Ensuring Efforts to Scale up, Strengthen and Sustain HIV Responses
Improving measurement of HIV incidence at sub-national levels and among key and vulnerable populations

Hosted by the Joep Lange Institute
30–31 January 2018

What's in this meeting report

Section 1 provides:
- An **introduction of the overall initiative**
- Background analysis as to the **rationale for the meeting**: the need for improvements in measuring HIV incidence

Section 2 summarizes some **regularly used and proposed methods for measuring HIV incidence in both general and key populations**. Also highlighted are:
- the PHIAs and their current findings on incidence;
- challenges and limitations to HIV incidence measurements in general and with specific tools and methods; and
- some considerations to keep in mind with all surveys and results in this area.

Section 3 summarizes presentations and discussion about **select HIV incidence measurement initiatives and history in four countries**: Rwanda, Uganda, Kenya and Brazil.

Section 4 consists of a list of **recommendations and suggested focus areas for further research and prioritization**. All were proposed at the meeting and are presented as a preliminary list to jumpstart efforts toward improved HIV incidence measures overall, and among key populations and at sub-national levels to the fullest extent possible.

Recommendations from the meeting are listed below. More detailed description of these recommendations is provided in Section 4.

- Viral load is the most important factor: Use the absolute number of unsuppressed people in a defined population as a measure for HIV transmission risk.
- Stimulate point-of-care (POC) viral load determination as a measure for HIV acute infection.
- CD4 determination at HIV diagnosis should be continued, as it can serve as a proxy for early infection.
- More incidence surveys of adolescent and key populations HIV incidence surveys are needed.
- More research is needed to better estimate key population sizes.
- Measuring extent of migration is an important complementary step to measuring HIV incidence.
- HIV incidence measurements should become outcomes of national HIV programmes.
- Building incidence into case-based surveillance: Outcome indicators should be redefined to include measures from infection to diagnosis and subsequent care.
- Strengthen human resources to identify HIV incidence through mobile phone–supported decision tools
- Assess whether self-testing can be used as a strategy for incidence identification.
- Use big data analysis/machine learning to 'heat map' (predict) HIV incidence in geographic areas and among populations.
- Conduct a review of data on HIV testing frequency to inform WHO guideline development.

1. Introduction and Overview

1.1. About the overall initiative

Ensuring Efforts to Scale up, Strengthen and Sustain HIV Responses is an initiative launched in April 2017 by the Joep Lange Institute. The initiative's overall objectives are to describe challenges to meeting current HIV targets and articulate an approach for the HIV response that takes sharp aim at:

- reducing the number of new HIV infections, with a focus on key populations, adolescents and young adults;
- streamlining and improving service delivery;
- efficiently targeting the use of resources; and
- building new and more sustainable approaches for funding.

A total of seven meetings will anchor the initiative's agenda. A comprehensive report and findings from those meetings will be launched at the International AIDS Conference in Amsterdam, July 2018. That report will be preceded and accompanied by additional work products to highlight research, communications and advocacy needs and strategies.

Three of the seven meetings are larger-scale, bringing together at least 25 participants from across a range of sectors—including government, donor, research/science, multilateral and technical agencies, and civil society. One of those three, held in September 2017, centred on the potential impact of reduced funding for HIV on countries' efforts and ability to scale up their responses and how limited resources can best be used effectively and responsibly. The second meeting, held in October 2017, considered approaches and strategies to make responses more efficient, with an emphasis on differentiated service delivery (DSD) and HIV prevention efforts for highly vulnerable populations. A third large-scale meeting, on innovative financing options and opportunities, will be held in late February 2018.

The 30–31 January 2018 meeting, **Improving measurement of HIV incidence at sub-national levels and among key and vulnerable populations,** is the first of four additional meetings that will further contribute to the overall process. This meeting is one of three that were planned and organized to respond to priority areas of more intensive work, as identified by participants at the first two larger meetings.

The second of these three meetings, on developing reporting mechanisms for community-based HIV service delivery in Kenya, is scheduled for late February 2018. The third, to be held by the middle of April 2018, will centre on primary prevention, especially from the perspective of key and vulnerable populations. The number of participants for these side meetings typically is not planned to exceed 20 people. Attendees tend to be from a narrower spectrum of expertise and experience than the larger-scale meetings because the intention is to do a deeper dive into a specialized topic area or areas. The seventh contributing meeting, scheduled for mid-March 2018, is focused on strategies and advocacy to address growing rates of HIV drug resistance.

Presentations from each of these meetings will be available through a dedicated page on the JLI website. Exceptions may include situations in which presenters have asked not to make their presentations publicly available for one reason or another.

1.2 Rationale for the meeting: need for improvements in measuring HIV incidence

Results released to date from about half of the planned 14 Population-based HIV Impact Assessment (PHIA) surveys[1] show notable progress in several high-burden countries in sub-Saharan Africa toward meeting the UNAIDS Fast-Track 90-90-90 targets. However, those and most other countries are unlikely to ensure strong, sustainable results and achieve epidemic control unless they can better target resources and interventions to where they are most urgently needed. Despite the success of HIV treatment scale-up in many countries—success that has resulted in lower HIV-related morbidity and mortality and lower HIV incidence in some countries—reaching the HIV treatment targets, on their own, will not succeed in controlling the HIV epidemic. Increased emphasis on primary prevention is essential. Improving knowledge about where and in whom HIV infections are occurring is crucial if these prevention efforts are to be successful.

PHIAs and other surveys can help address this need because most typically provide some information about who is disproportionately affected by national epidemics and where they live. For example, the PHIA survey in Malawi found widely varying HIV prevalence by geographic region, e.g., 18.2% in Blantyre and 5.3% in Central East province. Viral load suppression among those on antiretroviral therapy (ART) in Blantyre was lower, at 59.5%, than the 63.7% found in Central East.

Findings such as these offer some indication of where policy makers and other HIV response stakeholders should focus their efforts and resources. But many surveys do not include HIV incidence estimates, and those that do include them often can only provide estimates at national levels due to the large sample size requirements for HIV incidence estimation. Such estimates therefore are too general in scope to be of maximum use for resource prioritization.

Incidence refers to the occurrence of new cases of disease or injury in a population over a specified period of time. Because they expose trends and higher-risk areas and populations, comprehensive HIV incidence estimates are central to efforts to identify who is 'missing' in HIV responses. These missing individuals can sometimes play a key role in 'driving' epidemics, which implies that identifying them and engaging them in services to reduce new infections should be a top priority. Some may be located in isolated, poorly served districts and regions, for example, while others are members of key and vulnerable populations such as men who have sex with men (MSM), people who inject drugs, sex workers, and adolescent girls and young women.

The lack of easily obtainable, consistent, reliable incidence estimates in most contexts is a concern because, as one researcher noted, "Estimates of incidence are important for monitoring the growth of new infections, targeting prevention efforts, and designing prevention trials."[2] In other words, they can signal quite distinctly where HIV interventions should be focused.

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[1] The PHIA Project surveys are funded by CDC/PEPFAR and implemented by ICAP at Columbia University in New York in collaboration with ministries of health (and funded by CDC/PEPFAR). As of late January 2018, results had been released for surveys conducted in Lesotho, Malawi, Swaziland, Tanzania, Zambia, and Zimbabwe, with research fully completed and results to be imminently released for Uganda.
[2] Brookmeyer R, et al. Estimation of HIV Incidence Using Multiple Biomarkers. *Am J Epidemiol.* 2013 Feb 1;177(3):264-72. Epub 2013 Jan 9.

Measuring HIV incidence more effectively and easily among key and vulnerable populations as well as other discrete ones (e.g., discordant couples) and at sub-national levels can lead to more aggressive, rapid action to provide access to improved and more acceptable prevention and treatment options in high incidence contexts. As importantly, strong and reliable incidence estimates are vital for advocacy and accountability purposes, including in contexts where policy makers become complacent or otherwise think 'the job is done' as they near the 90-90-90 targets. Targeted incidence estimates are likely to prove them wrong as the extent of the epidemic's scope in the missing 10% is made clearer. Measuring progress to 90-90-90 targets at sub-national levels and within key populations will provide essential information about where to focus treatment and prevention scale-up efforts.

Unfortunately, the toolkit does not yet have the right tools. The main challenge is that current approaches and mechanisms for HIV incidence measurements are not necessarily adequate for meeting countries' needs and expectations as they scale up their HIV responses. It is thus not surprising that the "development of accurate, practical, and cost-effective approaches to estimation of HIV incidence is a priority among researchers in HIV surveillance because of limitations with existing methods."[3] The 30–31 January 2018 meeting in Amsterdam aimed to support efforts toward this priority goal by identifying a series of recommendations for potential future research and implementation. The goal of the meeting was to develop recommendations for research that aims to:

- Improve understanding of the impact of HIV prevention efforts in populations at increased risk of HIV acquisition through improved monitoring of HIV incidence and/or other indicators of rates of new infections
- Improve the ability to better target HIV prevention efforts based on improved incidence measurement and/or other indicators of new infections
- Identify the ways in which the political, social, economic, and environmental contexts of the populations and regions being studied affect the methods by which successful measurement of HIV incidence are developed and implemented.
- Determine the need for additional research and research funding to improve understanding of HIV transmission rates in key and vulnerable populations.

The options discussed and proposed are a mix of process, policy, and technical solutions. All are intended to improve one or more aspect of HIV incidence measurement and application of findings. Discussion of various methods also increases the opportunities for considering combinations of approaches that can improve efforts moving forward as well.

2. Proven and Proposed Incidence-Measuring Options and Overall Challenges

Estimating HIV incidence is difficult overall, but especially so at sub-national levels and for key populations, because small populations are even harder to survey. Addressing and overcoming the various barriers is a generally accepted priority due to the importance of incidence in guiding more effective HIV responses and programming. This section consists of summaries of recent studies that presented incidence estimates as well as proposed options across a wide spectrum of how to improve the overall endeavour. The section also includes a summary of overarching challenges, many of which are referred to in discussions of specific methods.

2.1 PHIAs

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[3] Brookmeyer R, et al. Estimation of HIV Incidence Using Multiple Biomarkers'. *Am J Epidemiol.* 2013 Feb 1;177(3):264-72. Epub 2013 Jan 9.

The comprehensive, ambitious PHIAs offer perhaps the most detailed recent information on epidemics, including progress along key parts of the treatment cascade. The surveys are cross-sectional and use two-stage cluster household sampling. Testing and analysis of HIV incidence rely on LAg-avidity and viral load testing. The nine surveys completed to date each include around 30,000 participants.[4]

The PHIAs have showcased progress toward the 90-90-90 Fast-Track targets. Substantial variations have been found by age, with the youngest cohort (15–24 year olds) having lower levels of success than others. The difference is widest for the first 90 target, with just 46.4% of survey respondents aged 15–24 across six initial PHIA countries saying they knew their HIV status. The comparable finding for those aged 35–59 was 77.8%.

To some extent, these big gaps are unsurprising: the longer people live, the more likely they will get tested and know their status. The finding exposes serious shortcomings in prevention and risk-reducing efforts among some of the most vulnerable people. These PHIA findings suggesting that the first 90 is a serious challenge. PHIA results from seven different countries in sub-Saharan Africa show that among adolescent girls and young women just 46.3% were aware of their HIV status. Overall, much better outcomes for this cohort were found for ART access (85.5%) and viral load suppression (81%). Getting those who have tested positive on ART and virally suppressed appears to be a successful effort in many countries, but the overall impact is weaker than desired because of the low levels of diagnoses at the first step.

Measured HIV incidence varies across the countries surveyed, with the highest in Swaziland and Lesotho (1.5% and 1.6%, respectively). Overall incidence in four other countries—Malawi, Tanzania, Zambia and Zimbabwe—was measured at between 0.3% and 0.7%. Incidence tends to be higher among women in all countries, although not significantly so.

These and other national-level findings of the PHIAs are reassuring in many ways, as they suggest that progress is occurring along many core care and treatment areas. Yet the PHIAs have not (and were not designed to) elicit more specific data and estimates about epidemic 'hot spots'. More detailed information about HIV incidence by sub-national unit (e.g., provinces or districts) and priority key populations would likely help to further improve resource and intervention decision-making. For each country and context, too, populations that might be considered 'key' are likely to be different.

2.2 Summary of other methods, tools and options

There are multiple methods to measure HIV incidence or surrogate markers for HIV incidence. These vary by factors including the following:
- Data level: individual or aggregate
- Data source: biomarker, interview, model-based
- Design: Cross-sectional, serial, or cohort
- Setting: Clinical, survey/surveillance
- Surrogates for incidence: e.g., population viremia

All current methods are limited by sample size challenges.

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[4] As noted previously, at the time of the January 2018 meeting results had been publicly released for seven of the nine PHIAs completed by then.

Generally speaking, the **challenges surrounding incidence measurement** can be framed in terms of two organizing principles: *sampling challenges and technical/lab aspects*. Large sample sizes usually are needed, including when conducting cross-sectional cohort studies. Because it is helpful to know what is happening in different stages of infection, an extensive collection of samples with 'known' infection time is needed to reliably characterize behaviour of assays in different stages of infection.

Other challenges include difficulties getting sufficient data, particularly in sub-Saharan Africa, and in recruiting study participants. In many countries and contexts, it can be difficult to obtain government approval for studies—especially those focused on MSM and other key and vulnerable populations that are criminalized or highly stigmatized. Protecting confidentiality is another critical consideration at all stages of measuring HIV incidence because of the stigma persistently associated with the virus. Studies and approaches must be designed with this in mind, and extra attention, planning and oversight are commonly required to ensure confidentiality when working with and among key populations.

Currently, too, incidence estimates are rarely available at sub-national levels in most countries. This gap persists despite a desire by some governments and stakeholders (e.g., PEPFAR) for district-level incidence estimates. The ongoing push for ever-lower *sub-national estimates*, disaggregated as fully as possible, has largely been stymied by the difficulties (and expense) in designing, implementing and interpreting studies that seek to estimate HIV incidence at such levels.

Some solutions might be suitable for sub-national incidence, such as small-area estimation. But the area of work is highly context-specific. Since all sub-national areas are different, not only across countries but within individual ones, effective and auxiliary data will vary. The same is true in regard to various key and vulnerable populations, including within sub-national divisions. The complexities and complications increase as the attempted HIV incidence measurement becomes more granular.


Box 1. Interpreting results: some considerations to keep in mind

HIV incidence assay performance is reflected in each assay's mean duration of recent infection (**MDRI**) and false recency ratio (**FRR**). A low FRR is required for precise incidence determination and a higher MDRI allows incidence to be estimated from a smaller cross-sectional survey sample size. An ideal biomarker profile today would have an FRR of less than 2% and an MDRI of greater than a year (in most cases). It has proven difficult to meet such targets with current incidence measurement methods used in the contexts and environments where they are most needed now. And, ultimately, an assay that has no FRR will be necessary for the exactitude preferred.
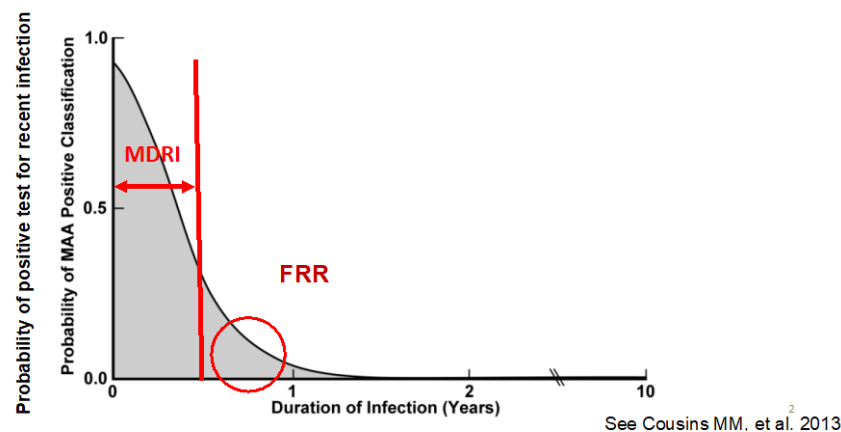
The **Hawthorne effect**[5] can negatively influence survey results, including those of prospective cohort studies. It is a major consideration in ongoing efforts to measure HIV incidence. One advantage of the cross-sectional approach is that the Hawthorne effect does not apply.

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[5] The Hawthorne effect: the alteration of behaviour by the subjects of a study due to their awareness of being observed.

Ideal Assay for Recent Infection

MDRI: mean duration of recent infection

FRR: false recent rate (%)

Cousins MM. et al. 2013[1]
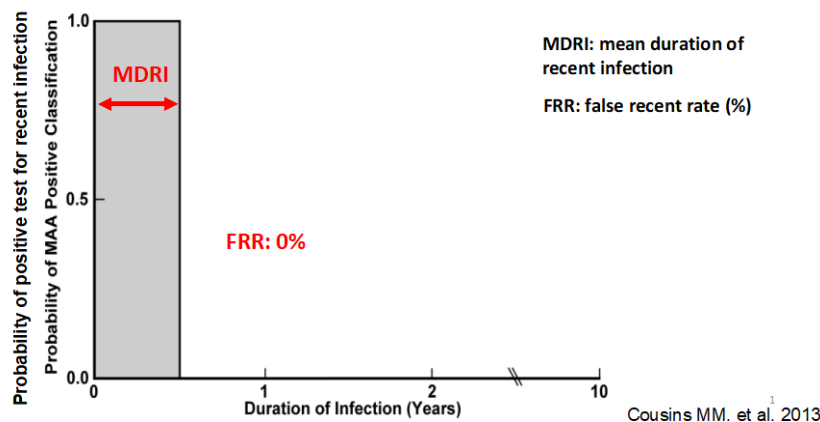
Realistic Assay for Recent Infection

See Cousins MM, et al. 2013[2]

Listed below are some methods, tools, approaches and mechanisms (and/or components of them) that are directly relevant for HIV incidence measurement or potentially could be useful to some extent.

Directly observed HIV incidence:

- **Prospective cohort studies**, such as longitudinal cohort. This is considered the 'gold standard', but it has limitations including that such studies typically take at least a year and are costly, logistically difficult, and prone to selection bias and the Hawthorne effect (see Box 1), among other things.
- **Cross-sectional incidence estimation** using biomarkers. Several different assays are commercially available, including serological assays such as LAg-avidity (used in the PHIA Project surveys) and Asante rapid recency assay, both of which were developed by the Centers for Disease Control and Prevention (CDC). Among the challenges with this method is that finding few recent cases can take a huge number of samples and the false recency ratio (FRR) is not negligible. Recency classification using the Lag-avidity assay includes viral load testing to minimize the FRR. Data are being evaluated at the CDC for the possible addition of ARV testing to further minimize the FRR. In addition,

shortly after the meeting was held in January 2018, UNAIDS published a guideline on incidence assays and their use HIV surveillance and program monitoring.[6]

The following are other examples of both incidence measurement and another overall approach, *indirect HIV incidence estimation*. Research papers exist for all of them:

- **Synthetic cohort estimation**. Somewhat of a crude method in some researchers' opinion, it refers to change of prevalence across two different surveys.
- **Back-calculation using case-based data**. This method uses certain characteristics of HIV-positive individuals at the time of diagnose (e.g., progression of HIV, CD4 count, testing history) to estimate timing of infection.
- **Prevalence trends among young adults or recent initiators** can be used as proxy for cumulative incidence.
- **Osmond's algorithm**. This method relies on knowing the approximate date of onset of risky behaviour. Thus, required data include HIV testing history and risk exposure (e.g., first anal sex encounter for MSM, or first injection for a person who uses drugs).
- **Age-based prevalence** can be imprecise because of factors such as changing risk by age and exposure.
- **Pooled nucleic acid testing (NAT)** of HIV-seronegative samples, which in some instances has found almost the same incidence estimates as have longer longitudinal studies, etc. NAT requires extensive laboratory work, but it can be used for acute HIV infection because it has a short window (usually less than two weeks). *This method has rarely been used, but it is proposed as one to explore 'local' and other incidence*.
- **HIV incidence surveillance in antenatal care (ANC) clinics**. To be useful, it would require routine testing in wide number of ANC sites. This method is not a useful option for key population incidence.
- **Viral load measures as surrogates for HIV incidence**. This idea is based on the recognition that when a denominator includes both HIV+ and HIV- cases, there is a strong correlation between (unsuppressed) viral load and HIV incidence. (The number of people with unsuppressed viral load is the numerator.) *Because population viremia can be a strong predictor of incidence, this method could be useful in helping to improve HIV incidence estimations among key populations*. Importantly, sample sizes can be expected to be lower than for cross-sectional HIV recency testing–based incidence estimation, for the similar relative precision.
- **Pooling multiple key population survey data** can facilitate overall incidence estimates where single surveys are lacking the necessary power. This has been done in India, for example, where many concurrent surveys for MSM and people who inject drugs had their data pooled to derive an incidence estimate with reasonable precision.

- To generate **local HIV-related estimates** (including HIV incidence), the following techniques are being employed:
  o Spectrum-based subnational projections (various options to achieve this are being used)
  o HIVE (geospatial modelling)

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[6] Recent infection testing algorithm technical update: Applications for HIV surveillance and programme monitoring (www.unaids.org/en/resources/documents/2018/infection_testing_algorithm).

- ○ 'Small area estimation' is an area of active research. It is based on assumptions, such as that incidence is geographically related. Partly for that reason, the statistical methodology is complex. It has other drawbacks, including that the results are not usually generalizable.

Summarized below are some other models, methods and approaches that were described in relatively extensive detail at the Amsterdam meeting. All were presented as being instructive for efforts to improve HIV incidence measurements in various setting:

- The European Center for Disease Prevention and Control (**ECDC**) has developed an **HIV modelling tool** that can be used to estimate the annual number of newly acquired HIV infections, the time between infection and diagnosis, and the undiagnosed population (stratified by CD4 count). The model relies on back-calculation. One big advantage is that this tool, which can be downloaded for free from the ECDC website, only needs routine surveillance data. One major downside is that it works best in countries with extensive data and cohorts, such as those in Western Europe; conversely, it is not easy to use in places such as many sub-Saharan African countries where limited data are available.

- In Kenya, a recently launched **proof of concept trial** called Tambua Mapema Plus aims to **improve diagnosis of acute HIV infection among adult patients seeking urgent care**. Funded by the National Institutes of Health (NIH), the three-year trial began in December 2017. The length of the trial and large cohort (2,875 persons) suggest that results will be highly anticipated for those seeking to improve capacity at identifying acute HIV infection at care seeking (from which incidence estimates may be derived).

- A **biomarker discovery trial** that ran from 2013–2016, funded by the Bill & Melinda Gates Foundation, aimed to identify new and unusual biomarkers for HIV incidence estimation. Among other things, researchers looked at plasma markers of inflammation and immunity, which could be linked to early HIV and show decline later in infection. One notable finding was that **IP-10 holds great promise as a potential triage biomarker for acute HIV infection**.[7] This marker declines quickly and is too non-specific to be an incidence biomarker itself, but because it is so sensitive it could be a proxy for acute HIV infection in some contexts. Its uptake and value likely depend on a rapid IP-10 screening followed by a confirmatory test. The costs and efficiency would be even greater if IP-10 could be tested through GeneXpert.

  Using GeneXpert to diagnose acute HIV—thus going above and beyond potential use for IP-10 and other surrogate markers—is a tantalizing prospect. Currently there are differences in opinion among scientists, researchers and lab technicians as to the feasibility of screening directly for acute HIV for individuals who have a high probability of recent exposure to HIV.

The range of methods, options and tools listed above is by no means complete. Having many possible components and approaches to choose from will make it easier to then select one or more optimal options to improve measurement of HIV incidence. Applying multiple methods and showing they are compatible with each other could, for example, show result in improved confidence intervals.

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[7] IP-10 = Interferon-γ–Inducible Protein 10

Some ***common characteristics of preferred solutions*** would be minimized sample sizes, reasonable cost-effectiveness and survey completion time, sufficient specificity, and relative ease in administration and evaluation. These are mostly subjective factors, however, and trade-offs may be necessary among one or more of them. Questions remain therefore as to when and how it will be determined that an incidence measurement method is 'good enough' for the time being.

These considerations are particularly relevant regarding ***precision***. How precise HIV incidence measurements can or should be may depend on the context, taking into account disparate factors ranging from cost of surveys to how often policy makers will rely on the confidence levels. For example: In places such as Russia and the Middle East, hardly any relevant data exist at all, including for key populations. In places such as the Netherlands, much larger sample sizes may be needed than high-burden African countries because the epidemics are so much smaller.

One area of consensus is that regardless of the context, enough precision is needed to see changes in trends. How that can be applied in practice is difficult. For now, respondent-driven survey (RDS) estimates, though imprecise, may be the best approach. Also from a practical standpoint, certain policy decisions do not or should not depend on the precision of incidence measurements; for example, a highly precise estimate is not necessary to recognize that one or more populations would benefit from pre-exposure prophylaxis (PrEP).

3. Incidence Measurement on the Ground: Select Country Examples

Summarized below are case studies of developments associated with HIV incidence measurement in a handful of countries. Some of the information and outcomes might be adaptable for other contexts and situations. (The countries are listed in order of their presentation at the meeting.)

3.1 Rwanda

Extensive research has been done in Rwanda to measure HIV response progress. The first nationally representative HIV incidence household survey, known as RAIHIS, was conducted in 2013–2014. It consisted of a three-stage complex sampling survey that reached more than 13,000 participants in 492 randomly selected enumeration areas across the country. All participants were tested for HIV using rapid and ELISA tests, with the negatives (92% of the total) then followed for a year before being retested. A total of 35 seroconverted, which translated into a prospectively observed incidence estimate of 0.27 per 100 person years. The results summarized below indicate that relatively detailed HIV incidence information of this sort can help to identify 'hot spots' as well as key and vulnerable populations that might need more or better services.

Among the notable findings was that 17 of the 35 new cases occurred in one province, which borders the Democratic Republic of the Congo (DRC). One village alone had multiple infections. Researchers believe that these findings within a random sample suggest the emergence of an outbreak in the specific area, which might be linked to specific populations such as people who regularly travel back and forth across the border. Another observation that Rwandan officials found notable is that 65% of new infections were among heterosexual couples. Such information from these and other surveys can help health officials at various levels to intensify

targeted prevention and treatment efforts, such as increased emphasis on couples testing and encouraging both partners to be tested before getting married.

Additional valuable information from Rwanda will be released when its PHIA is completed. Also, Rwandan officials currently are planning a longitudinal cohort study of female sex workers: the first arm will include 994 who test positive, with the second arm consisting of 813 who test negative. Those in the second arm will be tested after 12 months, thus giving incidence information. This study is seen as part of a vital effort to get better information about the epidemic's impact on female sex workers.

3.2 Uganda

Two large studies in recent years have sought to measure HIV incidence in a broad-scale in Uganda. One, the Rakai Health Sciences Project (RHSP), was a 10-year analysis of both HIV+ and HIV- individuals with a total of more than 94,000 person years of follow up. Beginning in 2012, HIV incidence significantly declined, a development correlated with ART uptake. By 2016, a 41% reduction in HIV incidence was found relative to the period before scale-up of ART and voluntary medical male circumcision.

The second large study was Uganda's PHIA, which has concluded but has not formally released HIV incidence or 90-90-90 results that are still being validated. The expectation is that as with other PHIAs, the Uganda report will provide important information about the country's HIV response and progress toward the 90-90-90 targets as well as overall HIV incidence in the general population, as sampling did not target MSM.

A third recent study in Uganda is notable in that it focused on HIV incidence in one of the country's most vulnerable populations, what is called the 'fishing communities' comprising over 100,000 people inhabiting many islands and lake shores. According to the study's published results,[8] HIV incidence was indeed higher in those communities than among the general population (where risk already is relatively high).

3.3 Kenya

The KEMRI-Wellcome Trust Research Programme[9] in Kilifi has had an open cohort (people being enrolled every year) of MSM since 2006. Data are available now on 839 individuals, through 2017. HIV incidence per 100 person-years of observation has remained relatively stable at between 6% and 9% over the years of the study.

Follow-up in 2017 with 172 HIV-negative MSM in Kilifi revealed characteristics that underscore the high levels of vulnerability and risk in the population. Of note is that it is a very young population, a high share of respondents reported receptive anal intercourse, and a larger share than anticipated said they only had sex with men. The scale up of pre-exposure prophylaxis (PrEP) programmes in Kenya, which includes provision to MSM, could have a transformative impact on reducing incidence among key populations.

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[8] Kamali A, et al. Heterogeneity of HIV incidence: A Comparative Analysis between Fishing Communities and in a Neighbouring Rural General Population, Uganda, and Implications for HIV Control. *Sex Transm Infect* 2016;92:447–454.

[9] KEMRI = Kenya Medical Research Institute

Based on their work over the years with this study in Kenya, the KEMRI-Wellcome researchers note the following factors that influence understanding of HIV incidence in MSM and should be considered when seeking to estimate it among key populations:

- closed vs. open cohort (i.e., ongoing recruitment)
- recruitment bias (high risk MSM)
- behaviour vs. gender orientation (whether, where and how to include transgender women, etc.)
- PrEP use and PrEP adherence

3.4 Brazil

The Brazilian government has partnered with Imperial College London on a mathematical study aimed at estimating HIV incidence from case-reporting data. The purpose of the model, an age-structured deterministic compartmental one, is to improve the UNAIDS Spectrum model—into which the new one is designed to easily fit.

Model outputs include two key indicators, prevalence and incidence. Results were unpublished as of late January 2018, but preliminary findings indicate a 'double peak' in incidence in Brazil over a 50-year period (1965 to 2015) that had not been previously captured by other incidence models. (The first peak for both women and men was around 1995–1996, with the second peak around 2010–2011.) Such findings indicate more complicated trends in the country that perhaps require closer attention.

The Brazilian model relies on a large amount of data for inputs. As such, it is not considered a likely candidate for usage in parts of the world where data are scarce or highly unreliable. It seems likely, though, to prove advantageous where case reporting and other surveillance data are collected routinely. It also can provide multiple estimates that have value for programming, including not only incidence and prevalence but also mortality and age distribution (among others).

The model tested was designed to work at national scale. As such, many of the 'missing' will be hidden. A finer-scale approach ultimately is needed to obtain good estimates for most key and vulnerable populations. For example, modelling at a national scale almost certainly will completely miss what many observers believe is a major ongoing trend: a huge surge in new infections among young MSM, including outside the main 'hot spots' of Rio de Janeiro and Sao Paulo.

4. Recommendations for Further Research and Prioritization

Based on discussion of the strengths and weaknesses of various incidence-measurement methods, participants at the Amsterdam meeting proposed a series of recommendations. They include areas deemed worthy of more aggressive or targeted implementation and those that could be prioritized for further research. Many overlap with one another, which is unavoidable due to the interconnectedness of many of the core issues. The focus areas identified and summarized below are not listed in any priority order.

(a) Measuring extent of migration is an important complementary step to measuring HIV incidence. Migration in and out of a discrete survey area or behaviour can be a major mitigating factor. For example, measuring cumulative incidence is hard to do effectively if sex workers only stay in such work for a couple of years before 'returning' to the general population, or when

seasonal laborers such as some fishermen in parts of Africa move around the country and region on a regular basis.

For such reasons, information on and analysis of migration trends and impact can be useful—and not only for incidence measurement specifically. For example, if data show more migration than a given specific number, then a stronger tilt of resources toward PrEP seems advisable. Conversely, if data show migration lower than this number, the tilt would be toward treatment as prevention. (Ideally both would be available and highly resourced, but that is not always possible in every context.)

(b) Viral load as most important factor: Use the absolute number of unsuppressed people in a defined population as a measure for HIV transmission risk. This suggestion is based on a belief among some that, instead of incidence, viral load suppression is the factor that should determine where the needs are greatest and where resources and attention should be directed in HIV responses. High rates of poor viral suppression in geographic areas and among populations signal urgent places to focus. Ramped up and routine viral load testing therefore is an essential priority.[10]

This suggested emphasis also is associated with the belief that HIV treatment cascade numbers provide a more valuable perspective than progress on the 90-90-90 targets, because the former give a clearer indication of where the core needs are for prevention and treatment. Based on this view, policy makers, programmers and other stakeholders should shift their focus from 'burden of HIV' to 'unsuppressed HIV'.

Proposal: a review paper should be prepared on viral load suppression as a marker for HIV incidence at population level. Such a paper would sort through various relevant papers already available, including one in 2017 lead-authored by Frank Tanser.[11]

(c) Stimulate point-of-care (POC) viral load determination as a measure for HIV acute infection. Accurate and reliable POC options do not yet exist. Qualitative DNA tests are used for infants, but they have not been used to find acutely infected adults.

Another area to consider might be incorporating IP-10 into a two-stage process. IP-10 screening would be followed by a POC test for confirmation.

(d) More adolescent HIV incidence surveys are needed. Far too little data are available on this vulnerable population. What is known, including from PHIAs, is that this group fares worse than other age cohorts along all three parts of the 90-90-90 Fast-Track targets. Yet the PHIAs are not designed to provide incidence estimates among adolescents or other groups within the general population in their findings, and a paucity of other surveys focusing on adolescent incidence makes it difficult to know when, where and how they are highly vulnerable.

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[10] The HIV treatment cascade—sometimes also referred to as the HIV care continuum—is a "model that outlines the sequential steps or stages of HIV medical care that people living with HIV go through from initial diagnosis to achieving the goal of viral suppression…and shows the proportion of individuals living with HIV who are engaged at each stage" (https://www.hiv.gov/federal-response/policies-issues/hiv-aids-care-continuum). The number of steps and stages in a comprehensive cascade is far greater and more detailed than the three referred to in the 90-90-90 targets, and cascades typically are considered descriptive and thus not associated with predetermined target levels.

[11] Tanser F, et al. Effect of Population Viral Load on Prospective HIV Incidence in a Hyperendemic Rural African Community. *Sci Transl Med*. 2017 Dec 13;9(420).

(e) More studies that estimate HIV incidence among key populations should be performed. The cohort method should be combined with analysis on key populations and vulnerable groups such as adolescent girls and young women. A lack of incidence measures means there is a lack of information needed to design effective interventions likely to have an impact among key populations.

(f) More research and discussion are needed around estimating key population sizes. Better population size estimates are vital for key populations to complement measures of prevalence and incidence: accurate numbers from studies, including proportions, rely on accurate population sizes. Social media might offer some solutions, such as MSM who connect through dating/meeting apps.

(g) HIV incidence measurements should become outcomes of national HIV programmes. A common programmatic goal for HIV responses everywhere should be to identify how many new infections have occurred, etc. This would mean that dedicated funding should be set aside for measuring incidence, including among key and vulnerable populations and at sub-national levels if and where it is viable in a context.

(h) CD4 determination at HIV diagnosis should be continued, as it can serve as a proxy for early infection. Although it generally makes sense now for CD4 testing to be de-emphasized for use in most stages of HIV disease, such a test at diagnosis still offers valuable information for clinical decision-making in addition to incidence trends. A CD4 result at baseline, for example, can be used to determine need for prophylaxes such as cotrimoxazole.

(i) Building incidence into case-based surveillance: Outcome indicators should be redefined to include measures from infection to diagnosis and subsequent care. Broadening the pool of data in this way can help to ensure that as much information as possible is available for case-based reporting.

(j) Strengthen human resources to identify HIV incidence through mobile phone–supported decision tools, e.g., using SMS or apps to encourage persons at likely high risk for acute/incident HIV to come forward for testing. Incentives will likely be needed for this to be successful.

(k) Assess whether self-testing can be used as a strategy for incidence identification. Self-testing is a potentially valuable area that should be researched and developed further, to consider how and if it could be an alternative strategy for incidence identification. It is rolling out now in several countries, including as pilot initiatives. Guidelines and information have yet to be fleshed out, though, including as to how and where self-testing fits within M&E frameworks and referrals for ART.

(l) Use big data analysis/machine learning to 'heat map' (predict) HIV incidence in geographic areas and among populations. This approach, which is a modelling exercise to some extent, would rely on a wide range of statistical, geographic, epidemiological and other data sources (e.g., surveillance and census data, among many others). The goal is to use data that already exist to predict areas with higher risk of incidence. Machine learning can crunch and correlate massive data inputs and thus help to find 'hot spots' and thus where to allocate money and other resources. The modelling could be modified throughout the process.

One proposal is to conduct an experiment by focusing on countries where PHIAs have been undertaken. The findings from this kind of big data analysis could then be validated with PHIA results. (This specific experiment would only be viable as PHIA data become publicly available.)

(m) Conduct a review of data on HIV testing frequency to inform WHO guideline development. Currently, the World Health Organization (WHO) does not provide guidelines regarding how frequently people should be tested for HIV. A review of current literature would be helpful as WHO considers what such guidelines should entail. There are a number of papers detailing population-based surveys, modelling studies and systematic reviews that could provide valuable input and observations as such guidelines are developed.Several of these papers are included in an extensive bibliography being developed for the overall intiative that this January 2018 consultation is feeding into. Extensive modelling has been done on testing strategies for South Africa and for other parts of southern Africa on the cost-effectiveness of testing programmes. Studies from such modeling have been prepared, some of which are awaiting publication..