in our identification of hotspots due to biases such as these is that they may direct attention and resources away from the locations of greatest need towards locations that may have the best testing programs already in place.**

Both of these issues were identified as limitations in a recent publication on the PEPFAR-funded recency testing program data in Malawi, but did not address them in any way nor were solutions proposed as to how they are to be handled in a real-time surveillance environment.[52]

Timeliness and Locality of the Data

As noted earlier, how LAg defines a "recent" infection is dependent on a number of factors. Studies have used different definitions of "recent"—generally anywhere from six months to two years—and the choice of a "recent" definition affects the MDRI, the false long-term rates, and the FRR, improving one at the expense of the other.

MDRI and FRR are used in the standard incidence estimation formula and both are ideally meant to be adjusted for local context. This is frequently not practical in the field and generally the MDRI and FRR are assumed based on test characteristics in other contexts. Importantly, both also matter greatly for understanding ***when*** **an incidence estimation is applicable to.** The "shadow" of an incidence estimate is a measure of how far back in time incidence is being assessed and is critically affected by MDRI and FRR.[53] As MDRI or FRR increase, the shadow also increases.

Shadow periods can be quite long. Estimates for the shadow period based on RITA using LAg<1.5 and VL>1,000 and using an MDRI of 134 days approaches two years (690 days).[54] This means that the incidence estimate is best understood as an indication of transmission rates nearly two years earlier and may not speak to the dynamics that are occurring now. For RTRI-based RITA testing with an estimated MDRI of 180 days, the shadow period is even longer.

While PEPFAR—as part of its real-time surveillance strategy—is not proposing to utilize recency data for the primary purpose of estimating incidence, it is nevertheless dependent on these same characteristics for interpreting recency data to identify hotspots. **This means that what PEPFAR is *inherently* talking about in terms of a "real-time" surveillance system is actually providing information that is itself multiple years behind where HIV transmission is happening now based on PEPFAR's recommended RITA.** For countries that aren't doing VL confirmation, researchers did not calculate shadows because the test is too inaccurate to do so.[55]

Finally, it must be noted that where people are diagnosed as "recent" does not inherently align with where they may have contracted HIV. Populations and individuals are mobile—especially over the 6-month to 2 year timeframe—and people do not always choose to access testing services nearest to where they live. Intensive follow-up to identify these additional patterns would be necessary which takes additional resources and time away from implementing actual programming.

This means that what PEPFAR is inherently talking about in terms of a "real-time" surveillance system is actually providing information that is itself multiple years behind where HIV transmission is happening now based on PEPFAR's recommended RITA.

[52] Telford C, Tessema Z, Msukwa M, et al., 2022, available at: https://doi.org/10.15585/mmwr.mm7109a1, stating: "The findings in this report are subject to at least five limitations. [...] Third, focusing only on HIV diagnoses overlooks persons with HIV who do not know their status or have not enrolled in treatment. Fourth, HIV testing frequency and behavior might vary across populations."

[53] Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al., 2013.

[54] Ibid.

[55] Ibid.

Recency testing as a means of Geographic Hotspotting and its (flawed) assumptions

The recent Malawi study used routine recency data to identify geographic transmission hotspots and is instructive for demonstrating how PEPFAR is bypassing the potential inaccuracy of the underlying data to push forward with recency-based geographic hotspotting.[56] In the study, researchers used routine RITA (RTRI + VL>1,000) data from October 2019–March 2020 to calculate incidence rates at 103 facilities in Malawi using clustered geospatial software that groups closely located facilities (<20km) to identify outliers in the data. Observed incidence estimates were calculated for the full data set and for each cluster to identify the relative risk of each cluster—with some adjustment for age and sex—to identify high outlier clusters.

There are several challenges with this process. Initially, the incidence estimate measure [# RITA positive / (# HIV-negative tests + # RITA positive)] does not take into consideration the MDRI, FRR, or false long-term rate. Instead, the straight RITA positive results are used as if they are a point in time estimate, but the RITA results—especially those obtained through routine program data—are not a point in time result. They are instead an evaluation of HIV transmissions over a several year period, not just in the past six months. Additionally, and most problematically—as noted in the limitations of the paper—"performance of the test used to identify recent infections was assumed to be similar across all facilities."[57] That's an unreasonable assumption given the shortcomings of LAg and RTRI/RITA implementation already discussed and further elaborated on below. But when evaluating results where the N's on recent infections are very small at the geographic level (in low 10s), that assumption is critical to any identified differential being meaningful.

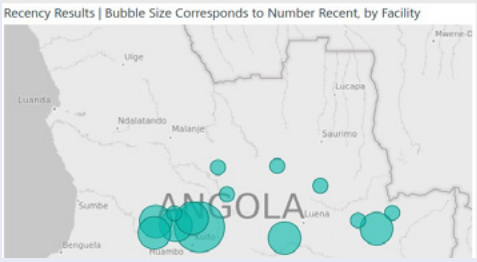
Moreover, as the scale of recency testing is expanded to over a thousand facilities, methodologies such as this are highly likely to become unstable. Any normalized distribution of that many sites will have outliers, but on a quarterly basis, the group of sites identified as "geographic hotspots" are likely to fluctuate significantly even if underlying dynamics are unchanged. **In trying to respond to those fluctuations in real time, programs are likely to be distracted responding to phantom outbreaks and constantly ramping up and ramping down services or investigations in different areas rather than properly focusing on delivering core services competently.**

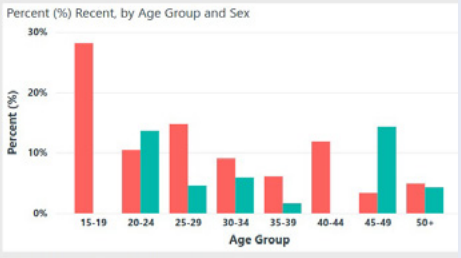
Finally, the methodology of geographic hotspot identification that PEPFAR is proposing countries adopt isn't even based on this more sophisticated (but flawed) methodology. Instead, the example recency dashboard on the PEPFAR-supported Trace Recency reference site is purely using the RTRI or RITA positive rates at each facility to identify hotspots.[58] This methodology is highly likely to result in "hotspots" being identified due to LAg sensitivity and specificity issues, biases in the testing programs, and implementation challenges as much as it's likely to be based on any real signal in the noise. All of these issues are exacerbated as the sample size at any given level of analysis gets smaller.

Moreover, the Trace-Recency *Public Health Response Strategy Using Recency Assays* document that is meant to guide how programs assess recency data and design interventions envisages deploying HIV outbreak response team investigations based not on quarterly data (where the N's are already small) but based on monthly facility-level assessments.[59] Every time the data are sliced into smaller specifics such as this, it increases the noise and decreases the actual signal in the data. **This is PEPFAR allowing itself to be misled by not treating these data with the care necessary given the characteristics and processes in the systems that generate them. The result will be the diversion of resources away from actual service delivery into outbreak investigations and recency testing itself.**

Image 2. Sample Recency Dashboard from the Trace-Recency Project

Region	District	Facility	Recent Result	Recent %	Long-Term Result	Valid Result	Missing VL	Reclassified Long-Term	Percent Reclassified Long-Term
Region 2	District 4	Facility 57	4	25%	12	16	0	1	20%
Region 1	District 1	Facility 4	3	21%	11	14	0	0	0%
Region 2	District 4	Facility 43	3	25%	9	12	0	0	0%
Region 2	District 4	Facility 45	3	33%	6	9	0	1	25%
Region 2	District 4	Facility 46	3	27%	8	11	0	0	0%
Region 2	District 4	Facility 58	3	20%	12	15	0	0	0%
Region 3	District 5	Facility 75	3	18%	14	17	0	1	25%
Region 1	District 1	Facility 14	2	20%	8	10	0	0	0%
Region 1	District 1	Facility 5	2	10%	18	20	0	0	0%
Region 1	District 1	Facility 8	2	14%	12	14	0	0	0%
Region 1	District 2	Facility 15	2	13%	14	16	0	0	0%
Total			**54**	**18%**	**248**	**302**	**0**	**5**	**8%**





The sample dashboard from the Trace-Recency website shows the utilization of facility level RTRI or RITA results in simplistic fashion to identify geographic hotspots.

[56] Telford C, Tessema Z, Msukwa M, et al., 2022, https://doi.org/10.15585/mmwr.mm7109a1, stating: "The findings in this report are subject to at least five limitations. [...] Third, focusing only on HIV diagnoses overlooks persons with HIV who do not know their status or have not enrolled in treatment. Fourth, HIV testing frequency and behavior might vary across populations."

[57] *MMWR*, p. 332.

[58] Trace-Recency, *Example Dashboard*, available at: https://trace-recency.org/example-dashboard/.

[59] Trace-Recency, *Public Health Response Strategy Using Recency Assays*, available at https://trace-recency.org/wp-content/uploads/2021/09/HIV-Public-Health-Response-Strategy_2021SEP18.docx, p. 4, stating: "Example threshold definitions:
1. ≥ 4 recent HIV infections by RTRI, (≥ 3 recent HIV infections by RITA) per facility per month
1. ≥ 4 recent HIV infections by RTRI per town/village by place of current residence per month,
2. Low-volume sites: ≥ 2 recent HIV infections by RTRI per low-volume health facility per month (< 10 new HIV positive cases/month),
3. High-volume sites: ≥ 5 recent HIV infections by RTRI per high volume health facility per month (≥ 10 new HIV positive cases/month)"

Recency Testing as a Mechanism to Understand Re-testing Among Those Previously Diagnosed

PEPFAR's training materials suggest utilizing an RTRI + VL>1,000 RITA is a useful metric for understanding re-testing among those previously diagnosed.[60] Re-testing is when PLHIV who have already been diagnosed and may or may not be on treatment present themselves for HIV testing as if they are unaware of their status.

There are many reasons that people may re-test for HIV. Civil society organizations and others have been pointing out for many years that re-testing is partially a result of poor retention in treatment programs, poor quality filing systems, and inadequate systems for patients transferring their care to different facilities.[61] In these circumstances, in order for the individual to start accessing treatment again, patients often are re-tested for HIV to confirm their result and re-start the treatment enrollment process.[62] This is avoidable re-testing that should be remedied through programmatic improvements. However, many people may also re-test for other reasons as well—concerns that they may have been misdiagnosed, difficulty accepting their status, misunderstanding about whether HIV can be cured, or simple curiosity. This is likely to be unavoidable re-testing.

While re-testing is worthy of understanding—particularly when it does result from failings in the healthcare system—it is not unique to PEPFAR programs. Ireland has implemented a recency-based surveillance system that uses a RITA inclusive of LAg <1.5, VL>1,000, CD4>200, clinical records searches, an AIDS-defining illness at time of diagnosis, and/or PEP usage in the past year (as PEP is an ARV that may invalidate the LAg result).[63] In 2018, of the 128 people who screened recent positive with LAg, 80 (63%) were re-classified as "long-term" based primarily on VL < 1,000 and prior-ART use in clinical records. All of these would be considered "re-testers" in a PEPFAR program.

Using a RITA re-classification rate as a proxy for understanding the prevalence of re-testing is flawed for another, more basic reason. Fewer than 10% of people initially screen recent positive. Using a VL<1,000 to then identify who is a "re-tester" only tells us about a small portion of people who re-test, potentially while they are actively on ARV treatment with no (or very limited) interruption. But this methodology won't tell us anything about the rates of re-testing going on in the 90% of patients who do not screen recent positive initially and where retesting and the motivations behind it may look quite different.

Ultimately, avoidable unnecessary re-testing should be addressed through programmatic and health systems improvements as well as funding of quality community-based treatment literacy interventions. Fixing the health system failings will naturally reduce re-testing that emanates from those failings, but we must also recognize that until those failings are remedied, re-testing is a primary pathway for patients to be (re)initiated on treatment. Trying to understand the phenomenon of re-testing among individuals who are active on treatment will bias our understanding of the likely much larger health systems failings and motivations behind re-testing and prioritize action that addresses only a small component of the problem.

What Are We Learning from the Data Thus Far?

To date, PEPFAR has not made the HIV recency data available in a usable format to the public. The data on their online dashboard (Panorama Spotlight) for individuals testing recent are not available for download. Some visualizations of recency data are available as well as some papers and presentations that have been prepared on the results.

Putting aside issues of accuracy and reliability at the small scales envisioned for programmatic applications, what we see thus far primarily describes patterns of incidence that are already well understood. Essentially, adolescent girls and young women and men are the most likely to be recently infected. This is neither surprising nor new information. While the patterns are somewhat different in concentrated epidemics such as those in the Asia Region or Western Hemisphere Programs, these are also already known and understood patterns of HIV transmission.

Additionally, even if geographic hotspotting was sufficiently accurate to produce near real-time assessments of transmission patterns, it still does not provide clear information about what to do with this information. Programming that reaches AGYW, young men, and key populations [men who have sex with men (MSM), sex workers, transgender people, and people who use drugs] is critically needed, but programming that adequately reaches AGYW, men, and key populations to provide HIV testing, prevention, and treatment services is lacking and underfunded. It has been well established that these populations have high incidence rates of HIV and findings

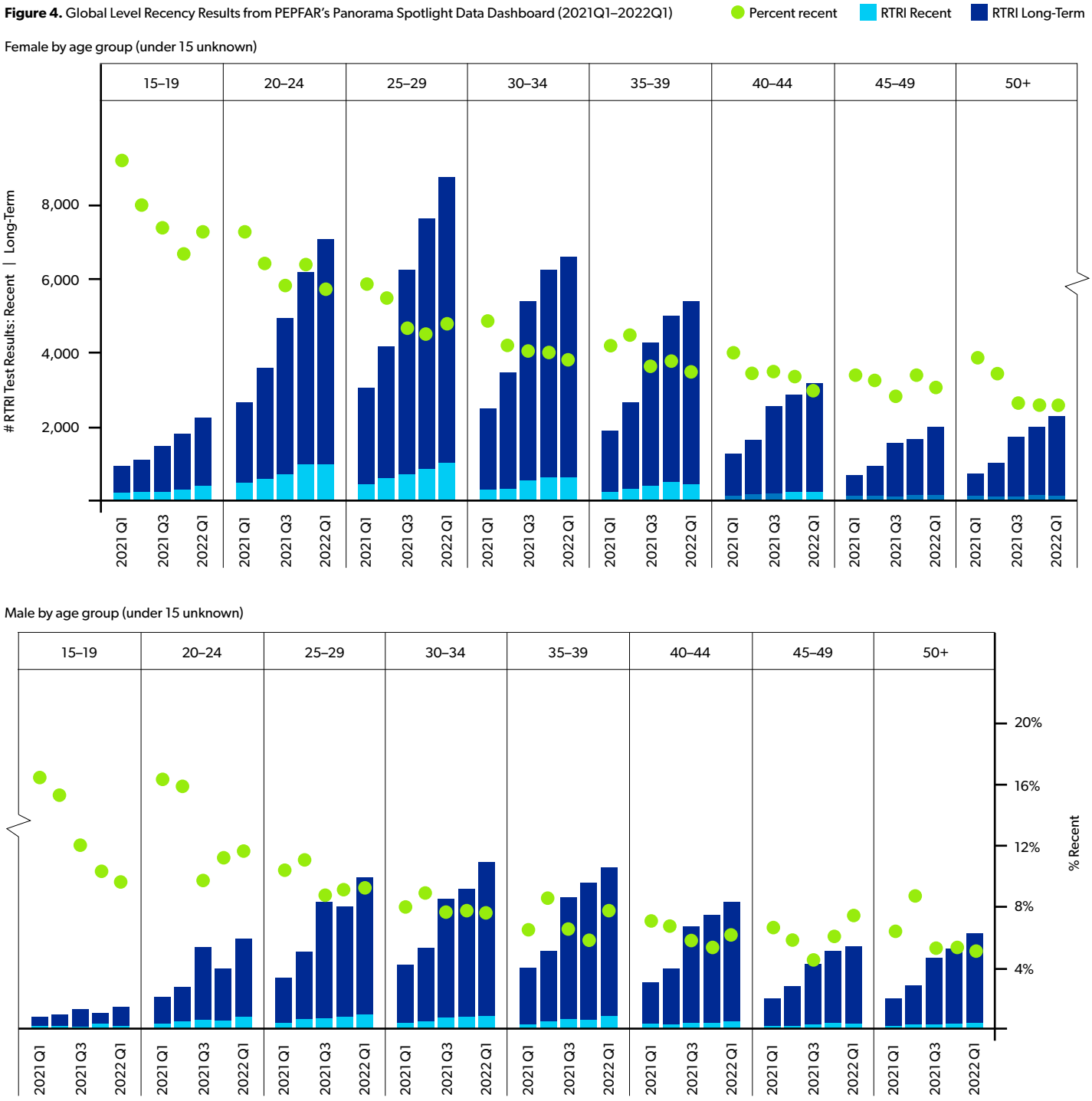
[60] Trace-Recency, *Public Health Response Strategy Using Recency Assays*, p. 20, available at: https://trace-recency.org/wp-content/uploads/2021/09/HIV-Public-Health-Response-Strategy_2021SEP18.docx, stating: "The limitation of the RTRI is that it can misclassify those who are already on ART and therefore not newly diagnosed as a recent infection. In countries implementing RITA, viral load measurement performed at diagnosis reclassifies those RTRI recent cases who have lower than 1000c/mL viral load to long-term. Reclassification data enables programs to estimate the level of non-disclosure of prior HIV diagnosis and ARV use that is occurring in the program. National programs should examine reclassification trends occurring at national and sub-national levels to understand the characteristics of individuals who seek repeat HIV-testing while already in-care and virally suppressed. Understanding the geographic areas, care settings or client characteristics of the repeat testing population is a first step towards to understanding client motivations for repeat testing. National surveillance partners should engage HIV testing partners to address repeat HIV testing that is detected through routine surveillance data."

[61] See e.g., People's COP19 South Africa: Community Priorities, p. 4, stating: "For example, in Khayelitsha, where Médecins Sans Frontières (MSF) has medical operations, a study showed that up to 25% of the HIV positive cohort cumulatively disengaged from care in the first two years of initiating ART. By 2014, close to half of those previously on ART had dropped out of care or had a substantial gap in care the preceding year. Of patients presenting to HIV services in Western Cape with a low CD4 count (<50 cells/ul) the proportion of ART-experienced patients increased from 14% in 2007 to 52% in 2017"); People's Voice Uganda (COP 19), p. 4, stating: "Adequate staff at the frontline of HIV and TB service delivery, and differentiated service delivery models, are critical to ensuring people remain in care and can access quality services that promote good linkage and retention."; People's COP19 Kenya, p. 4, calling for additional human resources to resolve HIV treatment retention problems; People's COP20 South Africa, p. 9, stating: "At many facilities, poor filing systems and/or lost files or cards were also observed or reported on by healthcare users. Messy and disorganised filing systems increase the delays to healthcare users being attended to, and increase the burden on already overstretched healthcare workers."; Liu Lathu Mu COP20 Our Voice Malawi, p. 6, stating: "COP20 must ensure that healthcare providers are trained to provide friendly services to PLHIV (including key and marginalised populations). COP20 should track if PLHIV returning to care are treated with dignity and respect as they return into care".; See also, People's VOICE Uganda (COP20); People's COP20 Kenya; Community COP20 Zimbabwe; People's COP21 South Africa; People's COP21 Kenya; Sauti Yetu COP21 Our Voices Tanzania; Lia Lathu Mu COP21 Our Voices Malawi; People's Voice Uganda (COP21); People's COP22 South Africa. All available at: http://pepfarwatch.org/resources/.

[62] Jacob N, Rice B, Kalk E, et al., 2020.

[63] HSE Health Protection Surveillance Centre, 2020.

Figure 4. Global Level Recency Results from PEPFAR's Panorama Spotlight Data Dashboard (2021Q1–2022Q1)



Source: PEPFAR, Panorama Spotlight, Testing Dashboard: Recency by Age and Sex, available at: https://data.pepfar.gov

from recency testing that validates this is not helpful but rather an ineffective use of the limited funding available.

Thus far, evidence of interventions responding to recency data are all theoretical—based on the idea that knowing the geographic locations of ongoing HIV transmission will enable deployment of HIV testing and prevention services—such as PrEP and index testing—to disrupt further transmission. But PEPFAR has yet to prove or demonstrate that such actions *based on recency surveillance data* have had any impact on actual transmission rates. **In fact, most of the interventions recommended in response to outbreaks are simply better delivery of the services that are already supposed to be in place, rather than any innovative intervention.** Index testing is already required to be offered to all patients who are newly diagnosed as HIV positive. PrEP is supposed to be available to all those who qualify under national guidelines, but PrEP programs are substantially underfunded and have shown poor persistence of people staying on PrEP in PEPFAR countries. These issues and interventions require additional resources and focus to resolve, not additional data systems to re-idenitfy patterns that are already well known.

HUMAN RIGHTS, ETHICAL CONCERNS, AND PATIENT EXPERIENCE

Recency testing additionally raises human rights and ethical concerns that may negatively affect the patient experience for newly diagnosed individuals. There are basic human rights principles that are implicated by a recency testing program implemented as part of national HIV testing processes. This includes the rights to bodily integrity, informed consent, and privacy, and the potential for increases in criminalization and violence towards PLHIV.

On bodily autonomy and informed consent, recency testing requires an additional finger prick or extra draw of blood for the recency test. Doing so inherently implicates clients' rights to bodily autonomy regardless of the level of risk or harm done to obtain additional blood. Where such intrusions are necessary, the only option is to obtain informed consent for the additional testing and/or blood draw. PEPFAR has consistently made clear in COP Guidance that informed consent is required from all individuals receiving a recency test. This is good but also the most basic of requirements.

Recency testing is further complicated by ethical considerations around whether the results of a recency test should be provided back to a patient. Criminalization of HIV transmission, key populations, potential for intimate partner violence (IPV) and the inaccuracy of recency test results all motivate against returning results—especially given that the test result has no clinical significance and has not been approved for diagnostic purposes by any medical device regulator.

PEPFAR has recognized these concerns, but simultaneously divorced itself of responsibility for making the determination on whether to return results in a program that it is the primary driver of. In the COP guidance they state:

> *PEPFAR OU teams should defer to countries' ethical and policy guidelines for return of recency results to individuals. In countries where criminalization of HIV exposure and key populations exist, OU teams should include clear information about harms and benefits and avoid any language suggesting causation in the informed consent and during the counseling session prior to administering the recency test.*[64]

It should initially be noted that when PEPFAR began introducing recency testing in COP2019, Sedia Biosciences' procurement agreement forbade any U.S. government purchaser from returning the results of the test to a patient, though this agreement no longer appears on its website.[65] Additionally, it's not clear that even standard informed consent processes can really communicate to patients who receive a result—whether recent or long-term—just how they should apply the result in their own lives given the accuracy issues identified above. This is especially true when results are returned based on a RTRI alone and are exacerbated by the fact that PEPFAR's own training materials do not include any discussion of the accuracy limitations of LAg-avidity as a methodology.[66]

The Trace-Recency Generic Protocol for Recency HIV Infection Surveillance does include sample informed consent and counseling information if countries are to return recency results.[67] Importantly, they only address the return of RITA results, not RTRI. However, there are reports of RTRI results being returned prior to viral load confirmation, partially because of

[64] COP20 Guidance, pp. 226-227, available at: https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance_Final-1-15-2020.pdf [see also, COP2021 Guidance, p. 283, stating: "PEPFAR OU teams should defer to countries' ethical and policy guidelines for return of recency results to individuals in accordance with WHO's 5Cs of HIV testing. OU teams should include clear information about harms and benefits (including mitigating the risk of Intimate Partner Violence and other adverse events) and avoid language suggesting causation in the informed consent and during the counseling session prior to administering the recency test." Available at: https://www.state.gov/wp-content/uploads/2020/12/PEPFAR-COP21-Guidance-Final.pdf].

[65] amfAR, AVAC, CHANGE, *New HIV Testing Strategies in PEPFAR COP19: Rollout and Human Rights Concerns*, February, 2019, available at: https://www.amfar.org/wp-content/uploads/2022/02/COP19.pdf, stating: "[N]either the institution [purchaser] nor its employees shall divulge the results obtained with the Asanté™ HIV-1 Rapid Recency™ Assay to research subjects, patients or their physicians, and that the Asanté™ HIV-1 Rapid Recency™ Assay shall not be used on samples from patients as a diagnostic or patient monitoring tool that may impact patient therapy and management." in reference to http://www.sediabio.com/LiteratureRetrieve.aspx?ID=136419.

[66] Trace-Recency, *Overview of RTRI: Assay Principle and Test Performance*, available at: https://trace-recency.org/wp-content/uploads/tools/training-materials/modules/01.-Overview-of-RTRI-Principle-and-Performance_April2021.pptx.

[67] Trace-Recency, *Generic Protocol for Recency HIV Infection Surveillance*, Appendix D, available at: https://trace-recency.org/wp-content/uploads/2021/02/Generic-Protocol-for-Recent-Infection-Surveillance_v5.0_29Jan2021.docx.

the challenge nurses face in subjecting individuals to testing and not providing them the results. The sample counseling scripts state:

> ***What does recent HIV infection mean?***
>
> *Recent HIV infection means a person likely got HIV within the past one year. [...]* ***There is a small (one in ten) chance that someone who got HIV more than one year ago will test as if they have a recent infection.*** *The test cannot tell exactly when you got HIV. The test cannot tell you who passed the infection to you.*
>
> ***What does long-term HIV infection mean?***
>
> *A long-term HIV infection means a person likely got HIV more than one year ago. [...]* ***There is a chance that someone who got HIV within the past one year will test as if they have a long-term infection.*** *The test cannot tell exactly when you got HIV. The test cannot tell you who passed the infection to you.*[68] *[emphasis added]*

Both of these statements fail to communicate the likely errors involved. While communicating a 10% (one in ten) after a confirmed VL<1,000 isn't unreasonable, the research cited above suggests that the range may be significantly larger. For long-term infection, however, this simplification to simply a "chance that someone" infected within the past year will test long-term dramatically understates the likelihood of that occurrence. **In reality, for an individual who did contract HIV within the past year, it is more likely than not that they will test long-term on a LAg-based recency assay.** Conveying this as simply a "chance" understates the reality of that chance. For those individuals, providing the results amounts to misinformation as much as actual information.

In environments where HIV transmission is criminalized or where key populations are criminalized, returning recency test results that indicate when they were infected could be used by clients as the basis of criminal complaints. Avoiding such scenarios would require working with police services and ministries of justice to ensure that evidentiary standards are clear that recency test results cannot be used for such purposes.

For intimate partner violence, the problems are similar and these concerns have been raised since the beginning of the recency testing program[69] and continue to be raised.[70] The Trace-Recency training materials do touch on the increased risks of intimate partner violence, but utterly fail to understand the actual concern. The Trace-Recency *Ethics and Consent* training module states with regard to the possible harms of participating in recency testing that there is "Increased risk of IPV or other adverse events associated with client's knowledge of recent infection."[71] This fundamentally misunderstands the risk of IPV associated with recency testing. The risk of IPV is not that a client will be exposed to IPV as a result of knowing their recency result, but that the client themselves will perpetrate violence against their sexual partner(s). The fact that PEPFAR-supported training materials misunderstand the very directionality of the concern indicates that PEPFAR has not sufficiently thought through the potential dangers of the recency program nor are they prepared to adequately respond to these issues when they inevitably arise.[72]

Critically, these problems are much less problematic in a genuine laboratory surveillance model where blood samples collected for other purposes—such as baseline CD4 or viral load testing—can be used anonymously for public health purposes. As these surveillance systems don't require any additional blood draws or direct linking to an individual's identity, ethical problems related to requiring informed consent are not present. While not all human rights concerns are necessarily cleared by running recency surveillance out of centralized labs, all the human rights concerns are exacerbated by running recency surveillance at the point of care.

Finally, recency testing has implications for the patient experience of HIV testing itself. Research in Malawi has shown that the addition of recency testing adds on average more than 30 minutes to the process for newly diagnosed clients.[73] This has real implications for how patients experience the processes of being diagnosed. Individuals who test positive for HIV and are potentially reeling from the shock of that experience are then expected to go through an informed consent process and additional testing that has absolutely no clinical benefit to them as an individual before moving forward with the process of further counseling and beginning the process of getting them enrolled onto treatment.

The risk of IPV is not that a client will be exposed to IPV as a result of knowing their recency result, but that the client themselves will perpetrate violence against their sexual partner(s).

[68] Ibid, Appendix D, p. 24.

[69] amfAR, AVAC, CHANGE, *New HIV Testing Strategies in PEPFAR COP19: Rollout and Human Rights Concerns*, February, 2019.

[70] Karim QA, et al., 2020.

[71] Trace-Recency, *Ethics and Consent Training Module*, available at: https://trace-recency.org/wp-content/uploads/2019/05/3.Ethics-and-Consent_31March2019.pptx.

[72] Similarly, the Data Security Module of Trace-Recency discusses the need to monitor and report protocol violations and adverse events. However, once again, the risks of IPV are misunderstood. Under "Adverse Event Reporting" adverse events are "[d]efined as events leading to serious psychological or physical harm to a client for being involved in a study." Again, the issue with returning the results of a recency test is it conveys to a client the perception of knowledge of who may be responsible for them contracting HIV and as a result of that knowledge or perception commit violence against that person. See Trace-Recency, *Data Security Module*, available at: https://trace-recency.org/wp-content/uploads/2019/05/17.Data-Security_31March2019.pptx.

[73] Arons M, Curran K, Msukwa M, et al., 2022.

THE COST OF THE RECENCY TESTING PROGRAM

Many of the issues outlined so far may not be fatal for a recency testing program in a world of unlimited resources. It may not be ideal that implementation as currently planned is unlikely to yield the highly reliable, real-time, actionable data that was once hoped for, but it's possible some limited data from the program could prove useful. Unfortunately, it is not the case that there are unlimited resources for the HIV response. The overall PEPFAR budget has been flat for over a decade, while the number of PLHIV on treatment has increased tremendously.[74] In this flat-funded environment, costly new programs like recency testing must be interrogated thoroughly to make sure they are worth the investment and are the best possible use of funds available.

Costs of the recency testing program are likely to fall into at least four categories. While there may be other costs, major cost drivers are commodities (the RTRI test kits and consumables for viral load confirmation or other steps of a RITA), the training and healthcare worker costs, and the data systems and additional surveillance staff to respond to the data.

The Sedia Asanté point-of-care test kits used by the PEPFAR program are currently available for $6.00 per test when purchased in bulk.[75] COP Guidance is that countries approaching epidemic control "should have recency testing at scale across all sites, whether supported by PEPFAR or by other entities and among all newly diagnosed HIV individuals age 15 years or older."[76] In PEPFAR-supported facilities alone last year, that amounted to just over 2.4 million people. Leaving aside any other costs associated with getting the tests to clinics, the test kits themselves would cost the program about $14.4 million per year.

Nearly all countries plan to implement viral load confirmation for the recency program, and the few that don't are being pressured to move that way.[77] Assuming 15% of new positives test as recent on the rapid test, this translates to 360,000 additional viral loads. At an assumed cost of $15 per test,[78] confirmatory viral loads are likely to cost about $5.4 million per year.

Commodities costs, however, are likely to be the smallest costs involved. Training testing staff across all sites to implement recency testing is costly and time consuming. The time spent not only in training, but actually implementing recency testing takes healthcare worker time away from delivering other healthcare services. As noted above, research has shown that the addition of recency testing adds approximately 30 minutes to each encounter with a patient newly testing HIV positive.[79] Those costs are substantial and will come at the direct cost of these healthcare workers providing testing services to others in need.

Moreover, training so many individual nurses (or other healthcare workers) to implement recency testing increases problems in the inter-reliability of test results. Testing procedures have to be followed precisely to achieve accurate test results and the RTRI tests have shown to have challenges in this regard. In Uganda, even laboratory implementation of RTRI tests showed only 72% agreement between two different labs assessing 200 samples.[80] At the laboratory level, it's possible to consistently, efficiently, and affordably assess such performance challenges. However, when rolled out to several thousand individual nurses such concurrence challenges are likely to go unresolved, despite the level of training provided. And maintaining that trained workforce, including ongoing quality assurance and quality improvement training, raises additional sustainability and affordability problems. These costs are not borne by PEPFAR alone, but are being offloaded to ministry of health budgets as they are the primary employer of most healthcare workers in most PEPFAR program countries.

Finally, resources must also be put into the data systems, data visualization platforms, analyses, health surveillance staff, and outbreak investigation teams to make use of any of the data generated. Those staff and systems pull resources and attention away from direct service delivery providing treatment or prevention directly to clients and towards more high-level data users.

The promise that PEPFAR has made is that the programmatic value of all of these costs and effort will be worth the expense to justify entrenching these systems as ongoing annual costs of HIV programming. But it has yet to show any comprehensive costing assessment of the recency testing program inclusive of all the above costs (whether paid by PEPFAR or others) and has yet to actually show any significant case studies of the data leading to reductions in HIV incidence or genuine improvements in tracking HIV transmission.

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[74] Kaiser Family Foundation. *The U.S. President's Emergency Plan for AIDS Relief (PEPFAR)*. October 2021. https://www.kff.org/global-health-policy/fact-sheet/the-u-s-presidents-emergency-plan-for-aids-relief-pepfar/.

[75] PEPFAR. "Recent Infection Surveillance." Slide deck shared with amfAR.

[76] COP21 Guidance, p. 282, available at: https://www.state.gov/wp-content/uploads/2020/12/PEPFAR-COP21-Guidance-Final.pdf; See also, COP2022 Guidance, p. 562.

[77] Ibid.

[78] amfAR's estimate, based on a change in budget from Zimbabwe after addition of confirmatory viral load.

[79] Arons M, Curran K, Msukwa M, et al., 2022.

[80] Galiwango RM, Ssuuna C, Kaleebu P, et al., 2021.

RECOMMENDATIONS

...investments into such a surveillance system based on methods of detection and analysis that are insufficient to support the real-time surveillance objective are wasteful and—more problematically—distract from the core work of delivering health services and improving health systems for people living with HIV.

As stated earlier, the rationale and the objective of having a real-time surveillance system for HIV to better target resources in an environment where epidemic control has been achieved is understandable. However, investments into such a surveillance system based on methods of detection and analysis that are insufficient to support the real-time surveillance objective are wasteful and—more problematically—distract from the core work of delivering health services and improving health systems for people living with HIV.

Based on this, we make the following recommendations to PEPFAR:

1. PEPFAR should immediately suspend its recency testing program (including HCW trainings) until an evaluation can be completed of how a LAg-avidity based surveillance system—especially one premised on informing site or small geographic region differences in real-time—can overcome the inherent accuracy challenges of recency testing.
2. PEPFAR must release a transparent accounting of the money that has been spent for COPs 2019–2021 on rolling-out recency testing, including commodities, training costs, surveillance staff, data systems, and an estimate of the costs of healthcare workers implementing recency testing whether those costs are borne by PEPFAR or not. Additionally, PEPFAR should develop cost expectations for the program over the next five years if expansion of the program were to continue as envisaged—scaling to all facilities whether PEPFAR supported or not in all countries approaching epidemic control.
3. PEPFAR should fund a rigorous and independent evaluation of the programmatic utility of recency testing to date, including how resources have been re-allocated in response to recency findings and hotspots, how programs have programmatically responded to those results, and what programmatic impact those responses have had on new HIV infections.
4. PEPFAR should conduct a full cost-benefit analysis of point-of-care recency testing systems compared with lab-based systems that includes assessments of sustainability and ability to adopt new recency surveillance methods should they be developed, the training costs required (including on-going quality-assurance and quality-improvement requirements), impact on healthcare worker time, and effect on client experience and access to care.
5. PEPFAR should fully evaluate alternative approaches to measuring HIV incidence in countries and regions where HIV epidemic control has been achieved.

REFERENCES

amfAR, AVAC, CHANGE. New HIV Testing Strategies in PEPFAR COP19: Rollout and Human Rights Concerns. 2015 Feb. amfAR We site. https://www.amfar.org/wp-content/uploads/2022/02/COP19.pdf. Accessed April 30, 2022.

Agyemang E, Kim A, Dobbs T, et al. Performance of a novel rapid test for recent HIV infection among newly-diagnosed pregnant adolescent girls and young women in four high HIV-prevalence districts—Malawi, 2017-2018. PLoS ONE. 2022 Feb 11; 17(2):e0262071. https://doi.org/10.1371/journal.pone.0262071.

Arons M, Curran K, Msukwa M, et al. Acceptability and feasibility of HIV recent infection surveillance by healthcare workers using a rapid test for recent infection at HIV testing sites—Malawi, 2019. BMC Health Serv Res. 2022; 22:341. https://doi.org/10.1186/s12913-022-07600-7.

CEPHIA (Grebe E, Facente SN, Hampton D, Cheng C, Owen R, Keating SM, Pilcher CD, Welte A, Busch M, Murphy G & Consortium for the Evaluation and Performance of HIV Incidence Assays). Asanté HIV-1 Rapid Recency® Assay Evaluation Report (1.0). Zenodo. 2019. https://doi.org/10.5281/zenodo.3509834.

Community COP20 Zimbabwe, Community Priorities: PEPFAR Country Operational Plan 2020. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2020/02/Zimbabwe-Community-COP20.pdf. Accessed May 10, 2022.

Galiwango RM, Ssuuna C, Kaleebu P, et al. (2021, December). Short communication: Validation of the Asanté HIV-1 Rapid Recency Assay for detection of recent HIV-1 infections in Uganda. AIDS Res Hum Retroviruses. 2021 Dec; 37(12):893-896. https://doi.org/10.1089/AID.2020.0279

Giguère K, Eaton J, Marsh K, et al. 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. Lancet HIV. 2021;8: e284–93. https://doi.org/10.1016/S2352-3018(20)30315-5.

HSE Health Protection Surveillance Centre. Monitoring Recent HIV Infection in Ireland, 2018. Dublin: HSE HPSC; 2020. https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2018reports/HIV_2018_recentinfection.pdf. Accessed April 30, 2022.

Jacob N, Rice B, Kalk E, et al. Utility of digitising point of care HIV test results to accurately measure, and improve performance towards, the UNAIDS 90-90-90 targets. PLoS ONE. 2020 Jun 30; (15)6:e0235471. https://doi.org/10.1371/journal.pone.0235471.

Kaiser Family Foundation. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR). 2021 Oct. https://www.kff.org/global-health-policy/fact-sheet/the-u-s-presidents-emergency-plan-for-aids-relief-pepfar/. Accessed April 30, 2022.

Karim QA, Macklin R, Gruskin S, et al. HIV recency testing: should results be disclosed to individuals tested? J Int AIDS Soc. 2020; 23(8):e25584. https://doi.org/10.1002/jia2.25584.

Kassanjee R, Pilcher CD, Keating SM, et al. Independent assessment of candidate HIV incidence assays on specimens in the CEPHIA repository. AIDS. 2014; 28(16):2439-2449. https://doi.org/10.1097/QAD.0000000000000429 .

Konikoff J, Brookmeyer R, Longosz AF, Cousins MM, Celum C, et al. Performance of a limiting-antigen avidity enzyme immunoassay for cross-sectional estimation of HIV incidence in the United States. PLoS ONE. 2013; 8(12):e82772. https://doi.org/10.1371/journal.pone.0082772.

Liu Lathu Mu COP20 Our Voice Malawi: Community Priorities, PEPFAR Country Operational Plan 2020. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2020/03/Liu-Lathu-Mu-COP20-Malawi.pdf. Accessed May 10, 2022.

Lia Lathu Mu COP21 Our Voices Malawi: Community Priorities, PEPFAR Country Operational Plan 2021. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2021/03/Liu-Lathu-Mu-COP21-Malawi.pdf. Accessed May 10, 2022.

Longosz A, Mehta S, Kirk G, et al. Incorrect identification of recent HIV infection in adults in the United States using a limiting-antigen avidity assay. AIDS. 2014 May 15; 28(8):1227–1232. https://doi.org/10.1097/QAD.0000000000000221.

Maxim Biodmedical. Products. Maxim Web site. https://www.maximbio.com/products. Accessed April 30, 2022.

Maxim Biomedical. Swift™ HIV Recent Infection Assay (RIA) Controls Kit. Maxim Web site. https://www.maximbio.com/swift-hiv-recent-infection-assay-controls-kit. Accessed April 30, 2022.

People's COP19 Kenya: Community Priorities, PEPFAR Country Operational Plan 2019. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2019/03/Kenya-Peoples-COP19.pdf. Accessed May 10, 2022.

People's COP19 South Africa: Community Priorities, PEPFAR Country Operational Plan 2019. PEPFAR Watch. https://ritshidze.org.za/wp-content/uploads/2020/11/Peoples-COP19-South-Africa.pdf. Accessed May 10, 2022.

People's COP20 Kenya, Community Priorities: PEPFAR Country Operational Plan 2020. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2020/02/Peoples-COP20-Kenya.pdf. Accessed May 10, 2022.

People's COP20 South Africa: Community Priority Recommendations, PEPFAR Country Operational Plan 2020. PEPFAR Watch. https://ritshidze.org.za/wp-content/uploads/2020/11/Peoples-COP20-South-Africa.pdf Accessed May 10, 2022.

People's COP21 Kenya: Community Priority Recommendations for PEPFAR Kenya in COP 21. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2021/03/Peoples-COP21-Kenya.pdf. Accessed May 10, 2022.

People's COP21 South Africa South Africa: Community Priority Recommendations, PEPFAR Country Operational Plan 2021. PEPFAR Watch. https://ritshidze.org.za/wp-content/uploads/2021/03/Peoples-COP21-South-Africa.pdf. Accessed May 10, 2022.

People's COP22 South Africa: Community Priority Recommendations for PEPFAR South Africa in COP 2022. PEPFAR Watch. https://ritshidze.org.za/wp-content/uploads/2022/03/Peoples-COP22-South-Africa.pdf. Accessed May 10, 2022.

PEPFAR. PEPFAR 2019 Country Operational Plan Guidance for all PEPFAR Countries. 2019. https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf. Accessed April 30, 2022.

PEPFAR. PEPFAR 2020 Country Operational Plan Guidance for all PEPFAR Countries. 2020. https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance_Final-1-15-2020.pdf. Accessed April 30, 2022.

PEPFAR. PEPFAR 2021 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries. 2021. https://www.state.gov/wp-content/uploads/2020/12/PEPFAR-COP21-Guidance-Final.pdf. Accessed April 30, 2022.

PEPFAR. PEPFAR 2022 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries. 2022. https://www.state.gov/wp-content/uploads/2022/02/COP22-Guidance-Final_508-Compliant-3.pdf. Accessed April 30, 2022.

PEPFAR. "Recent Infection Surveillance." Slide deck shared with amfAR.

PHIA Project Web site. https://phia.icap.columbia.edu/. Accessed April 30, 2022.

Rice BD et al. Can HIV recent infection surveillance help us better understand where primary prevention efforts should be targeted? Results of three pilots integrating a recent infection testing algorithm into routine programme activities in Kenya and Zimbabwe. JIAS. 2020; 23(S3):e25513. https://doi.org/10.1002/jia2.25513.

Rwibasira GN, Malamba SS, Musengimana G, Nkunda RCM, Omolo J, Remera E, et al. (2021) Recent infections among individuals with a new HIV diagnosis in Rwanda, 2018–2020. PloS One. 2021; 16(11): e0259708. https://doi.org/10.1371/journal.pone.0259708.

Sauti Yetu COP21 Our Voices Tanzania: Community Priority Recommendations for PEPFAR Tanzania in COP21. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2021/04/Sauti-Yetu-COP21-Our-Voices-Tanzania.pdf. Accessed May 10, 2022.

Sedia Biosciences Corporation. Asanté™ HIV-1 Rapid Recency. Sedia Web site. https://www.sediabio.com/asante-hiv-1-rapid-recency/. Accessed April 30, 2022.

Sedia Biosciences Corporation. Asanté™ HIV-1 Rapid Recency ® Assay Product Insert. Sedia Web site. https://www.sediabio.com/wp-content/uploads/2021/06/LN-6122-05-Product-Insert-Asante-HIV-1-Rapid-Recency-Assay.pdf. Accessed April 30, 2022.

Sedia Biosciences Corporation. Sedia® HIV-1 LAg-Avidity EIA Product Insert. Sedia Web site. https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf. Accessed April 30, 2022.

Sedia Biosciences Corporation. Sedia Biosciences launches the SEDIA BED HIV-1 Incidence EIA. Sedia Web site. https://www.sediabio.com/sedia-biosciences-launches-the-sedia-bed-hiv-1-incidence-eia/. Accessed April 30, 2022.

Telford C, Tessema Z, Msukwa M, et al. Geospatial transmission hotspots of recent HIV infection—Malawi, October 2019–March 2020. MMWR. 2022; v71(9). https://doi.org/10.15585/mmwr.mm7109a1.

The People's Voice Uganda (COP 19): Community Priorities, PEPFAR Country Operational Plan 2019. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2019/03/Peoples-Voice-Uganda-FINAL.pdf. Accessed May 10, 2022.

The People's VOICE Uganda (COP20): Community Priorities, PEPFAR Country Operational Plan 2020. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2020/02/Peoples-Voice-Uganda-COP20.pdf. Accessed May 10, 2022.

The People's Voice Uganda (COP21): Community Priority Recommendations for PEPFAR Uganda for 2021. PEPFAR Watch. https://healthgap.org/wp-content/uploads/2021/04/Peoples-Voice-COP21-Uganda.pdf. Accessed May 10, 2022.

Trace-Recency Web site. https://trace-recency.org/. Accessed April 30, 2022.

Trace-Recency. Data Security Module. Trace Web site. https://trace-recency.org/wp-content/uploads/2019/05/17.Data-Security_31March2019.pptx. Accessed April 30, 2022.

Trace-Recency. Ethics and Consent Training Module. Trace Web site. https://trace-recency.org/wp-content/uploads/2019/05/3.Ethics-and-Consent_31March2019.pptx. Accessed April 30, 2022.

Trace-Recency. Example Dashboard—Cluster Detection and Response. Trace Web site. https://trace-recency.org/example-dashboard/. Accessed April 30, 2022.

Trace-Recency. FAQs. Trace Web site. https://trace-recency.org/ufaqs/how-does-the-rtri-compare-to-the-hiv-1-lag-avidity-eia/. Accessed April 30, 2022.

Trace-Recency. Generic Protocol for Recency HIV Infection Surveillance, Appendix D. Trace Web site. https://trace-recency.org/wp-content/uploads/2021/02/Generic-Protocol-for-Recent-Infection-Surveillance_v5.0_29Jan2021.docx. Accessed April 30, 2022.

Trace-Recency. Overview of RTRI: Assay Principle and Test Performance. Trace Web site. https://trace-recency.org/wp-content/uploads/tools/training-materials/modules/01.-Overview-of-RTRI-Principle-and-Performance_April2021.pptx. Accessed April 30, 2022.

Trace-Recency. Public Health Response Strategy Using Recency Assays. Trace Web site. https://trace-recency.org/wp-content/uploads/2021/09/HIV-Public-Health-Response-Strategy_2021SEP18.docx. Accessed April 30, 2022.

UNAIDS. Understanding Fast-Track: accelerating action to end the AIDS epidemic by 2030. 2015. https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf. Accessed April 30, 2022.

Voetsch A, Duong Y, Stupp P, et al., HIV-1 recent infection testing algorithm with antiretroviral drug detection to improve accuracy of incidence estimates. J Acquir Immune Defic Syndr. 2021; V 87, Supp 1. https://doi.org/10.1097/QAI.0000000000002707.

Zhu Q, Wang Y, Liu J, Duan X, et al., Identifying major drivers of incident HIV infection using recent infection testing algorithms (RITAs) to precisely inform targeted prevention. IJID. 2020; 101: 131-137. https://doi.org/10.1016/j.ijid.2020.09.1421.

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