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Strengthening HIV Surveillance: Measurements to track the epidemic in real time

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Abstract

Surveillance for HIV as a public health initiative requires timely, detailed and robust data to systematically understand burden of infection, transmission patterns, direct prevention efforts, guide funding, identify new infections and predict future trends in the epidemic. The methods for HIV surveillance have evolved to reliably track the epidemic and identify new infections in real time.

Initially HIV surveillance relied primarily on the reporting of acquired immune deficiency syndrome (AIDS) cases followed by measuring antibodies to HIV to determine prevalence in key populations. With the roll-out of antiretroviral therapy (ART) resulting in better survival and the corresponding increase in HIV prevalence, the landscape of surveillance shifted further to track HIV prevalence and incidence within the context of programmes. Recent developments in laboratory assays that potentially measure and differentiate recent versus established HIV infection offer a cost-effective method for the rapid estimation of HIV incidence. These tests continue to be validated and are increasingly useful in informing the status of the epidemic in real time.

Surveillance of heterogeneity of infections contributing to sub-epidemics requires methods to identify affected populations, density, key geographical locations and phylogenetically linked or clustered infections. Such methods could provide a nuanced understanding of the epidemic and prioritise prevention efforts to those most vulnerable. This paper brings together recent developments and challenges facing HIV surveillance, together with the application of newer assays and methods to Fast-Track the HIV prevention and treatment response.

Keywords

Geospatial locations; HIV assays; incidence; phylogenetics; prevalence; surveillance

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Introduction

To advance the ambitious goal of ending the acquired immune deficiency syndrome (AIDS) epidemic, the post-2015 Joint United Nations Programme on HIV/AIDS (UNAIDS) Fast-Track aims to achieve ambitious targets over the next five years to include the 90-90-90 treatment strategy and zero discrimination by the year 2020 (UNAIDS, 2014a). These strategic milestones work within the new paradigm of realising an end to the HIV epidemic by 2030. These targets include reducing new HIV infections from the current 2 million (1.9 million-2.2 million) in adults and children to less than 500 000; to reduce the number of people dying from AIDS-related causes to less than 500 000 and to eliminate HIV-related discrimination. Reaching these targets could avert 28 million new HIV infections including 5.9 million infections in children and 21 million AIDS-related deaths by 2030 (UNAIDS, 2014b, 2015d).

Achieving these Fast-Track milestones necessitates timely, detailed and robust HIV surveillance; and the efficient use of these activities could facilitate better understanding of transmission patterns, direct prevention efforts, guide funding, evaluate the impact of HIV related services, predict future HIV burden of infection and identify new trends (Wilson & Halperin, 2008; Puren & Takuva, 2011; UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011; Parkin et al., 2016).

Surveillance relies on diverse and multiple data sources to obtain a well-defined picture of the epidemic and trends over time, and is crucial in monitoring the disease globally. Whilst surveillance data provides extensive knowledge on the prevalence of HIV, information on prevalence alone is not sufficient to understand the rate of new infections (incidence), including where and within which networks viral transmissions might be occurring. HIV incidence remains a key indicator for monitoring the impact of HIV related programmes, especially in countries which bear a disproportionate burden of HIV/AIDS (WHO, 2004). As the field of HIV surveillance evolves, additional tools and techniques are in development for the rapid, concurrent systematic measurement of incidence in real time to assess the achievements of the Fast-Track targets (UNAIDS, 2010; Mastro, 2013; Rosenberg, Pilcher, Busch, & Cohen, 2015).

Laboratory tests for recent infection (TRIs) are increasingly being used to identify and differentiate new and established infections, though these require additional biological marker information such as HIV-1 RNA viral load and exposure to antiretroviral therapy (ART). These improved surveillance tools for incidence measurements are important applications for more accurate testing of recently acquired infections; to identify concentrated localised sub-epidemics and sexual networks of individuals who are less likely to test for HIV or be linked to care and could therefore contribute to sustaining the epidemic (Tanser, de Oliveira, Maheu-Giroux, & Barnighausen, 2014; UNAIDS, 2015c).

Using a combination of tests to improve surveillance would further assess the impact of scaled up HIV services for diagnoses, treatment and prevention interventions and ultimately move countries closer to the post 2015 Fast-Track targets.

This paper aims to describe and critique methods used for the measurement of existing and new HIV-1 infections complemented by the use of phylogenetics and geospatial epidemiology, including the complex convergence of these tools for surveillance.

Sources of data for HIV Surveillance

HIV antibody tests have been the mainstay of sentinel surveillance of pregnant women attending public sector primary health care clinics for antenatal care. These data sources have been supplemented by national population based household surveys and surveillance of HIV in high risk individuals attending specialist clinics for sexually transmitted infections (STI) and tuberculosis (TB) (Calleja et al., 2005; Mahy, Garcia-Calleja, & Marsh, 2012). Traditionally these data sources provided a reliable understanding of the total number of existing HIV infections (prevalence) in contrast to understanding where new HIV infections are occurring (incidence). As HIV is linked in time, place, and population group, it is critical to know where prevalent and incident infections are occurring and the modes of transmission. Furthermore, aggregating the data by age and gender is useful to identify key populations, and assist in understanding trends and dynamics of transmission (Sun et al., 2007; Puren & Takuva, 2011).

Whilst these traditional surveys generate important reliable data on national estimates, as epidemics mature with increasing coverage of ART, prevalence of HIV infection becomes a less reliable marker of the evolving epidemic since survival improves, prevalence increases and masks new infections; especially in key populations such as young adolescents, men who have sex with men (MSM), sex workers (SW) and people who inject drugs (PWID) (UNAIDS, 2014b).

Methods of Measuring HIV Incidence

Accurate and timely measurements of HIV incidence are critical elements of HIV surveillance (Moyo et al., 2015) especially in the context of HIV intervention efforts. However, none are without limitations. Table 1 provides a summary of methods to estimate HIV incidence, reviewing the benefits and limitations of each method.

Cohort estimation

Measurement of HIV incidence through prospective cohorts is the gold standard method as well defined groups of HIV-negative individuals are followed and tested and retested for new infection over time (Puren & Takuva, 2011; UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011). However, there are intrinsic disadvantages of this method as it is influenced by biases that could lower or exaggerate incidence measurement, especially true for high HIV endemic and resource-limited regions (Mastro et al., 2010; Puren & Takuva, 2011). As the high-cost of establishing cohorts and potential lost to follow-up are key challenges of cohort studies, there is a drive for robust HIV surveillance strategies that directly measure incidence in real time that are accurate, cost-effective and less resource-demanding. Such tests would facilitate measurement of true incidence dynamics of the HIV epidemic and assist with better planning, tracking, and evaluation of HIV

prevention and treatment strategies in a timely manner (Diaz, De Cock, Brown, Ghys, & Boerma, 2005; Pervilhac, Stover, Pisani, Brown, & Mayorga, 2005; Mahy et al., 2012).

Mathematical modelling

HIV incidence and trends have been estimated using input parameters such as prevalence, mortality data, and ART use within mathematical models. Models have been valuable for informing HIV trends but have limitations due to the readily availability of reliable prevalence data, prevention and treatment programme coverage, fidelity of interventions and geographical region (Stover, Brown, & Marston, 2012) as well as the bias of inaccurate assumptions within the model. Models include the Asian Epidemic Model (AEM), and the Estimation and Projection Project (EPP/Spectrum) which are annually-updated and continues to adapt for correcting biases and inclusion of additional information sources (UNAIDS, 2010; Brown et al., 2014). Within EPP/Spectrum, the model generates estimated predictions on, amongst others, HIV prevalence, treatment requirements and mortality rates; and calculates incidence from prevalence data while taking into consideration the number of people on ART (UNAIDS, 2010; Stover et al., 2012). Data from incidence assays could be incorporated into the EPP model to potentially narrow parameters and improve estimates (Bao, Ye, & Hallett, 2014). Estimates from models assist countries with their health service planning, policy development and budgeting. Furthermore, comprehensive behavioural data collection and information regarding population size and STIs in key populations assist with determining HIV infection patterns and correspondingly the effectiveness of HIV programmes and initiatives (Gouws, White, Stover, & Brown, 2006). The need for such thorough data may therefore limit the programmatic utility in resource-limited settings and specifically in countries already carrying the highest HIV burden. Modelling is less financially and labour intensive than population based surveys and therefore commonly used for estimating incidence. However, these models can still have a time delay, and remain dependant on the quality and accuracy of available empiric data sources used for estimation (Brookmeyer, 2010).

Inferring HIV incidence from prevalence among pregnant women 15–24 years

Prevalence of HIV infection among pregnant 15 to 24 year olds attending antenatal clinics could be used to approximate trends in incidence with an assumption that prevalence is due to recent sexual debut mirroring recent infection in this age group (Zaba, Boerma, & White, 2000). While this is not a direct measure, it has been used as a proxy, especially in countries with generalised epidemics (Ghys, Kufa, & George, 2006). However, over time as ART use increases and changes in behaviour occur (i.e. with a shift towards delayed sexual debut), this method is likely to become less reliable.

Laboratory Tests to estimate HIV incidence

The comprehensive use of laboratory tests to estimate HIV incidence is growing. These tests measure immunologic biomarkers in HIV-acutely and recently infected persons from cross-sectional samples (McDougal et al., 2005; Mastro et al., 2010; Kassanjee et al., 2011). The major advantage of these tests is that only one sample is required to classify an infection as acute (new) or established (long term) (UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011). Prior to implementation of a testing programme for

incident infections for surveillance, epidemiological factors complement and guide the application of test-specific pre-requisites such as calibration, validation, quality assurance, and performance characteristics that may influence interpretation. When properly and judiciously applied, the capacity of these tests to enhance surveillance would provide precise and timely analysis of the dynamics of the epidemic and assess the effectiveness of public health interventions.

Markers of acute (new) HIV infection—HIV-1 RNA and p24 antigen are the first set of biomarkers that are readily detectable prior to seroconversion (Daar, Pilcher, & Hecht, 2008). The nucleic acid amplification test (NAAT) for the detection of HIV-1 RNA and p24 antigen assays are both highly sensitive and specific, with HIV-1 RNA having an added advantage of being detected much earlier than p24 antigen (Quinn et al., 2000; McDougal et al., 2005). HIV-1 RNA testing was developed for the purpose of patient monitoring and has more recently been adopted as a way to identify acute (new) HIV infection, i.e. identifying acutely infected individuals by pooling and testing HIV seronegative samples. Several surveillance programmes utilized NAAT of pooled HIV seronegative specimens to estimate HIV incidence (Quinn et al., 2000; McDougal et al., 2005). A further advance in diagnosing acute HIV infection for estimating HIV incidence has been the development of fourth generation HIV-1 assays which detect p24 antigen and HIV antibody simultaneously (Daar et al., 2008). However, the detection levels of these assays differ as key viral markers evolve rapidly in acute HIV infection with a “window-period” of approximately 28 days (Cohen, Gay, Busch, & Hecht, 2010). Assays which identify acute (new) HIV infection are useful to estimate HIV incidence, but require large sample sizes (McDougal et al., 2005).

Markers of recent (early) HIV infection—To determine recent (early) infection and estimate HIV incidence, the BED capture enzyme immunoassay (BED assay) (UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011) had been used extensively. However, the test misclassified early HIV infection even after many years of infection, resulting in an overestimate of true population incidence. Misclassification was particularly high among individuals on ART and those with very low CD4 cell counts, therefore data on ART and CD4 cell counts at the individual level are collected to exclude such persons from the incidence analysis. Compared to the BED assay, the newer TRIs have overcome many of the misclassification issues and are less likely to be affected by advanced HIV disease or low CD4 cell counts. Whilst assay misclassification rates have been shown to vary across countries (Busch et al., 2010; Longosz, Serwadda, et al., 2014), by using adjustment factors, assay-derived estimates can be calibrated to correct for misclassification or incorporated into the mathematical formula to improve incidence estimates (UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011; Stover et al., 2012).

The newer TRIs for recent (early) HIV infection are based on antibody avidity, i.e. the maturity of the HIV antibody response which increase over time following seroconversion (Duong et al., 2012). Antibody avidity is more robust than antibody titre because it is a functional property of maturing antibodies. Antibodies of low avidity are usually indicative

of recent (early) infection and could be used for HIV incidence determination (Parekh BS et al., 2002; Duong et al., 2012).

Several new assays are currently being evaluated to determine their accuracy in distinguishing recent (early) from established (long term) HIV infection and translate this to measuring HIV incidence on a population level (UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011). These include the *rIDR-M-Avidity Index Assay (rIDR-M AI EIA)* developed by the CDC GAP Serology/Incidence laboratory. This test is an avidity index assay using a recombinant protein (*rIDR-M*) which incorporates 3 sequences derived from the immune-dominant region (IDR) of gp41; representing divergent HIV-1 subtypes A through E (group M) (Wei et al., 2010). This assay uses a pH 3.0 buffer to dissociate low avidity antibodies which are characteristic of recent infection. The greater the proportion of high avidity antibodies remaining bound increases the avidity index, therefore indicating established (long term) infection (Suligoi et al., 2002). The *Bio-Rad Avidity EIA* is a modification of the GS HIV-1/HIV-2 Plus O EIA (Redmond, MA) (Hauser et al., 2014). This assay uses 0.1M diethylamine (DEA) to dissociate low avidity antibodies characteristic of recent infection. The greater the proportion of high avidity antibodies remaining bound increases the avidity index, therefore indicating established infection. The *Limiting Antigen (LAg) Avidity EIA* developed by the CDC GAP Serology/Incidence laboratory is an avidity-based assay that the same recombinant multi-subtype protein (*rIDR-M*), but at a limited coating concentration, such that it is even easier to dissociate low avidity antibodies. Advantages of the *LAg* are that the test requires only a single well as opposed to two wells, therefore allowing for an increased number of specimens to be tested, is also easier to perform and is able to dissociate low avidity antibodies more readily. Furthermore, the *LAg avidity EIA* has been evaluated, commercially available avidity-based HIV-1 incidence assay and used in several national population based surveys in Kenya (Kimanga. et al., 2014), South Africa (Simbayi et al., 2014) and Swaziland (Swaziland Ministry of Health, 2012).

The two main performance parameters of TRIs are the mean duration of recent infection (MDRI) – the average time spent ‘recently’ infected (usually a period of 4–12 months); and the false-recent rate (FRR) – the misclassification of recent with non-recent infection (Welte, McWalter, Laeyendecker, & Hallett, 2010; Kim et al., 2011; Kassanjee, McWalter, Barnighausen, & Welte, 2012). Therefore, an accurate estimate of MDRI is required for a more precise incidence estimation (Hanson et al., 2016). TRIs could fail to correctly identify recent infections due to the following variances: unique viral progression and immune system responses, dissimilar HIV subtypes between different individuals and populations (Busch et al., 2010; Mastro et al., 2010; Puren & Takuva, 2011; Mastro, 2013; Longosz, Mehta, et al., 2014), elite controllers (i.e. people who sustain low viral RNA and low antibody responses to HIV) (Puren & Takuva, 2011; UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance, 2013), ART status (those having low HIV progression due to drug-induced suppression therefore have decreased antibody concentration) and those with AIDS having a low CD4 cell count and low HIV antibody concentration (Mastro et al., 2010). These factors can lead to varying MDRI (Parekh et al., 2011) and FRR (Kassanjee, 2011; Kassanjee et al., 2011; WHO/UNAIDS, 2013), depending on the assay used. Such misclassification can lead to biased incidence estimates; therefore it is not yet recommended that TRIs be used for individualised testing and diagnosis of recent

HIV infection or as stand-alone tests for incidence measurement but can be applied at a population level in a form of an algorithm (UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, 2011).

Combination of HIV testing algorithms—To address limitations of individual incidence assays and improve accuracy, TRIs are often applied through Recent Infection Testing Algorithm (RITA) (WHO, 2009) and Multiple-Assay Algorithm (MAA) (Laeyendecker et al., 2013). These algorithms involve utilizing two or more incidence assays that detect different components of the recent/early HIV infection together with other clinical indicators such as CD4 cell count, ART use and HIV-1 RNA viral load (Busch et al., 2010; Longosz, Serwadda, et al., 2014). While improving accuracy of test results, this method can be impeded by cost especially in resource-limited regions since CD4 cell count requires the whole blood sample, immediate testing and not dried blood spots which are usually used in national surveys (Busch et al., 2010; Mastro et al., 2010). Samples with detectable ART and with viral load of <1000 copies/ml have been excluded from analysis in order to increase the accuracy of TRIs (Mastro et al., 2010) as ART use may lead to misclassification (Laeyendecker et al., 2009). However, even with the exclusion of those on ART or with AIDS, misclassification still occurs (Longosz, Mehta, et al., 2014). TRIs continue to undergo extensive validation for use in RITA for HIV (Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA); Hanson et al., 2016).

Methods to enhance understanding of viral transmissions

Essential to surveillance and targeted response is knowing and understanding the biological and behavioural risk factors contributing to HIV viral spread. The novel areas of phylogenetics and using locations to prioritize target populations, are methods to further understand epidemic incidence dynamics.

Concept of HIV-1 phylogenetics

Phylogenetics is a molecular epidemiological strategy that explores viral evolution, diversity, transmissions and characterizes epidemics on the basis of the genetic interrelatedness of HIV-1 viral sequences. Phylogenetic analysis has been used to determine the emergence of HIV globally from non-human primate reservoirs, estimate the age of Simian Immunodeficiency Virus (SIV) and map the spread of HIV between continents early in the epidemic (Courgnaud et al., 2002). In the context of HIV-1, this technique takes advantage of the high error rate and rapid pace of HIV replication, which leads to a predictable rate of evolution over long periods of time, or a ‘molecular clock’. Phylogenetic trees can be generated and used to determine the most recent common ancestor in a given set of sequences, revealing linkages that define their transmission history (Grabowski & Redd, 2014). Sexual networks contributing to HIV acquisition are poorly understood in many regions for various reasons. Among these include mis-and under-reporting of sexual relationships, social desirability bias, the transient nature of risky relationships, migrancy and various cultural factors. Furthermore, traditional methods to map sexual networks are labour-intensive and require extensive engagement with participants and verification of

relationships. Therefore, HIV-1 sequence data could be used as a tool to gain information on networks that are otherwise difficult to obtain.

Phylogenetic linkages have empirically been assessed in HIV-1 clinical trials as in the HPTN 052 (Cohen et al., 2011) and Partners in Prevention HSV/HIV Transmission trials (Campbell et al., 2011). The analysis of HIV-1 *pol* sequences from HIV-1 seroconversions showed that at least a quarter of these occurred within stable partnerships, were unlinked and demonstrated the magnitude of sexual networks that potentially sustain epidemics. Recently, phylogenetic methods have been applied to generally understand HIV transmission, especially among MSM to detect transmission clusters leading to outbreaks (Brenner, Roger, Otis, & Wainberg, 2013; Middelkoop et al., 2014; Ratmann et al., 2016). Fewer studies have been carried out in Africa. However, based on the phylogenetic analyses of the *gag* and *env* genes, a major study conducted in the Rakai district of Uganda provided some indication that viral transmissions occurred beyond household partnerships and were common from outside the communities (Grabowski et al., 2014). Applying phylogenetics to understand "linked" or "clusters of linked" HIV transmission in the areas most affected by the pandemic could assist with optimal direction for targeted interventions to interrupt viral transmission (Castro-Nallar, Pérez-Losada, Burton, & Crandall, 2012). A recent phylogenetic study showed that a higher escalation in cluster size was linked with recently infected persons, which may indicate individuals with new infections are a driving force of the epidemic (Ragonnet-Cronin et al., 2010). Estimating recent HIV infection by diversity has also been performed in many studies (Cousins et al., 2011; Ragonnet-Cronin et al., 2012; Yang et al., 2012; Andersson et al., 2013; Xia et al., 2014). These methods are based on the premise that HIV diversity increases as the duration of infection increases (Andersson et al., 2013). Therefore, HIV diversity has been shown to be a possible biomarker for classifying HIV infection as recent or non-recent (Cousins et al., 2011; Yang et al., 2012).

The high resolution melting (HRM) assay is one of the methods that has shown a great potential for determining HIV incidence using viral diversity as a biomarker (Cousins et al., 2011). This assay has also shown that AIDS is not correlated with misclassification as in serologic incidence assays (Cousins et al., 2011). The markers obtained from this assay are less related to markers of serological methods and therefore has the potential to be used in an HIV algorithm together with serological tests to further reduce misclassification (Cousins et al., 2011). This approach has been used with the MAA (James et al., 2013). However, ongoing evaluations are needed to set parameters and standardise this assay for its use across various populations. It should be noted that HRM has its own limitations i.e. not entirely showing the sequence differences in a DNA fragment (Tong & Giffard, 2012). Intra-patient pattern-based viral genetic diversity methods have also been used to measure recent (early) infection (Yang et al., 2012). This method is also based on diversity patterns from recently (early) and established infected individuals and is unaffected by AIDS, HIV-1 RNA viral load and ART use. The MDRI for this method is 200 to 350 days to potentially detect recent infections (Yang et al., 2012) in combination with serological tests. As surveillance requires high-throughput of specimens, these methods may be difficult to establish in resource-limited settings.

Phylogenetic analysis of HIV-1 sequences are therefore useful to identify linked sequences in dyads and potentially characterize the epidemiologic relationships of these in clusters. HIV transmission clusters within high-risk groups (Poon et al., 2014) and including demographic, geographic and behavioural characteristics of individuals in clusters could provide crucial information of evolving HIV strains and transmission dynamics ('phylodynamics') for prevention initiatives (Castro-Nallar et al., 2012).

Concept of locations to prioritising populations

Scaling up HIV testing to identify newly infected individuals is key to achieving the Fast-Track targets, especially within hyper-endemic regions consisting of concentrated localised sub-epidemics which tend to cluster and sustain the epidemic (Tanser et al., 2014; Chen et al., 2015; UNAIDS, 2015b).

Analysing the nature of the epidemic at a local level, using location-based approaches to deliver high-impact and locally relevant programmes in populations with the primary need (high burden) to have the greatest impact underscore the Fast-Track approach (UNAIDS, 2014a). Thus, surveillance systems must include spatial analytical methods to identify gaps in HIV prevention programs and hot-spot geographies that are currently driving the epidemic (UNAIDS, 2013; UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance, 2013). The location-based approach also includes Fast-Track cities within different countries as they are known to contribute significantly on the epidemic, with 156 cities within 30 countries contributing 89% of all new infections (UNAIDS, 2015a). The HIV epidemic in sub Saharan (SSA) tends to be higher in urban compared to rural communities and it is estimated that by 2030, 60% of the global population will live in cities including areas in SSA and Asia which are currently less urbanised (UNAIDS, 2015a).

ART use together with HIV prevention strategies targeting key populations and hot-spot geographies (areas of high incidence and/or prevalence) have the greatest potential to reduce HIV acquisition, as compared to a general approach, due to existence of high heterogeneity of HIV infections within different regions (Wand & Ramjee, 2010; Anderson et al., 2014; Jones et al., 2014). Geographically targeted prevention interventions have proven successful where geographical clustering of HIV incident cases within sub-groups (Aral & Cates, 2013) and commercial sex work (Halperin, de Moya, Perez-Then, Pappas, & Garcia Calleja, 2009). "Knowing your epidemic" is key to meeting the UNAIDS targets, and this requires knowing the profile of the local epidemic, in order to choose the right combination of interventions that have the greatest, longest-lasting impact and are cost effective (Wilson & Halperin, 2008).

The future of HIV surveillance is tailored towards a more location-specific approach and incorporating RITAs, CD4 cell count and HIV-1 RNA viral load testing of the participants (UNAIDS, 2013; WHO, 2015). Understanding the epidemiology and location is crucial; however, most national surveillance studies do not include this data due to lack of resources. Such an approach requires geo-referenced HIV data at a local level with data only available by large geographic units (Wilson & Halperin, 2008; UNAIDS, 2015b).

The major limitations to full scale implementation of a location-based approach are the lack of geo-referenced data, trained and qualified staff and the cost of commercial software programs. The issues of privacy and confidentiality related to disease status are significant challenges when addressing HIV because of stigma (Mbonu, van den Borne, & De Vries, 2009), meaning the target of zero discrimination is equally important to the 90-90-90 treatment target. However, different geographic masking methods can be used to protect privacy of HIV infected individuals and communities.

Conclusions

Estimating HIV incidence rapidly and accurately offers great benefit to population-based HIV surveillance, particularly in the era of post-2015 Fast-Track targets. Surveillance continues to evolve and countries cannot use a “one-size fits all” approach. This paper is not an exhaustive list of all methods but it is intended to stress the importance of incidence measurements and bring together some of the more recent developments and ongoing challenges.

New biomarkers and methods that are cost effective, commercially available, with good quality assurance, simple to use, accurate and less affected by factors such as ART use and advancing state of infection remain essential. An ideal incidence test would diagnose HIV and give an accurate estimation of how recent the infection occurred simultaneously. Such an assay could allow robust surveillance studies to accurately measure incidence and therefore more meaningfully inform public health programmes. HIV epidemic control is achieved when the numbers of new infections are below the numbers of AIDS-related deaths. However, the global drive is moving beyond simple epidemic control to advocate for drastic reduction and an eventual end of the HIV epidemic. This reality will only be achieved through concentrated and targeted investments and interventions adjusted to the local specific geographies where the people most affected by HIV are rapidly identified and linked to treatment in an effective care cascade. Fast-tracking the response to HIV involves monitoring the epidemic through effective, timely and targeted surveillance systems. This is especially true for resource-poor regions which continue to face a disproportionate share of the global burden of HIV/AIDS.

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Table 1

Summary of methods to measure HIV incidence

Research Method		Principle	Data Source	Advantages	Disadvantages	Going Forward
Prospective Cohort Studies		• Directly observed measure of incidence - Follow HIV-uninfected people over time and test for HIV at fixed intervals	• Observational studies • HIV prevention preparedness studies. • Clinical trials	• Considered "gold standard" • Direct measure of HIV seroconversion	• Large sample size required • Costly • Logistically challenging • Loss to follow-up, particularly those at high-risk • Intrinsic bias (participant behaviour change) • Infrequently conducted	• Improve retention of study participants
Biological Assays Testing for acute/new and recent/ early infections	Antigen based tests for acute/new HIV infection	• Uses 'biomarkers' such as HIV-1 RNA or P24 antigen that develop during the recent/ acute stage of infection prior to seroconversion	• Large scale cross-sectional surveys	• Single sample required • Follow-up not required • Can distinguish between acute HIV infection in absence of HIV antibodies and post seroconversion. • Acute HIV infection stage used for incidence estimation	• Inadequate sensitivity and specificity • Short duration of detection period (~28 days) • Misclassification of acute with post seroconversion infections • Requires confirmatory testing • No 'gold standard' test	• Development of new fourth generation HIV antibody assays decreases the "window-period" of acute HIV infection in absence of HIV antibodies
	Antibody avidity maturation based tests for recent/ early HIV infection	• Several tests available which use antibody avidity maturation following	• Large scale cross-sectional surveys	• Follow-up not required • Detection period (~130 days) • Can distinguish between early	• Requires confirmatory testing • Requires additional information on ART exposure	• Requires monitoring and estimation of incidence as HIV treatment is

Research Method		Principle	Data Source	Advantages	Disadvantages	Going Forward
		seroconversion to determine recent/early HIV infections		and established HIV infection • Early HIV infection used for incidence estimation	and HIV-1 RNA viral load • No ‘gold standard’ test	moving towards test and treat strategy – more recently infected individuals may be on ART, and this could affect accuracy of incidence measurement
Combination of HIV testing algorithms		• Combination and sequence of assay tests for detecting ‘recency’ of HIV infection with clinical data	• Cross-sectional surveys	• Multiple tests selected to streamline for improving accuracy • Addition of clinical data to reduce correct for misclassifications for interpreting results	• Expensive • Still requires correction for misclassification despite addition of clinical data	• Data obtained with this approach is crucial to compare with other incidence estimates obtained by other methods such as cohorts and mathematical modelling) • Field validation using population-based surveys is required • With increase in ART roll-out, surveys that include individuals on ART are required
Mathematical modelling		• Several models based on parameters of HIV	• Cross sectional surveys providing HIV prevalence trend data	• Cost-effective	• Depends on accuracy of prevalence and measurements of	• Cross sectional surveys need to have

Research Method	Principle	Data Source	Advantages	Disadvantages	Going Forward
	prevalence data, modes of transmission, assumptions about survival after infection and mortality, risk behaviour, population size, STI prevalence, incubation information and ART coverage	• Sentinel HIV prevalence data routinely collected	• Moderate-high levels of confidence • Relatively simple	• population size, ART coverage, mortality • Can have high uncertainty range • Time between studies may affect precision of results • Key populations may not be representatively sampled	• greater inclusion of adolescents and key populations • Less reliance on young people as proxy for sexual debut and recent infection