WHO WORKING GROUP ON HIV INCIDENCE ASSAYS MEETING REPORT

ESTIMATING HIV INCIDENCE USING HIV CASE SURVEILLANCE

10–11 DECEMBER 2015
GLION, SWITZERLAND

World Health Organization

UNAIDS

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CONTENTS

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ALPHA	Analysing Longitudinal Population-based HIV-AIDS data on Africa
ANC	antenatal clinic
ART	antiretroviral therapy
ARV	antiretroviral
CASCADE	Concerted Action on SeroConversion to AIDS and Deaths in Europe
CDC	Centers for Disease Control and Prevention
CEPHIA	Consortium for the Evaluation of the Performance of HIV Incidence Assays
CI	confidence interval
DBS	dry blood spot
DHS	Demographic Health Survey
DRC	Democratic Republic of the Congo
ECDC	European Centre for Disease Prevention and Control
EIA	enzyme immunoassay
EPP	Estimation and Projection Package
FIND	Foundation for Innovative New Diagnostics
FRR	false recent rate
GUM	genitourinary medicine
GUMCAD	genitourinary medicine clinic activity dataset
HIV	human immunodeficiency virus
ID	identity document
LAg	SEDIA HIV1 Lag-Avidity enzyme immunoassay
MDRI	mean duration of recent infection
MeSH	Measurement and Surveillance of HIV Epidemics
MPES	Multi-Parameter Evidence Synthesis
MSM	men who have sex with men
PEPFAR	President's Emergency Plan for AIDS Relief (United States)
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission
PHE	Public Health England
PrEP	pre-exposure prophylaxis
PWID	people who inject drugs
RITA	recent infection testing algorithm
SOP	standard operating procedure
SWOT	strengths, weaknesses, opportunities and threats
TPP	target product profile
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNSW	University of New South Wales
VL	viral load
WB	western blot

1. BACKGROUND

In 2008, WHO established a Working Group on HIV Incidence Assays to look into the issues and challenges involved in assay-based estimation of HIV incidence (i.e. the number of new infections that occur in a population per period of time). The Working Group comprises epidemiologists, laboratory specialists and public health officials, and has worked to standardize terminology in the areas of assay calibration and validation.

Several meetings to advance the agenda have been held, and copies of reports are available on the Working Group's webpage.[1] The meetings have successfully brought together a wide group of assay users (in particular, from countries affected by the epidemic who may consider using HIV incidence assays in the future) and key experts in the field who apply laboratory-based methods for estimating HIV incidence. They have also highlighted the importance of HIV incidence as a key indicator of national programme success or failure. Clearly, ministries of health need to be aware of the complexities of producing estimates based on data generated by the currently available assays.

In collaboration with the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, the Working Group has:

- produced a guidance document on how to estimate HIV incidence at the population level using HIV incidence assays in cross-sectional surveys; and
- provided technical updates in the use of HIV incidence assays.

This information has been incorporated into the updated guidelines on monitoring the impact of the HIV epidemic using population-based surveys (*1*). In addition, UNAIDS/WHO have produced regular technical updates.[2]

In many countries, surveillance of HIV infection relies mostly on HIV or AIDS case-based surveillance. Such surveillance is currently defined as a reporting system through which all new cases of HIV infection detected (i.e. diagnosed) at any stage are reported over time. HIV case notification makes reference to the methods used to capture information at the individual level about those diagnosed with HIV infection. However, the variable and often long time between infection and diagnosis means that HIV case surveillance does not directly reflect current patterns of virus transmission or incidence. Trends in the number of reported cases can result from changing patterns in HIV incidence, uptake of HIV testing or both. This limitation in the interpretation of diagnosis data underscores the need to measure HIV incidence to monitor HIV transmission.

Several methods for estimation of HIV incidence have been used in both developed and developing countries, including cohort studies, back calculation, modelling of repeated cross-sectional measures of prevalence, and cross-sectional use of biomarker assays for recent infection. The use of data from HIV case-based surveillance poses a new challenge to HIV-estimation methodology.

The United States and some European countries have developed and applied methods that use data from routine case-based surveillance to estimate HIV incidence. These approaches are promising and their implementation could be expanded to other developed countries.

An overview of the development of guidance for estimating HIV incidence with a recent infection testing algorithm (RITA) using case-based surveillance data was presented at the Working Group meeting in Barcelona in 2014. Consensus was reached during the meeting that the guidance should continue to be developed, because case reporting is becoming increasingly common in middle- and lower-income countries. In addition, WHO and partners are developing a guide to case surveillance and patient monitoring, to promote and improve HIV case reporting and the HIV national response in the health sector. These systems develop and link different databases; therefore, the UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance is exploring how these new information sources could be used in estimating incidence.

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[1] http://www.who.int/diagnostics_laboratory /links/hiv_incidence_assay/en/

[2] http://www.who.int/hiv/pub/me/tech_update_0513/en/

2. OBJECTIVES, METHOD OF WORK AND EXPECTED OUTCOMES

Incidence assays and other data collected in a case-surveillance system are used for two purposes: to identify new infections among diagnosed cases and to estimate HIV incidence at population level. The objectives of the workshop were to:

- review the different approaches used to estimate new infections and incidence in countries;
- agree on the inputs needed and the assumptions for new HIV infection cases, and how to estimate incidence using data collected by HIV case-reporting systems;
- agree on the methods and conditions for the application of the HIV incidence testing; and
- develop final recommendations on the methods and requirements for using HIV case-reporting data to estimate HIV incidence.

The 2-day meeting was dedicated to discussion of how to estimate HIV incidence using case reporting, and the methods used in some countries to achieve this. Expected outcomes were to:

- share progress on application of HIV incidence assays on HIV case reporting in different countries, and other methods such as CD4 count and back calculation; and
- provide a matrix of methods that can be used for HIV incidence estimation, with the parameters needed and the conditions under which to use such methods in countries with HIV case-reporting systems.

3. UPDATES ON HIV INCIDENCE ASSAY WORK

3.1 Highlights from the 2015 technical update on HIV incidence assays for surveillance and monitoring purposes

The session began with an overview of previous meetings and publications of the WHO Working Group on HIV Incidence Assays. Key meetings of the Working Group were:

- Mexico 2008 – the initial meeting;
- North Carolina 2009 – initiation of the Consortium for the Evaluation of the Performance of HIV Incidence Assays (CEPHIA);
- Geneva 2010 – development of the first incidence assay guidelines; and
- Barcelona 2014 – presentation of CEPHIA results.

To date, CEPHIA has evaluated and characterized seven assays, none of which come close to meeting the target product profile (TPP) in populations where a high proportion of people are on antiretroviral therapy (ART). Although the SEDIA HIV1 Lag-Avidity (LAg) enzyme immunoassay (EIA) had a low false recent rate (FRR) of 1.3% (95% confidence interval [CI]: 0.3–3.2%), the FRR was 58.8% (95% CI: 49.2–68%) in ART-treated persons, and was also affected by subtype D. Incorporating viral load testing may reduce the FRR to <1%.

In 2011, UNAIDS/WHO published guidance on HIV incidence estimation using tests for recent infection in cross-sectional surveys (2). Since then, there have been two technical updates to this guidance (3,4). Separate guidance is available for conducting population-based surveys (1). Many developed and middle-income countries have established case-reporting systems, and the United States and some countries in Europe have used these data in conjunction with incidence assays to generate population-based HIV incidence estimates. UNAIDS/WHO is currently developing guidance on such systems. The guidance will cover key issues in the use of case-reporting data, such as:

- how new HIV diagnoses are influenced by testing patterns, reporting and migration, in addition to transmission; and
- how estimates may be subject to numerous biases, including missing data, reporting delay, repeat testing and regional differences.

The goal is to end the HIV epidemic by 2030. Among the many indicators that are being used to measure these targets are HIV incidence, with a global target of fewer than 200 000 new infections by 2030 (5). A review of incidence estimation approaches will inform the development of final recommendations for the methods and requirements for using HIV case-reporting data to estimate HIV incidence. Challenges to be addressed are:

- RITA, in relation to whether viral load data or ART testing are required, and the effect of early or discontinued ART (or both);
- how to manage high FRRs in subtypes D and possibly A, and untested subtypes such as recombinants;
- that, in some settings, no subregional estimates are possible because of sample size issues (depending on prevalence and expected incidence); and
- the increasing difficulty of performing local estimates of FRR, because of widespread use of ART and the increased coverage and use of pre-exposure prophylaxis (PrEP).

3.2 Target product profiles update: case-based surveillance and HIV incidence assays

The Foundation for Innovative New Diagnostics (FIND), in collaboration with CEPHIA, has been overseeing the development of HIV incidence assays. A Target Product Profile Working Group was established and, with input from stakeholders, identified eight use cases for incidence assays. Five of the use cases were related to incidence estimation:

1. National surveillance (of HIV incidence).
2. Programme, prevention or trial planning – to provide incidence estimates in subpopulations.
3. Key or sentinel populations – to provide incidence estimates in special subpopulations using targeted (non-probability) sampling methods.
4. Assessing the impact of population-level interventions (e.g. comparing incidence before and after an intervention).
5. National or regional incidence estimates via case-reporting surveillance.

The remaining three use cases were not related to incidence estimation:

6. Research purposes (e.g. identification of persons with incident infection for cohort studies).

7. Individual patient management (e.g. to prioritize contact tracing).
8. Targeted prevention planning to enable risk-factor analysis among those with incident or recent infection.

The group defined TPPs for the various use cases, with each TPP defined based on the mean duration of recent infection (MDRI) and the FRR. MDRIs ranged from 120 to 365 days, and FRRs from 0.25% to 5%, and were required to generate a feasible sample size for a survey (as a minimum 30 000). Scenarios of incidence to prevalence ratios were simulated based on data from several countries; also, combinations of MDRI and FRR that fell into the TPP ranges were reported (e.g. MDRI 180 days, FRR 1%; or MDRI 270 days, FRR 0.5%).

Common characteristics of the required assay made it possible to consolidate the use cases to create three TPPs. Minimum requirements were that the assay should:

- correctly classify recent and non-recent cases for subtype C specimens;
- be unaffected by minor variations in assay time, temperature, analyte concentration and volume, humidity or altitude, or other prevalent materials (e.g. antimalarials);
- not contain any hazardous materials; and
- be suitable for use in low-resource settings (including method for disposal; i.e. should not require sophisticated installations for safe disposal).

Minimum TPP requirements for assay performance for the five use cases related to incidence estimation (use cases 1–5) are shown in Table 1. Optimally, the TPP for these use cases is MDRI 365 days, FRR 0.25%.

Other considerations for the assay were:

- the required facilities – either an academic research, clinical or surveillance laboratory with Level 3 controlled temperature, humidity and electricity;
- able to be used by moderately trained laboratory staff and to allow processing of batch sizes of up to hundreds per day;
- time to result, which ideally should be <48 hours, with the reagents stable for at least 12 months at 4° C; and
- sample types – acceptable types being whole blood, plasma, serum, dry blood spot (DBS), urine, saliva, peripheral blood mononuclear cell or stool, depending on the analyte.

Currently, the LAg assay meets the minimum requirements for use cases 1–3 and 8 in certain populations when incorporating viral load information, but does not meet the requirements for use cases 4 and 5, because these would require sample sizes of more than 10 000. The MDRI and FRR are determined largely by the biology of the biomarkers used; hence, it is unlikely that this assay could be modified to improve these features.

3.3 Incorporation of HIV incidence assays into population-based surveys: crossover issues for case-reporting systems

National population-based surveys measuring HIV prevalence – such as the Demographic Health Survey (DHS), AIDS indicators surveys and population-based HIV impact assessments (PHIA) – differ from case-based surveillance in that there is a survey period

Table 1. MDRI and FRR values needed to provide the required performance for use cases 1–5

Use case	MDRI (days) / FRR (%) pairs for most stringent assay performance				
	Minimal TPP requirement				Optimal TPP requirement
1	120/0	180/≤0.5	240/≤1.5	300/≤2.5	365/0.25
2	120/0	180/≤1.0	240/≤2.5	300/≤4.0	365/0.25
3	120/0	180/≤1.0	240/≤2.5	300/≤3.5	365/0.25
4	Not tested	Not feasible	240/≤0.5	300/≤1.5	365/0.25
5	120/≤0.25	180/≤0.25	240/≤0.25	300/≤1.5	365/0.25

FRR, false recent rate; MDRI, mean duration of recent infection; TPP, target product profile

and a target sample size often ranging from 1000 to 100 000 participants. Survey participants are usually aged between 15 and 59 years, but more recently include those of all ages. HIV-related biomarker testing uses data on incidence assay, viral load, exposure to ART and CD4 count. By the end of 2014, 78 surveys had been conducted in 38 sub-Saharan countries and 10 other countries, including Cambodia, Dominican Republic, Haiti, India, Mexico and Viet Nam.

In 2015, the UNAIDS/WHO 2005 guidelines for national population-based surveys were updated with input from over 15 implementing partners and health ministries (*1*). The primary objective of the guidelines is to assist with measuring the 90–90–90 targets (*5*) both nationally and subnationally. The guidelines are intended for settings where HIV prevalence among adults aged 15–49 years exceeds 2%. However, they also include information on how to estimate HIV prevalence among children nationally where the prevalence among women aged 15–49 years is ≥5%, fertility is high and prevention of mother-to-child transmission (PMTCT) coverage is relatively low. Inaddition, the guidelines provide information on how to use RITA to measure HIV incidence nationally where HIV prevalence among adults aged 15–49 years is ≥5% and HIV incidence is estimated to be ≥0.3%. The recommended RITA comprises the incidence assay result and viral load information with optional ART testing. The recommended assay is the one with the longest MDRI and smallest FRR.

Issues raised at the joint UNAIDS/WHO consultation meeting on including RITAs in population-based surveys (held on 8–9 June 2015) were:

- the MDRI for the LAg assay and a specific viral load threshold;
- whether seroconversion is to be estimated from the date of infection or the date of immunoblot (western blot [WB]) seroconversion;
- the impact of the FRR relative to the MDRI; and
- whether testing for ART should be undertaken.

Two different values have been published for the MDRI of LAg + viral load: 188 days by CEPHIA and 130 days by CDC. A comparison of CEPHIA and CDC specimens showed differences in the distribution of samples by subtype. In CEPHIA, more than half of the specimens were of subtype B, whereas in the CDC panel more than half were of subtype CRFO1_AE. When stratified by subtype, the MDRI estimates were similar, suggesting that subtype-specific (or possibly location-specific) MDRIs may be required. Work is under way to pool and reanalyse the available data.

The time since infection may be defined as the estimated date of infection or the date from seroconversion as detectable by the assay of the testing algorithm. The latter is currently used by CEPHIA. At the June 2014 meeting, participants favoured the use of the date of estimated infection, which would increase the MDRI. Consensus on the best approach will be sought at the next reference group meeting.

Suggestions or assumptions that the inclusion of viral load or ART testing data in algorithms reduces the FRR to 0% prompted a literature review of LAg plus viral load (LAg+VL) studies. Simulations showed that an FRR of <1–2% can significantly distort HIV incidence and must be considered.

Finally, data from South Africa showed that, without incorporating ART testing data, 13 of 146 LAg recent specimens would not have been identified as false recent, despite using viral load. In Kenya, antiretroviral (ARV) agent testing or self-reported ART in addition to a LAg+VL RITA did not affect incidence estimates. Additional studies are needed to determine the usefulness of including ART in RITA.

A formal process will be established to update the guidelines in about 3 years as further research becomes available and outstanding issues are resolved.

3.4 Development of WHO guidance on case-based surveillance and patient monitoring systems

UNAIDS/WHO are developing guidelines for case-based surveillance systems that collect individual-level, routinely generated clinical data on people living with HIV (PLHIV). These data are sent from service delivery points to subnational or national central collection points for de-duplication, analysis and reporting. The latest guidance on clinical HIV stages was revised in 2006 (*6*).

There is presently no standard case definition for primary HIV infection. The infection can be identified by recent appearance of HIV, by detecting HIV-RNA or HIV-DNA, or by detecting ultrasensitive HIV p24 antigen with negative (or weakly reactive) HIV antibody. The case definitions for HIV infection in adults and children aged ≥18 months are a positive HIV antibody test (rapid or laboratory-based EIA) confirmed by a second test relying on different antigens or operating characteristics; and/or a positive virological test (HIV-RNA or HIV-DNA or p24 antigen confirmed by a second test through separate determination). For children aged <18 months, a virological test is required confirmed by a second test at least 4 weeks after birth.

WHO recommends that countries standardize their case-reporting practices to include all HIV cases, and all advanced HIV disease and AIDS cases. Detailed components of a case-reporting form should contain a unique patient identifier, and information about

demographic and HIV status (including whether the patient is alive), HIV clinical stage, immunological information, HIV testing history and HIV transmission risk. Outputs from these data are the distribution of patient demographic and risk characteristics, trends in HIV diagnoses and testing history, clinical stage at time of diagnosis, linkage to care, level of ART use and viral suppression, number of HIV- and non-HIV-related deaths, and types of opportunistic infections.

Despite these recommendations being published in 2006 (*6*), the uptake in case reporting has been low, particularly in sub-Saharan African countries. WHO, in collaboration with the Measurement and Surveillance of HIV Epidemics (MeSH) Consortium, is working on developing new guidance that includes more detail on how to set up HIV case reporting and patient monitoring systems. The aim is to improve the health care of persons diagnosed with HIV and to inform programme management at subnational, national and global levels. Guidelines for HIV patient monitoring were revised in 2012 (*7*). Work has been ongoing to scope the minimum datasets required for a standard database to generate longitudinal registers for the follow-up of patient outcomes.

Ideally, HIV case-reporting guidelines should include recommendations for data required to estimate HIV incidence. This could be in the format of a matrix detailing which methods are currently available, what data inputs are required (and to what level of quality), the key assumptions the methods are based on, how to handle missing data and any tools available.

4. INCORPORATING HIV INCIDENCE ASSAYS INTO PROGRAMMES AND CASE-BASED SURVEILLANCE SYSTEMS

4.1 Incorporating HIV incidence assays into genitourinary medicine clinics in England

HIV incidence assays have been incorporated into routine HIV surveillance in England since 2009. Clinics and laboratories submit specimens for testing to the Virus Reference Department at Public Health England (PHE). The proportion of new HIV diagnoses (~6000 each year) tested increased from 23% in 2009 to 53% in 2013.

Between 2009 and 2013, PHE used the Abbott AxSYM HIV 1/2 gO assay, modified to determine antibody avidity and with 80% as the cut-off for recent infection. Data are linked to reports of new HIV diagnoses using pseudo-anonymized information (e.g. clinic identifier, soundex,[3] sex and date of birth). RITA is used for final classification of recent infection (e.g. CD4 <50 cells/mm3, viral load <400 copies/mL, and clinician report of prior ART or AIDS within a year).

At PHE, the genitourinary medicine clinic activity dataset (GUMCAD) collates information on every attendance and service provided at sexual health clinics in England, which is where 80% of HIV diagnoses are made. Population-based survey data show that a high proportion of people from key risk groups have attended a GUM clinic for an HIV test – 52% of men who have sex with men (MSM), 46% of black African women and 44% of black African men. With comprehensive data on HIV testing, incidence was estimated in GUM clinic attendees using the cross-sectional survey approach (2); that is, RITA data were used to estimate number of incident cases (numerator) and GUMCAD was used for HIV testing data (denominator). Locally, an FRR of 1.9% (95% CI: 1.0–3.4%) was determined among 580 patients known to have been infected for ≥1 year, and 181 days was used as the MDRI. (The FRR among those infected for ≥2 years was 1.8%.)

Overall, the proportion of recent HIV infection increased from 9.8% in 2009 to 19.3% in 2013. This increase was observed among all risk groups over that period. The number of negative HIV tests increased from 238 873 in 2009 to 357 343 in 2013 among all attendees and all risk groups. Estimated HIV incidence was 0.13% (0.10–0.16%) in 2009, increasing to 0.20% (0.17–0.23%) in 2013. Incidence was highest among MSM, with 1.24% in 2009 increasing to 1.46% (1.23–1.70%) in 2013 (although this increase was not statistically significantly). Among heterosexuals, incidence was stable at between 0.03% (0.02–0.05%) and 0.05% (0.03–0.07%) over the 5-year period, but was about fourfold higher among black African heterosexuals, fluctuating between 0.15% (0.05–0.26%) and 0.19% (0.04–0.34%).

Limitations of this approach are the sampling bias that may exist because of variations in population-level testing patterns, the non-randomness of attendance and the incomplete coverage of RITA testing. In addition, in GUMCAD, patients can only be uniquely linked within and not between clinics, potentially overestimating the number of HIV tests. However, these are the first incidence estimates for heterosexuals and show the disparity among the different subgroups.

4.2 Considerations for incorporating HIV incidence assays into case-based surveillance systems in central Asia

An overview of HIV surveillance in central Asia was presented, representing the countries Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. Central Asia is one of only two regions in the world where the number of HIV infections is increasing. In this region, the HIV epidemic is concentrated in people who inject drugs (some of whom are also sex workers at risk of sexual transmission) and along the drug transportation corridors in Afghanistan. Estimated HIV prevalence among adults is 0.1% in Uzbekistan, 0.2% in Kazakhstan, 0.3% in Tajikistan and 0.4% in Kyrgyzstan (no data were available for Turkmenistan). Prevalence was highest among people who inject drugs (PWID): 3.8% in Kazakhstan, 8.5% in Uzbekistan, 14.6% in Kyrgyzstan and 16.3% in Tajikistan.

In Uzbekistan, the most populous country in central Asia, there has been a rise in HIV diagnoses, increasing from 0.06 per 10 000 persons in 2000 to 1.33 per 10 000 persons in 2013 (with a peak in 2009, of 1.45 per 10 000 persons). Mathematical models projecting the HIV epidemic through to 2023 predict a continued rise,

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[3] Soundex is a phonetic index that converts an alphanumeric string to a four-character code; it groups names that sound alike but have different spellings.

reaching 2.3 per 10 000 persons in 2023. About half (54.5%) of new HIV diagnoses in 2013 were among men. The main mode of transmission was injecting drug use (46.1%) followed by heterosexual transmission (37.2%). Mother-to-child transmission accounted for 3.7%.

Testing for recent infection in Uzbekistan could help to monitor the epidemic and identify those groups that are at most risk. The proposed plan is to establish a surveillance system to directly monitor trends in recent infection among newly diagnosed persons, with a secondary objective of estimating HIV incidence. The intended study population will be all those presenting to providers or for laboratory testing between 2015 and 2016 (estimated to be ~1.5million people). About 6000 people were newly diagnosed in 2014–2015 using two EIAs and a WB, and it is assumed that 1% of these will be recently infected. This sample size is expected to yield an incidence estimate of 0.4% (95% CI: 0.3–0.5%) with a coefficient of variation of 30%, assuming a design effect of 1.

Routine HIV testing will be carried out at regional laboratories. Additional blood sample and demographic and behavioural data will be requested from positive specimens, which will be tested at a central laboratory using two EIAs and a WB. Remnant specimen will be tested for recent infection using the LAg EIA, and reactive samples will then be further tested for viral load (threshold 1000 copies/mL). The proportion with recent infection and HIV incidence will be determined using programme monitoring data, to establish the number of people tested for HIV using the MDRI and FRR values recommended by the developers of the assay. Data will be adjusted for individuals that tested positive at the regional laboratory but chose not to have a confirmatory test at the central laboratory (estimated to be 20%).

Considerations are that the country team has not yet determined whether the HIV testing data are available or whether viral load testing is possible on the specimen type. In addition, rapid testing may replace EIA-based testing, affecting the ability to conduct a test to detect recent infection recency testing. A rapid test of this type is currently in development.

Given that there is a population of 30 million in Uzbekistan, only a fraction of whom (1.5 million) are undergoing testing for HIV at testing centres, it was questioned whether data coming from HIV testing centres would be an appropriate denominator to estimate incidence because the case-reporting data are also not a random sample.

4.3 Potential contributions of assays for estimating HIV incidence in the prevention of mother-to-child transmission programme, Democratic Republic of the Congo

The Democratic Republic of the Congo (DRC) has a population of 75 million and an estimated HIV prevalence of 1.2% among persons aged 15–49 years (based on 2014 DHS survey). The (US) President's Emergency Plan for AIDS Relief (PEPFAR) has been supporting antenatal clinic (ANC) surveillance in DRC since 2007, and is scaling up PMTCT services. At present, PEPFAR supports 1038 sites in three provinces (Katanga, Kinshasa and Orientale), and provides services to over 200 000 women per year. Testing uptake is 97%, of which 1.7% women were diagnosed HIV-positive in 2014. Estimating incidence is critical to programme planning and to evaluating the impact of PEPFAR programmes; hence, PEPFAR has been supporting large population-based surveys that have been powered to estimate incidence. One primary objective is to generate serial cross-sectional estimates of HIV incidence among pregnant women enrolled at PMTCT services, and to collect data for 5 years starting from 2016. A secondary objective is to compare incidence estimates using the LAg assay with those from Spectrum, to establish whether estimates from PMTCT sites can be used to determine estimates for the general population.

LAg testing is to be undertaken among women attending PMTCT sites for the first time during their current pregnancy who are diagnosed with HIV-1. One hundred PEPFAR PMTCT sites, which together see more than half of the HIV-positive patients identified each year, will participate. The target sample size is 2700 per year, requiring testing of about 130 000 women. Assuming a design effect of 1 and that 3% of infections are recent, this may generate an incidence estimate of 0.08% (95% CI: 0.04–0.12%). LAg testing will be conducted at a central laboratory using DBS specimens. The RITA algorithm that will be used incorporates viral load (threshold <1000 copies/mL). Other data collected will be demographic and clinical information kept in registers.

Areas for further consideration are:

- how PMTCT data can be used to describe incidence in the general population;
- whether changes in incidence can be measured to sufficient precision for decision-makers; and
- how other methods can be incorporated to estimate incidence using programme data.

4.4 Opportunities for incidence assay validation and estimation in the ALPHA Network

An overview of the ALPHA (Analysing Longitudinal Population-based HIV-AIDS data on Africa) Network in sub-Saharan Africa was presented. ALPHA aims to help with HIV community cohort studies in terms of:

- analysing the studies' longitudinal demographic health data;
- comparing and pooling data from different sites to strengthen analytical conclusions;
- presenting analyses in a way that is useful to national and international health policy-makers; and
- building the capacity of study sites to analyse data locally.

ALPHA study sites are based in Kenya, Malawi, South Africa, Tanzania, Uganda and Zimbabwe, with 10 centres, seven of which have sufficient data to determine HIV incidence. Site sizes range from 25 000 to 96 000 participants, and the latest HIV prevalence estimates range from 7.0% to 33.2%. At the sites, demographic surveillance, HIV surveillance (sera surveys) and combined surveillance are conducted at various intervals; some sites have been active since 1989 whereas others only started in 2012. Five of the sites have data from before ART was available.

A major advantage of the ALPHA studies is that they capture the experience of whole communities, with a participation rate of 99%. Some 98% of deaths are reported, with autopsies for 95%. The cohorts are open, minimizing a selective study population over time. Historically, many sites used informed consent without disclosure (pre-ART). The HIV status is recorded for more people (80–90%) than had ever been diagnosed (30–50%) in these cohorts. More recently, sites are offering participants the option of providing one sample for a research test and of providing another sample at a different venue for a diagnostic test. Disadvantages are that these are small populations that are not nationally representative, the protocols vary across sites, and data linkage between community and clinic data is only complete for four sites.

ALPHA data have been used to undertake HIV incidence studies, and to directly measure trends and age–sex patterns, and the change in community-based incidence during the roll-out of ART. These data may be able to enhance case-based surveillance through data linkage. A concern is the large-scale and selective nature of clinic losses to follow-up (e.g. in Tanzania, up to 40% of people were lost to follow-up 7 years after the start of treatment). In addition, the guarantee of anonymity in voluntary counselling and testing centres is a barrier for unique patient identifiers.

Treatment cascades using the ALPHA Network data were presented for four sites. They showed the discrepancy between the number of HIV-positive people (determined through research specimens) and the number diagnosed. No viral load data were available to determine the proportion with undetectable viral loads. Of note was that 15–25% of deaths were among those who were undiagnosed.

The scope for collaboration between ALPHA sites for incidence assays may be a set of validation studies using current seroconverters and stored samples of historical seroconverters, to compare with incidence assay results. The performance of assays among people on ART may be explored where linked clinic and community data are available. With respect to incidence estimates to be generated from case-based surveillance, the ALPHA study may be able to adjust estimates for those dying without diagnosis, for those dying between diagnosis and care, and for the duplication of links from diagnosis to care. Where data are linked, information on CD4 count may also be available.

4.5 MeSH support for HIV surveillance case-reporting guidelines and tools: measuring impact

An overview of the work of the MeSH Consortium was presented. The main members of the steering group are WHO, UNAIDS and CDC, together with other academic partners. The objectives of the consortium are to develop, test and implement innovative and efficient methods for routine HIV surveillance; to maximize the potential of data routinely collected through HIV surveillance and service delivery platforms; and to assist in updating guidelines for HIV surveillance to improve HIV treatment and prevention outcomes. The three MeSH working groups are:

- Routine HIV Case-based Surveillance;
- Size and HIV Epidemic Dynamics among Key Populations;
- Measuring HIV-related Mortality, Guideline Development and Dissemination.

The work of the Routine HIV Case-based Surveillance Working Group has two phases. Phase 1 is to develop a protocol or tool for the situational assessment of HIV case-based surveillance (strengths, weaknesses, opportunities and threats [SWOT] analyses). Phase 2 is to provide technical and strategic input to adapt or develop patient information systems to report to case-based surveillance, and develop approaches to measure outcomes along the continuum of care.

SWOT analyses for case-based surveillance have been performed in South Africa and Tanzania with respect to assessing feasibility and informing strategic planning for implementation. The SWOT analysis comprises a document review, interviews with national and international partners and regional and district leaders, and site visits. The SWOT tool is a document review or interview guide checklist on the situational assessment including the HIV notification process, other notifiable diseases, leadership and human resources, clinical care and patient monitoring, individual-level data sources, and ascertainment of recent infections and deaths.

In Tanzania, strengths were that the country had the foundations for case-based surveillance, with patient-level data entered into the country's Ministry of Health paper and electronic registers. Existing practice was that clinics were reporting aggregate data nationally and subnationally. Weaknesses were over-reliance on paper-based registers, inadequate unique identifiers (duplicates), data-quality issues, and lack of training or supervision to conduct data-quality checks. Opportunities identified included stakeholder interest in building a case-based surveillance system, and ongoing work to define a unique identifier that would link HIV services and facilitate de-duplication and recognition of the need for better data-quality systems. Threats were limited resources and staff, issues concerning patient confidentiality and unresolved data-quality issues.

Preliminary thoughts about the SWOT analysis in South Africa were that there were opportunities to use data-collection tools to aid improvement of clinical care, and to use a tier-based system that would allow some facilities to use paper registers, others a computerized system (which might not be networked) and – for those with the resources – a networked computerized system. The national laboratory network that conducts viral load and point-of-care testing could be used. In South Africa, a national identity document (ID) is used, and work is currently being undertaken to develop a health-systems ID. In addition, national and provincial standard operating procedures (SOPs) for data standards are being introduced. Weaknesses are multiple electronic medical record systems and failure to make full use of the data that are currently collected. Threats include the high number of cases burdening data security systems, confidentiality and the high number of people ineligible for a national ID.

In conclusion, standards for case-based surveillance should incorporate both data collection and quality control of tests to develop data linkage within and between sites, and to use information from ANCs to improve coverage and reduce bias. Next steps for MeSH are to conduct additional SWOT analyses for Ethiopia, Haiti and Malawi. Phase 2 will subsequently be initiated to collect diagnosis and care data, to develop unique identifiers, and to better understand which systems will feed into case-based surveillance.

For the guidance of incidence assays in case-based surveillance, MeSH can provide information on data quality and variables collected. The Size and HIV Epidemic Dynamics among Key Populations Working Group, and the Measuring HIV-related Mortality, Guideline Development and Dissemination Working Group can provide input on optimizing population-size approaches, and on issues relating to death reporting, recording and linkage.

4.6 Developing recommendations for incorporating HIV incidence assays into HIV case-based and programme surveillance

There are numerous methods for estimating HIV incidence using case-based surveillance. A group work exercise was proposed, in which the group would develop a matrix listing the different methods, the input data needed, the parameters used and the assumptions they are based on, how to handle missing data, and any existing tools and countries that are currently using those tools. Ideally, the case-based surveillance guidelines will have a section on how to estimate HIV incidence at population level using incidence assays, but will also provide information on other estimation methods. The document was originally intended for countries with established, high-coverage, case-based surveillance systems with good-quality data.

A point raised was that HIV incidence models have traditionally been developed based on available data and specific features of a surveillance system, rather than being adapted to a particular system. However, the guidelines could provide an opportunity for countries to collect the necessary data based on a chosen model. Many middle-income countries have case-based surveillance systems that need strengthening. The guidelines could inform on how this is done and whether incidence assays are the best approach in light of other methods.

5. EXPERIENCES IN ESTIMATING NEW HIV INFECTIONS IN HIV CASE-BASED SURVEILLANCE SYSTEMS

5.1 Estimation of HIV incidence in the United States

The National HIV Surveillance System in the United States captures information on HIV diagnoses, CD4 and viral load measures, drug resistance testing, AIDS diagnoses and deaths. The biomarker approach is a component of the country's National HIV Surveillance System. It collects supplemental data on HIV testing and treatment history and HIV recency results, using the BED EIA HIV-1 incidence test (2006–2013) and the avidity-based, modified Bio-Rad HIV-1/HIV-2 plus O EIA (2014 to present). The stratified extrapolation approach is used to estimate HIV incidence. This approach applies a weight to each new diagnosis deemed recent equal to the inverse probability that a person would test for HIV in the recency period (8). The weights of all individuals are summed for total incidence. Not all states undertake incidence testing, and results are extrapolated accordingly.

The second approach used for estimating HIV incidence is the extended back-calculation model (9). Estimates from this model for the most recent years were for a 4-year average. This model has now been improved to provide annual estimates that may question the added value of the biomarker programme.

A third approach is the Bayesian hierarchical model, which can estimate the annual number of new infections, the prevalence and the number of persons undiagnosed (10,11). Data required for the extended back-calculation and Bayesian hierarchical models are the annual number of HIV and AIDS diagnoses. In the United States, these data are adjusted to account for underreporting of early HIV cases (not reported in all states until 2008) and reporting delays. The number of new infections in a given year is the sum of new HIV diagnoses and AIDS cases that have been diagnosed over the years but are estimated to have occurred in the year. Model parameters are the mean number of infections for a year (estimated), the HIV testing hazard (estimated) and the AIDS diagnosis hazard (from the published literature). For the hierarchical model, the joint model likelihood and posterior distributions of the parameters can be simulated using the Markov Chain Monte Carlo method with Gibbs sampling. The HIV testing hazard and annual mean number of infections can be estimated from posterior distributions.

Table 2. Comparison of incidence estimation models

	Biomarker-based sample survey	Bayesian-based backcalculation	CD4-based back calculation
Data needed	Single/multiple years, all new diagnoses Recency/TTH at diagnosis	Entire epidemic, all new diagnoses, AIDS status at diagnosis	Recent (8+) years, all new diagnoses, first CD4 after diagnosis
Estimates	Incidence only for years data are available (published)	Incidence, prevalence and undiagnosed (published)	Incidence, prevalence and undiagnosed (new method)
Strengths	More accurate on recent infections	Annual estimates available	Historical data not required
Weaknesses	False recents, TTH accuracy	(In US) HIV data in earlier years incomplete	Relies on CD4 depletion model

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; TTH, testing and treatment history; US, United States

The United States is currently developing an incidence estimation model based on CD4 depletion (*12-14*). CD4 values are used to estimate the date of infection and incidence by modelling the delay from infection to diagnosis (*15*). The number undiagnosed can be deduced by subtracting the estimated number of infections in a year from the number diagnosed.

Data needed for this model are all HIV cases diagnosed in recent years, CD4 at diagnosis or before treatment, and demographic and mortality information. The model uses CD4 data to estimate the date of infection, and a survival analysis to estimate the diagnosis weight detail. Incidence can be derived by summing the weights from all diagnosed cases. Key assumptions are that the CD4 depletion model is correct, that patients have not had ART before the CD4 count and that the diagnosis delay is stable for recent years. This method can estimate the prevalence and undiagnosed proportions for recent years, in addition to incidence trends over time.

Future plans are for data collection to include ARV use to monitor pre- and post-exposure prophylaxis. Also, a new diagnostic algorithm will be introduced that will include acute infection.

5.2 Estimation of HIV incidence in Australia

In Australia, two models are used for HIV incidence estimation using case-reporting data. A publication by the Working Group on Estimation of HIV Prevalence in Europe reviewed a number of methods that are also applicable to incidence models; it describes three approaches (*16*):

- a statistical approach in which aggregate data on new HIV diagnoses are used – the data are transformed to incidence estimates using a delay (distributions of time from infection to diagnosis);
- a back projection using CD4 count; and
- a transmission model in which the whole process of HIV is modelled, from infection to diagnosis, including the risk of mortality.

Numerous methods use aggregate data:

- the Cambridge method – a multistate Bayesian model;
- the Atlanta method – distribution of time from infection to diagnosis;
- the Bordeaux method – a Markov model including treatment uptake;
- the Paris method – time-dependant intervals from infection to diagnosis; and
- the Ottawa/Sydney method – hybrid methods using AIDS and HIV diagnoses, markers or other evidence

of recent infection to develop time-dependent distributions of time from infection to diagnosis.

A CD4-based method is the London method, which uses counts of diagnoses by CD4 stratum. An extension of this method is that developed by the University of New South Wales (UNSW), which uses individual-based CD4 counts in the model. Both these models have been used in Australia to accommodate the availability of different data.

For the Ottawa/Sydney model, data requirements are the annual number of HIV diagnoses, AIDS diagnoses and recent infections. The model considers three states: recent infection, asymptomatic infection and AIDS. There are two testing rates: the asymptomatic testing rate, which is an exponential distribution, and a symptomatic testing rate, which increases as CD4 declines. The model fits these two testing rates to the data to estimate the time since infection.

Australia has comprehensive CD4 data; therefore, the UNSW method was developed using individual-level data on the date of HIV diagnosis, age and CD4 count within 3 months of the diagnosis. The method is based on the relationship between CD4 count and time since infection. The distribution of CD4 counts among healthy individuals was informed by a meta-analysis of 20 published estimates (found to have a log-normal distribution with a median of ~900). CD4 decline was estimated to be a square root decline of –1.6, and was similar to a linear decline with a median of 61 (40–80) cells/year. Using the CD4 count distribution, the testing rates were estimated by deriving the probability of diagnosis per year given a particular CD4 count at diagnosis. Estimating undiagnosed infection is also possible with this model. Results showed that during the decade 2000–2010, the number of incident cases was similar to the number of new diagnoses (~300 in 2010).

The Ottawa/Sydney method is a simple model in which data requirements can easily be met. However, it is highly dependent on assumptions of the testing rate and cannot be used if the rate is not constant (or available). The UNSW method is more complex, with significant data requirements that are currently only met in high-income countries. This method is more flexible towards changing testing rates but remains dependent on assumptions; in general, it performs well in data-rich contexts for historical projection.

Ideally, methods should incorporate all available data sources such as case reports, prevalence surveys, sentinel sites, programme data, demographic and mortality data, and information on testing patterns. This is possible with a process model, and may be particularly useful in contexts where case-reporting data are unreliable or incomplete. The CD4 method works well for historical incidence if sufficient data are available but is inadequate for estimates for recent years.

5.3 Estimation of HIV incidence in France

In France, the prevalence of HIV is about 0.22%, which corresponded to 150 000 people in 2010. There is good coverage of reporting of new HIV diagnoses, with 6600 diagnosed in 2014. Just over half of diagnoses are among heterosexuals, followed by MSM (45%); also, 60% of heterosexual men and 75% of heterosexual women diagnosed were born abroad.

France uses biomarker data and the stratified extrapolation approach to estimate HIV incidence (*8*). This method stratifies observed recent infections into groups by categories (e.g. transmission risk and geography); it then calculates a probability of inclusion for each group, which is a function of the MDRI and testing behaviour. Probabilities are calculated for repeat and new testers separately. For repeat testers, the assumption is that the infection date is uniformly distributed between the last negative and the first positive test. For new testers, the assumption is that the time from infection to first test has an exponential distribution until AIDS. This exponential distribution is derived from the AIDS incubation period and the probability that the first test is before AIDS. Incidence is estimated by dividing the number of observed recent infections by the probabilities for each stratum.

Overall, the general trend was a decrease in incidence among heterosexual risk groups from 2003 to 2012. Over this period, the annual number of new infections decreased from 2500 to 1500 among heterosexual men and also decreased among heterosexual women. Among MSM, incidence was highest over this period but was stable, with about 3500 new infections each year. Nearly half of new HIV infections were in Paris and a similar proportion were in mainland France, with some in the French Caribbean, particularly among MSM.

A second biomarker method used in France estimates the posterior distribution of infection time based on the RITA value as a continuous variable. This method requires information on the diagnosis date, the clinical stage, the RITA result and the date of the last negative HIV test. The main difference between the stratified extrapolation approach and the posterior distribution approach is how the biomarker data are used (*17*).

France has also used the back-calculation method (*18*). This model requires the date of HIV diagnosis and information on the clinical stage. Results of all methods were similar, with the only differences being trend estimates among those born outside France.

Work is ongoing towards a simulation study. This involves a comparison between the two biomarker methods, using a computer to simulate incident cases with the growth of RITA markers, assign testing patterns and generate sets of diagnoses data. This study will be used to estimate bias and compare confidence intervals to examine

whether incidence can be estimated precisely. Missing data will be accounted for – data may be missing because of underreporting (estimated to be ~30%), incomplete coverage of RITA testing (~25%), and missing information on transmission risk group (~25%) and testing history (~50%).

Other work ongoing is the evaluation of the IDE-V3 assay by CEPHIA for better characterization. Of note is that the RITA algorithm currently does not adjust for CD4 count (only AIDS) because CD4 data collection started in 2008. Exposure to ART is also a new item in the surveillance system. At this stage, the biomarker approach is not considered superior to the back-calculation method.

5.4 Estimation of HIV incidence in the United Kingdom

In the United Kingdom of Great Britain and Northern Ireland, HIV prevalence is estimated using the Multi-Parameter Evidence Synthesis (MPES) model and incidence using the back-calculation model based on CD4 strata (*19*). The MPES model uses information from cross-sectional studies; for example, on HIV prevalence and the size of the population at risk. The back-calculation model requires trends in the number of new HIV diagnoses. In the MPES model, the total number of infections is the sum of the number of infections prevalent in different risk groups, which differs between diagnosed and undiagnosed infections. The number of infections in the risk groups is multiplied by the magnitude of the population. Parameters that need to be estimated are the proportion of the risk group in the population at a given time and in a given region that are infected, the corresponding prevalence of HIV and the proportion of infections diagnosed in that risk group in the region. Any other quantities can be derived from these. In the United Kingdom there are 13 risk groups (e.g. MSM, PWID, heterosexuals by sex and sub-Saharan African born heterosexuals) and three regions (England, Scotland and Wales). The MPES model attempts to include all available relevant data sources; currently, it includes case-based surveillance data, census data, community and clinic-based convenience sample surveys and population-based cross-sectional studies. The model is able to provide estimates for the total number of PLHIV (~104 000 in 2014) and the number diagnosed (86 000) by transmission risk group and sex over time. The snapshots over the years can also be used to generate an incidence estimate. The method is being continuously developed as data sources change over time, and has been applied in the Netherlands (*20*) and Poland (*21*). It is appropriate for concentrated epidemics where multiple sources of information are available.

The back-calculation method using CD4 count data has been presented in Section 5.1. The original model requires the number of new AIDS diagnoses over time and their

incubation period time distribution. It uses these data to estimate the expected number of new infections. The model uses a multistate approach with information on CD4 count at the various stages of decline before AIDS; affected persons continue to become diagnosed either during one of these pre-AIDS stages or at the AIDS stage. The probabilities of being tested at various stages of the disease change due to immune system decline and, over time, individuals are more likely to test positive. The basic model parameters are the expected number of new infections over time (estimated), the proportion of undiagnosed individuals in a particular CD4 state diagnosed over time (estimated) and the proportion of undiagnosed individuals in a particular CD4 state progressing to the next CD4 state (known from the Concerted Action on SeroConversion to AIDS and Deaths in Europe [CASCADE] cohort). A crucial source of information is the distribution of CD4 count at diagnosis, which is available in the United Kingdom (~90% complete). Information on the progression rates through CD4 stages is available from CASCADE. Among MSM, it is estimated that there are about 2500 new infections each year.

This model can also estimate the number of people remaining undiagnosed; it is estimated that about half of undiagnosed MSM have CD4 >500. A comparison of the estimates of undiagnosed infection from MPES and the back-calculation models over time showed similar trends. The model is now packaged in the HIV modelling tool, courtesy of funding from the European Centre for Disease Prevention and Control (ECDC).

The United Kingdom has also estimated population-based incidence using RITA and the stratified extrapolation method (see Sections 5.1 and 5.3). In England, the coverage of RITA testing is about 50% of the estimated 6000 new HIV diagnoses annually. The estimated number of new HIV infections was about 3000 among MSM, which is comparable to outputs of back-calculation models. Work is ongoing to review some of the assumptions the model is based on, such as accurate testing history data and the impact of changes in testing behaviour over time. Further, a review is being conducted to compare and bridge results of two different assays: the AxSYM avidity assay (2009–2013) and the LAg assay (2013 onwards).

5.5 Estimation of HIV incidence in Canada

New HIV diagnoses data in the Canadian surveillance system are relatively complete at the national level. They include information on the year of diagnosis, province, sex, age, exposure category and ethnicity. Some of the data required for the determination of recent infection are incomplete; for example, CD4 data, date of the last negative HIV test and incidence assay data are only available on a subset from some provinces. Incidence testing has been ongoing for up to 12 years; in the early

years Vironostika was used and more recently (until 2012) BED. Complete data are available on AIDS at first diagnosis but not on AIDS after a first HIV diagnosis.

Surveillance data show that, over the past 7 years, there has been a steady decline in the number of new diagnoses (from 2600 in 2008 to 2044 in 2014). Multiple methods are used to estimate national HIV prevalence and incidence, and these methods have been published (*22-24*). The number of new HIV infections showed two peaks over the course of the epidemic (5500 in 1984 and 3500 in 2005) and was at 2500 in 2014. As in France and the United Kingdom, no decline in the number of new infections was observed among MSM; infections have been stable at about 1500 since 2005. A decline has been seen among PWID and heterosexuals born both within and outside of Canada.

Efforts were made to validate these estimates. The decline in the number of new infections among PWID has been reflected in research data from different parts of the country, such as within a cohort of PWID and needle-exchange programmes elsewhere. The total number of persons estimated to be living with HIV in Canada was 75 000 in 2014, of which half were MSM and 15% PWID. Attempts were made to compare figures with the number of people on HIV treatment registers, which was estimated to be about 60% of those diagnosed. Local public health officials considered these estimates reasonable based on their experience.

The proportion of undiagnosed cases is estimated for each province separately and then combined to obtain a national level estimate. Input data are the cumulative diagnoses data (from surveillance) and the cumulative deaths data (from Vital Statistics: births and deaths); the difference between the two provides the number of people living with diagnosed HIV. The number undiagnosed is obtained by subtracting the number of people living with diagnosed HIV from the overall estimated prevalence. In 2014, it was estimated that 21% were undiagnosed. Some direct measures of the proportion undiagnosed are available from population surveys, which show similar proportions.

Further detail was presented on modelling aspects of the Ottawa/Sydney model. Aspects included assumptions for the testing rate and age imputation on highly aggregated case-reporting surveillance data with wide age intervals, and the application of these for HIV incidence estimation by year of infection and birth cohort.

First, the testing rate in the Ottawa/Sydney model can be described as an additive hazard model that is the weighted average of two hazard functions, depending on the calendar year and time since infection. Once this hazard function has been determined it can be expressed as probabilities. The first part of the additive hazard model is referred to as the frailty model of proportional hazard,

in which individuals follow different hazard functions proportionally to a baseline hazard. The baseline of the hazard is assumed to be a constant that gives the frailty model a decreasing hazard function of a Pareto form. These tests are for persons where testing is not driven by symptoms. A second part of the additive hazard model is a disease progression model with an increasing hazard function (Weibull hazard shape parameter 2.08 for progression to CD4 <200.) The final model depends on the time since infection of the two hazard functions and the calendar time via the weighting function. Different shapes are determined by the weighting function; if there is a high testing rate in later years, testing is driven by symptoms, but if there is a high testing rate in earlier years, testing is driven by a higher frequency of testing in the population. A current limitation is that the weighting function is modelled as an increasing function of calendar time since the year HIV testing was initiated, and it cannot accommodate a situation where HIV testing rates were lower in previous years or where there are sudden changes in HIV testing.

In Canada, data are aggregated at province level and age imputed on highly aggregated data with wide age intervals (6-year intervals). A mathematical distribution function was found to impute HIV diagnosis numbers into every age using a three-parameter model that was evaluated for goodness of fit using likelihood ratio statistics. This imputation was conducted for all years from 1985. Visual examination of the goodness of fit was performed by re-aggregating the imputed data and comparing it to the original data.

Outputs of the Ottawa/Sydney model showed that the trends in the number of new HIV infections among MSM across provinces had a similar shape. Examining the data by birth cohort showed that although the number of new HIV infections had remained stable over the past decade, contributions from younger birth cohorts had increased. Those born since 1970 accounted for 73% of all undiagnosed cases by 2014, and those born since 1980 for 50%. Analysis for infected but not diagnosed MSM should be stratified by birth cohort, providing more targeted epidemiological information to guide prevention.

5.6 Estimation of HIV incidence in ECDC

At ECDC, two methods have been developed or evaluated that can estimate the number of new infections, the average time between infection and diagnosis, the number undiagnosed and the number in need of treatment using only routinely collected HIV and AIDS data.

The back-calculation method – referred to as the ECDC HIV modelling tool – is available as a free, user-friendly tool from ECDC's website.[4] This tool was developed in

collaboration with the ECDC HIV team, and groups from Switzerland and the United Kingdom. It comprises two methods: the incidence method and the London method. The incidence method requires historical data, with which it is possible to estimate incidence over time, time from infection to diagnosis and the undiagnosed population. The London method requires only 1 year of data and can estimate the undiagnosed population in need of ART (e.g. CD4 <200 or 350 cells/mm^3). Both methods require data on transmission risk and AIDS diagnoses. In addition, the incidence method requires data on HIV diagnoses, AIDS diagnoses up until the year ART became available (1996), and multiple years of data (CD4 data optional), whereas the London method needs CD4 at diagnosis and high-quality data (information on HIV symptoms optional).

The concept underlying the London method is that if 200 person-years are observed with a CD4 <200, with an AIDS rate of 0.25 per year, 50 people would be expected to develop AIDS over a year. The reverse reasoning is also true; if 50 people with HIV/AIDS are observed with a CD4 <200, then it is possible to infer 200 person-years of undiagnosed HIV among those with a CD4 <200.

The incidence method uses the back-calculation approach. With an observed pattern of HIV diagnoses over time, the number of infections in the past that gave rise to the diagnosis pattern can be estimated. The distribution of the time between infection and diagnosis must be known, and may vary by calendar time and trends in testing frequency. The underlying model is inspired by Sweeting et al. (*25*), whereby people are infected at time t; experience primary HIV infection, which they leave at a given rate (chosen or known); and pass through one of five compartments of unobserved CD4 counts. People may progress to the next CD4 stage at a given rate and finally progress to death (with the progress rate obtained from CASCADE) (*12*). Diagnosis can occur at a given rate for each CD4 stage and, once diagnosed, individuals may continue to progress to the next CD4 stage until death. This method is only valid before the availability of ART. The diagnosis rate is input from country experts and can be manually entered into the tool. It is also possible to specify whether there is a sudden increase in the diagnosis rate or the diagnosis rate differs by CD4 count.

In the Netherlands, HIV surveillance is carried out using the ATHENA national observational HIV cohort, which collects information on HIV and AIDS diagnoses, CD4 at diagnosis, migration and deaths. The number of new HIV infections among MSM showed a peak in the mid-1980s of about 900 cases, and decreased to about 200 infections each year from 1990 to 1999. This was followed by another increase to almost the same level as in the mid-1980s, but has been decreasing again since 2005. The average time to diagnosis decreased from 11.5 years in 1980 to 2.6 years in 2012. Overall, it is estimated that 11% of all those infected remain undiagnosed. The Netherlands

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4   http://ecdc.europa.eu/

is close to achieving the UNAIDS 90–90–90 targets, with 85% (of 22 000 PLHIV) diagnosed, 85% of those diagnosed on treatment and 92% of those on treatment having supressed viral loads. It is estimated that among the undiagnosed, about 50% had a CD4 <500 and 10% a CD4 <200; also, 30% had an infection for <1 year and 16% for >5 years. Comparison with the London method in the tool showed similar results. Estimates with partially missing data were also simulated for two scenarios: CD4 counts missing at random for 10%, and the proportion of CD4 missing higher among cases with CD4 <200. Results showed that numbers of new HIV infections were similar and that estimates were robust, even with missing data. However, estimates for time to diagnosis were affected, in that a shorter time to diagnosis was generated if missing counts were higher among cases with CD4 <200.

Planned work is to update the London method in the tool with rates of developing non-AIDS symptoms, to adapt the incidence method to be applicable in countries with reasonable amounts of data but not covering the whole epidemic (e.g. France), to compare estimates with the UNAIDS Estimation and Projection Package (EPP) and with Avenir Health's Spectrum method for selected countries, and to enable incidence estimation by age group.

5.7 Estimation of HIV incidence in Brazil

In Brazil, results of a mathematical model to estimate HIV incidence (*26*) were compared with incidence estimated using the LAg assay in two cities, Curitiba and Recife. Brazil has a national information system (SISCEL) that monitors CD4 and HIV viral load data to evaluate patients' treatment with ART. This is the most appropriate data source because HIV notification became compulsory in June 2014, and the system is considered complete because it is based on reimbursement by the government. However, SISCEL does not include tests in the private sector (estimated to be 28%).

The mathematical model is based on the CD4 depletion model, in which the square root of the first CD4 count is related to the time of infection through a linear mixed model (*12*). For use in Brazil, the model was adapted to calculate the slope by sex and age because transmission risk data were not available. All cases with CD4 ≥500 and the last count before ART (at least 1 year after the first count) were considered. The slope was estimated as the ratio between the difference in the square root of CD4 and the time period between the first and last count. Estimates were similar to the Lodi model. For each treatment-naive HIV case reported, the depletion model was used to estimate the time between infection and first CD4 count based on the linear model coefficients. Testing in the private sector was accounted for by weighting according to health plan insurance data by place of residence. Incidence was estimated for males and females separately as a sum

of cases reported up to 20 years post infection. If the time from infection to diagnosis was <1 year, the infection was assigned to the most recent year. Results showed that about 30–35% of persons were diagnosed within a year of infection, increasing slightly over time. The median time between infection and first CD4 count was 4 years. In 2013, it was estimated that the incidence rate was 38.7 per 100 000 population, 16.6 per 100 000 women and 27.4 per 100 000 men. This corresponds to 42 000 infections a year. Between 2006 and 2013, estimates showed an increase in incidence among men and a slow decline among women. Men accounted for 70% of new infections in 2013, probably due to an increasing rate among MSM.

LAg assay testing was performed in Curitiba and Recife in 2013. In these cities, HIV prevalence among women is higher than the Brazilian average. The main subtype in the southern region (Curitiba) is subtype C, whereas in Recife, the main subtype is F, which accounts for 15–20% of infections. Diagnostic samples were collected from laboratories and the assays applied to 49% (497/1013) of diagnoses in Curitiba and 59% (528/902) in Recife. The proportion of recent infection was 10.5% in Curitiba and 13.1% in Recife. In a separate study (*27*) it was estimated that the probability that an individual had been tested in 2013 was 44%. The estimated number of new HIV cases was 612 and 683 (MDRI 141 days, FRR 2%), which implied an incidence rate of 41.1 in Curitiba and 53.1 in Recife.

5.8 Estimation of HIV incidence through UNAIDS country support

An overview of the updates made to Spectrum was presented. Many countries use Spectrum for monitoring their epidemic as well as for contributing to global estimates. Spectrum typically models epidemic trends using ANC surveillance data, population-based survey data and size estimates of key populations. However, countries that may have limited, sporadic surveillance data that may produce distorted and unreliable epidemic trends may be deterred from producing estimates. UNAIDS has been increasingly trying to provide better support to these countries, and has made improvements in the Spectrum AIM software for countries with established case-reporting systems. Currently, there are wide differences across countries between reported new HIV diagnoses and UNAIDS estimated diagnoses. This is also the case for reports and estimates of AIDS mortality.

Spectrum AIM has a strategy for including direct measures and incidence estimates from other models. A pilot commenced in 2014 to fit estimates to mortality and case-reporting data, and was rolled out in 2015 as a tool in Spectrum that was further improved in 2016. A broad recommendation was made for when countries should use

the "fit to programme data" tool. The recommendation was to select this tool when programme data (case reports, death registration and estimates of PLHIV) are superior to surveillance data and have been validated and assessed for quality. Optional data inputs may be:

- the number of PLHIV and the proportion undiagnosed;
- the number of new HIV cases, the estimated time to diagnosis in years and the estimated undercount; and
- the number of AIDS-related deaths and estimated undercount.

The tool is a curve-fitting tool that fits a double logistic incidence curve. The assumption is that it is minimizing the chi-squared distance between the number of PLHIV and the data added via the tool. Further work has been completed to obtain the uncertainty around these estimates using the inverse of the hessian matrix and percentile method.

There has been an increase in the use of the tool in Latin America and the Middle East. Some countries preferred the EPP outputs; these countries include Colombia, Ecuador, El Salvador, Iran, Libya, Mexico, Paraguay and Tunisia. Three countries – Lebanon, Oman and St Kitts – did not previously have Spectrum files and successfully used the "fit to programme data" tool. Many countries were switched from EPP to this tool (e.g. Costa Rica, Venezuela and various western European countries). Advantages are that the tool requires few adjustments, produces more realistic curves and is more transparent because countries can observe the link between their data and Spectrum outputs. The tool has also resulted in strengthening of case-reporting systems, including an emphasis on the role of CD4 and viral load data.

Some of the limitations of the tool are that data are currently not disaggregated by key populations, which is crucial in countries with concentrated epidemics. Stronger guidance is needed on acceptable data inputs and adjustments, and types of historical data. There have been challenges in reconciling different estimates between results produced by EPP and the "fit to programme data" tool, which requires good assumptions around underreporting and misclassification. Areas for further improvement are the inclusion of other HIV surveillance and clinical data, evidence of recent infections and incidence assay estimates, as was done previously with EPP.

To date, UNAIDS-supported pilot activities include the Middle East and North Africa (MENA) workshop in March (2015) where Iran, Morocco and Tunisia explored back-calculation methods, and a Latin American workshop that explored the Spectrum and HIV Modelling Consortium tools. An ECDC and Spectrum validation workshop took place in February 2016 and included three countries in eastern and western Europe. In January 2016, the new Spectrum software became available, and Spectrum files were reviewed by the end of February, meaning that revised estimates would be available for release in time for the International AIDS Society conference in Durban 2016.

6. GENERAL DISCUSSION ON METHODS PRESENTED AND PARAMETERS NEEDED AND APPLICABILITY; DATA REQUIREMENTS FOR COUNTRIES

Case-based surveillance data are likely to become increasingly available as many countries move towards offering ART to all persons with newly diagnosed HIV (e.g. Brazil and South Africa). WHO/UNAIDS will produce HIV case-based surveillance and patient monitoring guidelines in 2016, which will include information on how to generate HIV incidence estimates and the number of undiagnosed infections from case-based surveillance data. One purpose of the guidelines is to provide guidance on the type of information needed and whether using incidence assays would be of additional value, particularly when ART and/or viral load data may not be available, as well as whether applying back-calculation models is appropriate where CD4 data are incomplete. It was proposed that countries contribute to this by summarizing information on incidence estimation models including data requirements, the complexity of calculations and whether software is available to aid calculations. As coverage of case-based surveillance may vary substantially between countries, it was suggested that, where possible, information be provided on how sensitive the models are to incomplete or low-quality data. The guidance document could further be developed into a technical paper providing an overview of HIV incidence estimation methods using case-based surveillance data.

7. DRAFT MATRIX: HIV INCIDENCE ESTIMATION MODELS USING CASE-BASED SURVEILLANCE DATA: DATA REQUIREMENTS, ASSUMPTIONS, EXISTING TOOLS AND OUTPUTS

Name of model	Data required[a]	Parameters used	Assumptions	Missing data[b]	Outputs	Existing tools	Countries using it	Key publications
Biomarker model using the stratified extrapolation approach	Annual number of HIV diagnoses, a RITA consisting of an incidence assay result and information on AIDS status at diagnosis, testing history data; geographic and demographic information	MDRI, FRR, AIDS diagnosis hazard (from published literature, no treatment before AIDS)	Infection date is uniformly distributed between last negative and first positive test; testing rate is constant among those never tested with HIV; MDRI is well defined; incidence is relatively constant over the previous 2 years	Missing HIV incidence assay results and HIV testing history data can be imputed (conditional on data missing at random)	Annual number of new infections stratified by risk and demographic variables	SAS code (to be developed: WHO guidance document on application of HIV incidence assays to case-based surveillance data)	US, France, Australia, UK	Karon et al. 2008 (8) Prejean et al. 2011 (28) Le Vu et al. 2010 (29)
Extended back calculation	Annual number of HIV diagnoses from the entire epidemic; AIDS status at diagnosis	HIV testing hazard (estimated); AIDS diagnosis hazard (from published literature); annual mean number of infections (estimated)	Testing has not changed significantly over previous years		Average annual number of new HIV infections (4-year average for most recent years), prevalence and number undiagnosed	SAS code	US	Hall et al. 2008 (9)
Bayesian hierarchical-based back calculation	Annual number of HIV diagnoses from the entire epidemic; AIDS status at diagnosis	HIV testing hazard (estimated); AIDS diagnosis hazard (from published literature); annual mean number of infections (estimated)	Testing has not changed significantly over previous years		Annual estimates of incidence, prevalence and number undiagnosed	Estimation code in R	US	Hall et al. 2015 (11) An et al. 2015 (10)
CD4-based back calculation (US method)	All new HIV diagnoses (recent years), CD4 count at diagnosis, cumulative numbers of HIV diagnoses and deaths	CD4 depletion rate stratified by risk and demographic variables (published by CASCADE)	CD4 depletion model is correct; no ART before first CD4 count; time from infection to diagnosis is stable in recent years	Cases without CD4 were counted using weights applied to cases with CD4 and similar characteristics at diagnosis	Annual number of new HIV infections, prevalence and number undiagnosed, stratified by risk and demographic variables	SAS code	US	Lodi et al. 2011 (12) Hall et al. 2015 (15) Song et al.2014 (30)

Name of model	Data required[a]	Parameters used	Assumptions	Missing data[b]	Outputs	Existing tools	Countries using it	Key publications
CD4-based back calculation (London method)	HIV diagnoses for at least 1 year, CD4 count at diagnosis; data on symptoms optional	CD4 depletion rate (published by CASCADE)	CD4 depletion model is correct		Annual number of new HIV infections, number undiagnosed by CD4 stratum	Yes: http://ecdc.europa.eu/en/healthtopics/aids/Pages/hiv-modelling-tool.aspx#	UK, Netherlands, ECDC HIV modelling tool users	Lodi et al. 2011 (12)
Incidence method, back-calculation approach (Netherlands)	All new HIV diagnoses; AIDS diagnoses up to 1996 (pre-ART); CD4 data optional	CD4 depletion rate (published by CASCADE)	Distribution of time between infection and diagnosis; trends in testing frequency; CD4 depletion model is correct	Estimates stable for 10% of CD4 counts missing at random; however, affected if CD4 data are not missing at random	Annual number of new HIV infections; time from infection to diagnosis; if CD4 data are available, number of undiagnosed infections by CD4 strata	Yes: http://ecdc.europa.eu/en/healthtopics/aids/Pages/hiv-modelling-tool.aspx#	Netherlands, ECDC HIV modelling tool users	Van Sighem et al. 2015 (31) inspired by Sweeting et al. 2005 (32) Lodi et al. 2011 (12)
Ottawa/Sydney model	Number of HIV diagnoses; number of AIDS diagnoses (optional); number of recent HIV infections	HIV testing hazards for recent/asymptomatic infection; HIV testing hazard for AIDS cases; distribution of time from infection to AIDS (published)	Testing rate is constant; not applicable if testing rate data are not available		Annual number of new HIV infections	None available to date	Australia, Canada	Mallitt et al. 2012 (33) The Kirby Institute 2013 (34)
UNSW model	Date of HIV diagnosis; date of birth of age (optional); CD4 count within 3 months of diagnosis; date of last negative test or evidence of recent infection (optional); seroconversion illness at diagnosis (optional); indeterminate WB at diagnosis (optional)	CD4 depletion rate (based on a weighted average of a number of studies). HIV testing rates derived using the probability of diagnosis per year given particular CD4 count at diagnosis.	CD4 depletion model is correct; probability of diagnosis given a particular CD4 count is correct		Number of new HIV infections, number undiagnosed	None available to date	Australia	

Name of model	Data required[a]	Parameters used	Assumptions	Missing data[b]	Outputs	Existing tools	Countries using it	Key publications
Spectrum	In high-burden epidemic areas: data from sentinel surveillance sites at ANCs, data from population-based surveys (optional). In low-level epidemics: estimates of key population size and surveillance data over time. For all epidemic types: number of men, women and children on ART.	Transition parameters: these include the amount of time a typical HIV+ person spends in each CD4 category, the distribution of new infections by CD4 category, HIV-related mortality by CD4 category without ART, HIV-related mortality on ART by CD4 count at the initiation of treatment, and the effects of HIV infection on fertility.	Transition parameters are correct		Annual number of new infections, HIV prevalence	Yes: http://www.unaids.org/en/dataanalysis/datatools/spectrumepp	Many, worldwide	Bao, Ye and Hallet 2014 (35) Brown et al. 2014 (36) Bao et al. 2012 (37)
Bayesian multistate model (Cambridge method)	Data on new HIV diagnoses over time (both AIDS diagnosis without a previous HIV test and HIV diagnosis). Information on the distribution of CD4 at HIV diagnosis.	Information on HIV progression through CD4 disease stages (from CASCADE cohort)	Data on distribution of CD4 at HIV diagnosis is representative	Missing information on CD4 at HIV diagnosis is at random	Estimates of the number of new infections over time and estimates of time and CD4 stage specific testing rates. Estimates of number of HIV infections undiagnosed by CD4 stage.	R package	UK	Sweeting et al. 2005 (25) Birrell et al. 2011 (38) Birrell et al. 2013 (39) CASCADE, unpublished manuscript
Inserm, Paris Back-calculation method	Data on new HIV diagnoses, including date of diagnosis, demographic information (sex, nationality and HIV exposure category), and clinical status at diagnosis (PHI, AIDS or neither AIDS nor symptoms of PHI)	AIDS incubation time		Missing data can be imputed and underreporting estimated and accounted for	Number of new HIV infections, time between HIV infection and diagnosis	None available to date	France	Ndawinz 2011 (18)

Name of model	Data required[a]	Parameters used	Assumptions	Missing data[b]	Outputs	Existing tools	Countries using it	Key publications
Inserm, Bordeaux method (summing weighted posterior densities of infection times for HIV diagnosed subjects)	Data on new HIV diagnoses, including date of diagnosis, demographic information (sex, nationality and HIV exposure category), and clinical status at diagnosis (PHI, AIDS or neither AIDS nor symptoms of PHI); RITA results; testing history information	Parameters of the estimated model for the dynamics of RITA biomarker(s)		Missing data can be imputed and underreporting estimated and accounted for	Number of new HIV infections	None available to date	France (only simulation results for now)	Sommen et al. 2011 (17)

ANC, antenatal clinic; ART, antiretroviral therapy; ECDC, European Centre for Disease Prevention and Control; FRR, false recent rate; MDRI, mean duration of recent infection; PHI, primary HIV infection; RITA, recent infection testing algorithm; SAS, statistical analysis system; UK, United Kingdom; UNSW, University of New South Wales; US, United States; WB, western blot

[a] Demographic data are needed for all models to enable stratified estimates

[b] For all models: underreporting of new HIV diagnoses will underestimate HIV incidence in previous years

ANNEX 1. AGENDA: MEETING AGENDA

Thursday, 10 December 2015		
Time	**Session**	**Presenter**
08:30–09:00	Participant registration	
09:00–09:20	Welcome remarks, meeting objectives and expected outcome and review of agenda	Txema Calleja
09:20–09:30	Introductions	Group

Session 1	Updates on HIV incidence assay work	
09:30–09:45	Highlights from the 2015 *Technical update on HIV incidence assays for surveillance and monitoring purposes*	Txema Calleja
09:45–10:00	Target product profiles update: case-based surveillance and HIV incidence assays	Stefano Ongarello
10:00–10:15	Incorporation of HIV incidence assays into population-based surveys: crossover issues for case-reporting systems	Kimberly Marsh
10:15–10:30	Development of WHO guidance on case-based surveillance systems and patient monitoring systems	Txema Calleja

Session 2	Incorporating HIV incidence assays into programmes and case-based surveillance systems (Facilitator: Kimberly Marsh)	
10:30–10:50	Incorporating HIV incidence assays into genitourinary medicine clinics in England	Adamma Aghaizu
10:50–11:10	Considerations for incorporating HIV incidence assays in case-based surveillance systems in Central Asia	Andrea Kim
11:10–11:40	Coffee break	
11:40–12:10	Potential contributions of assays for estimating HIV incidence in Democratic Republic of the Congo's (DRC's) prevention of mother to child mother-to-child transmission (PMTCT) programme	Mahesh Swaminathan
12:10–12:30	Opportunities for incidence assay validation and estimation in the ALPHA Network	Basia Zaba
12:30–13:00	Measurement and Surveillance of HIV Epidemics (MeSH) support for HIV surveillance case-reporting guidelines and tools: measuring impact	Brian Rice
13: 00–14:00	Lunch	
14:00–15:30	Group work: Developing recommendations for incorporating HIV incidence assays into HIV case-based and programme surveillance	Txema Calleja
15:30–16:00	Coffee break	

Session 3	Experiences in estimating new HIV infections in HIV case-based surveillance systems (Facilitator: Txema Calleja)	
16:00–16:30	Estimation of HIV incidence in the United States: model development, methods, validation approaches and results	Irene Hall
16:30–17:00	Estimation of HIV incidence in Australia: model development, methods, validation approaches and results	Cliff Kerr

Thursday, 10 December 2015		
Time	Session	Presenter
09:00–09:30	Estimation of HIV incidence in France: model development, methods, validation approaches and results	Stéphane Le Vu
09:30–10:00	Estimation of HIV incidence in the UK: model development, methods, validation approaches and results	Adamma Aghaizu
10:00–10:30	Estimation of HIV incidence in Canada: model development, methods, validation approaches and results	Chris Archibald
10:30–11:00	Estimation of HIV incidence in ECDC: model development, methods, validation approaches and results	Ard van Sighem
11:00–11:30	Coffee break	
11:30–12:00	Estimation of HIV incidence in Brazil: The HIV Modelling Consortium model development, methods, validation approaches and results	Orlando Ferreira
12:00–12:30	Estimation of HIV incidence in Brazil: Fiocruz model development, methods, validation approaches and results	Tara Mangal
12:30–13:00	Estimation of HIV incidence through UNAIDS country support: Avenir Health's Spectrum model development, methods, validation approaches and results	Kimberly Marsh
13:00–14:00	Lunch	
14:00–15:30	General discussion on methods presented and parameters needed and applicability; data requirements for countries	Stéphane Le Vu
15:30–16:00	Coffee break	
16:00–16:30	Next steps and meeting closure	Txema Calleja

ANNEX 2. LIST OF PARTICIPANTS

Dr Adamma Aghaizu
Senior Scientist (Epidemiology)
HIV/STI Surveillance & Prevention
Health Protection Services
Health Protection Agency
London, United Kingdom
Email: adamma.aghaizu@hpa.org.uk

Dr Chris Archibald
Director Surveillance and
Epidemiology
Public Health Canada
Ottawa, Canada
Email: Chris.Archibald@phac-aspc.
gc.ca

Dr Colin Norman John Campbell
Centre d'Estudis Epidemiològics sobre
les
Infeccions de Transmissió Sexual i
Sida
de Catalunya (CEEISCAT)
Hospital Universitari Germans Trias i
Pujol
Badalona, Spain
Email: ccampbell@iconcologia.net

**Dr Orlando Da Costa Ferreira
Junior**
Professor Federal University of Rio
Ministry of Health
Rio de Janeiro, Brazil
Email: orlandocfj@gmail.com

Dr Anindya De
Division of Global HIV and TB (DGHT)
Statistician TBD
Centers for Disease Control and
Prevention (CDC)
Atlanta, United States of America
(USA)
Email: and2@cdc.gov

Dr Daniela De Angelis
Programme Leader
MRC Biostatistics Unit
Institute of Public Health
Cambridge, United Kingdom
Email: daniela.deangelis@mrc-bsu.
cam.ac.uk

Dr Irene Hall
Branch Chief, HIV Incidence and Case
Surveillance Branch
CDC
Atlanta, USA
Email: ixh1@cdc.gov

Dr Cliff Kerr
Senior Research Associate
University of New South Wales
(UNSW)
Sydney, Australia
Email: ckerr@kirby.unsw.edu.au

Dr Andrea Kim
Epidemiologist
CDC
Atlanta, USA
Email: bwd2@cdc.gov

Dr Stéphane Le Vu
Imperial College London
London, United Kingdom
Email: s.le-vu@imperial.ac.uk

Tara Mangal
Research Associate
Imperial College London
London, United Kingdom
Email: t.mangal@imperial.ac.uk

Dr Stefano Ongarello
Senior Biostatitian
Foundation for Innovative New
Diagnostics (FIND)
Geneva, Switzerland
Email: Stefano.Ongarello@finddx.org

Dr Brian Rice
Senior Lecturer
HIV Measurement and Surveillance
Methodology Consortium
London School of Hygiene & Tropical
Medicine (LSHTM)
London, United Kingdom
Email: Brian.Rice@lshtm.ac.uk

Dr Ruiguang (Rick) Song
Mathematical Statistician
CDC
Atlanta, USA
Email: rzs0@cdc.gov

Dr Mahesh Swaminathan
CDC
Atlanta, USA
Email: iyq0@cdc.gov

Dr Ard van Sighem
Senior Researcher
Stichting HIV Monitoring
Amsterdam, The Netherlands
Email: a.i.vansighem@amc.uva.nl

Dr Ping Yan
Research Manager
Public Health Canada
Ottawa, Canada
Email: Ping.Yan@phac-aspc.gc.ca

Dr Basia Zaba
Professor of Medical Demography
LSHTM
London, United Kingdom
Email: Basia.Zaba@lshtm.ac.uk

Partners

Dr Kim Marsh
Epidemiologist Senior Adviser
UNAIDS
Geneva, Switzerland
Email: marshk@unaids.org

WHO Secretariat

Dr Jesus Maria Garcia Calleja
Technical Officer
Strategic Information and Planning
Department of HIV/AIDS
World Health Organization
Geneva, Switzerland
Email: callejaj@who.int

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