Target Product Profile for Tests for Recent HIV Infection

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FIND

Because diagnosis matters

Acknowledgements

This document was prepared by Pete Dailey, Jennifer Osborn and Stefano Ongarello from FIND with input from key stakeholders. Halteres Associates was contracted by FIND to define use cases and draft corresponding target product profiles. These draft target product profiles were revised through multiple rounds of stakeholder feedback from FIND's Target Product Profile Working Group. A target product profile consensus meeting was convened by FIND and the World Health Organization (WHO) as part of a WHO Technical Working Group on HIV Incidence Assays meeting, hosted in Boston, MA, USA on 26 February 2016. A detailed report from the Boston meeting includes the consensus discussion and stakeholder feedback. This document was finalized following consideration of all comments and suggestions by stakeholders and summarizes consensus target product profiles. This work was supported by a grant to FIND from the Bill & Melinda Gates Foundation.

We would like to gratefully acknowledge considerable contributions from Halteres Associates (Mickey Urdea, Laura Penny and David Hendricks) and the Target Product Profile Working Group members Jesus Maria (Txema) Garcia Calleja (WHO), Andrea Kim (CDC), Oliver Laeyendecker (Johns Hopkins University), Kim Marsh (UNAIDS), Michele Owen (CDC), Bharat Parekh (CDC), and the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA), including Michael Busch (Blood Systems Research Institute), Gary Murphy (Public Health England), Christopher Pilcher (UCSF) and Alex Welte (SACEMA). Other key contributors included participants of the stakeholder surveys and the consensus meetings. These individuals are listed in Appendix A.

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Abbreviations

CE	Conformité Européenne (CE marking indicates compliance with EU legislation)
CEPHIA	Consortium for the Evaluation and Performance for HIV Incidence Assays
CDC	U.S. Centers for Disease Control and Prevention
CRFs	Circulating recombinant forms
DBS	Dried blood spots
FRR	False recent ratio
ISO	International organization for standardization
HIV	Human immunodeficiency virus
ILB	International laboratory branch, CDC
MDRI	Mean duration of recent infection
PBMCs	Peripheral blood mononuclear cells
POC	Point of care
RITA	Recent infection testing algorithm
RSE	Relative standard error
RUO	Research use only
SACEMA	South African Centre for Epidemiological Modelling and Analysis
TBD	To be determined
TPP	Target product profile
TWG	Technical Working Group on HIV Incidence Assays (of WHO)
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS

Introduction

HIV incidence is the "fundamental quantity that specifies the current state of the epidemic" *(1)*. HIV incidence tells us where and how much HIV is currently being transmitted – critically important information for effectively targeting HIV prevention interventions and measuring their impact in reducing new infections.

A consensus is forming around the importance of HIV incidence estimates in global reporting. In May 2015, the WHO released new strategic information guidelines detailing a set of 10 key indicators, one of which is HIV incidence *(2)*. These indicators have been prioritized as essential information in the HIV prevention, care, treatment and support continuum. They are aligned to new programmatic recommendations and reflect the future of reporting requirements for measuring progress and for global accountability. In addition, HIV incidence has been proposed as one of the indicators for the newly approved Sustainable Development Goals, which will guide global health and development priorities through 2030.

The purpose of a target product profile (TPP) is to inform product developers of key characteristics and the performance specifications of a test that are required to meet the end user's needs for a defined use case (see Table 1 for examples). TPPs often include an optimal and minimal definition for each test performance characteristic. Ideally, products should be designed to achieve as many of the optimal characteristics as are feasible, while still satisfying the minimal criteria for all defined features.

The first TPP for tests for recent HIV infection was published in 2011 by the Incidence Assay Critical Path Working Group *(3)*. This TPP was intended for the use case of obtaining national population level incidence estimates from cross-sectional surveys using tests for recent HIV infection. As current tests were being evaluated against these product requirements, it was clear that most available tests did not meet the minimal characteristics as defined by the TPP. It was also evident that there were several other use cases of tests for recent HIV infection not described in the TPP. To further define the needs for tests for recent infection, the Bill & Melinda Gates Foundation funded FIND to identify critical use cases, develop a consolidated TPP, and update the previous market assessment *(4)*, published separately, to consider these alternative use cases and identify the anticipated future market for these tests over the next 5-10 years.

Developing target product profiles

The TPP development process is shown in Figure 1. In brief, FIND, working with Halteres Associates, compiled a comprehensive list of use cases after several rounds of key stakeholder interviews. Through this iterative process, eight use cases were identified and are summarized in Table 1.

Target product profiles were developed for each use case. TPPs were then consolidated to the smallest possible number to meet the largest number of use cases, resulting in three consolidated TPPs (TPPs A, B, and C). Another round of stakeholder feedback was solicited from a TPP working

group as part of the governance under the FIND grant. The TPPs were then further refined following stakeholders' feedback. The top 20 key characteristics were identified from the original set of 95.

Table 1: Summary of use cases for tests for recent HIV infection

Use	Description of use
Uses for TRIs related to estimating incidence	
National surveillance	To provide national estimate of incidence; may be part of a broader demographic study[1]
Program, prevention or trial planning	To provide incidence estimates in sub-populations for planning, prioritizing, or other instances when an estimate of incidence is required. Often may be for only a city or region (Example: prioritize programs or investments, or identify sites for intervention trials)
Key or sentinel populations	To provide incidence estimates in special sub-population using targeted sampling methods[2]
Impact assessment	To assess the impact of a population-level intervention (e.g., community-level intervention) by comparing incidence before and after the intervention
Uses for TRIs NOT related to estimating incidence	
Case-based surveillance	To provide national or regional population-level information on recent infections via case-based reporting of newly identified HIV+ individuals[2,3]
Research purposes	Identification of individuals with "recent" infections for multiple potential applications (e.g., recruitment of recently infected individuals into longitudinal cohort studies)
Individual patient management	Identification of patients with recent infections for to guide clinical management and/or public health programs (e.g., selecting therapy, and/or prioritizing contact tracing)
Targeted prevention planning	To provide population-level data on recent infections to enable risk factors analysis or identify hot-spots to inform targeted prevention planning (no incidence estimate is obtained)

[1] Probability sampling methods
[2] Non-probability sampling methods
[3] Testing alone is not used to obtain incidence estimates, though recency test results incorporated into modelling have been used to extrapolate incidence estimates, and methodologies vary greatly by country.

Delphi-like process

To obtain consensus, a Delphi-like process was employed enlisting stakeholder input from 58 content experts, of which 94% had over 10 years of experience in the field of HIV incidence. Stakeholders were surveyed to obtain input on the top 20 key characteristics for the consolidated TPPs A and B. Survey participants were asked to rank their level of agreement based on a Likert

scale ranging from 1 to 5 (1-disagree, 2-mostly disagree, 3-don't agree or disagree, 4-mostly agree, 5-fully agree). Individuals were asked to provide comments when they scored a characteristic at 3 or lower. Consensus was pre-specified as >50% of responders agreeing with the proposed characteristics (Likert Score of 4 or 5). A TPP consensus meeting was held at the 2016 WHO Technical Working Group meeting in Boston, co-hosted by FIND, WHO and UNAIDS. A detailed meeting report summarizes the key survey results and the stakeholder discussion that commenced on TPP characteristics that did not achieve full consensus, and the resulting agreed upon revisions to the TPP documents. In brief, survey results were presented and high priority characteristics were discussed that achieved < 75% consensus. Overall, consensus was achieved for all but once characteristic on TPP A (19 of 20 of TPP A characteristics had > 50% agreement, and 10 of 20 of TPP A characteristics had > 75% agreement) and consensus was achieved for all but two characteristics on TPP B (18 of 20 of TPP B characteristics had > 50% agreement and 12 of 20 of TPP B characteristics had > 75% agreement).

Revisions to characteristics were proposed and discussed at the meeting. A critical output of the consensus meeting was to consolidate TPP A and B into a single TPP that also described the test performance characteristics by use case. Other revisions were also made to the optimal and minimal requirements discussed to incorporate feedback and were vetted by a final survey round from the TPP working group. An overview of the entire TPP development process is summarized in Figure 1.

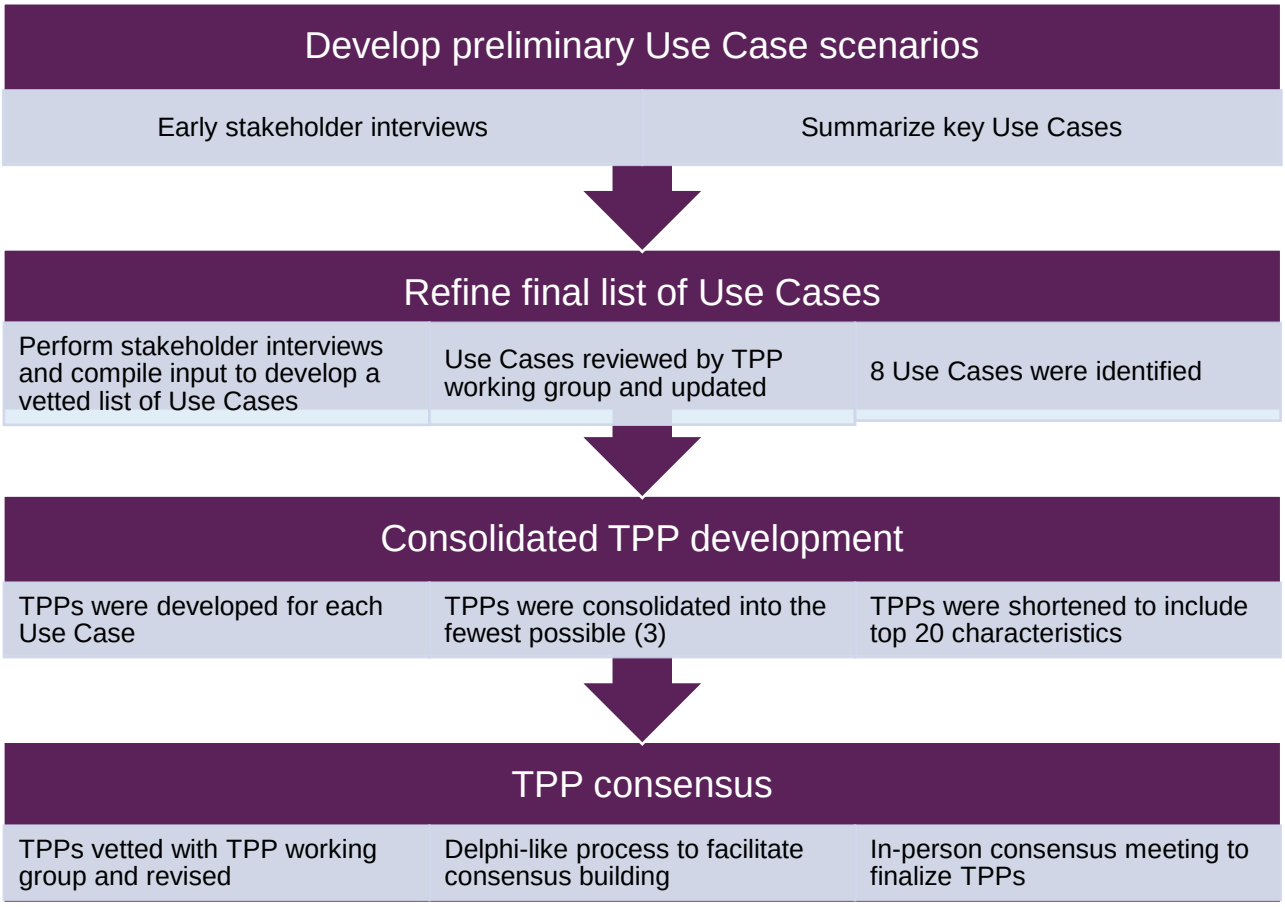

Figure 1: Overview of the TPP development process

Revised target product profile for a test for recent HIV infection at the population or sub-population level

The following intended use for the TPP describes a test to identify recent HIV infection to provide population-level information (national, regional or sub-population) for countries with generalized epidemics or for key or sub-populations with high burden of disease. TPP characteristics listed here apply to all use cases listed (as described in Table 1).

Table 2: Key TPP characteristics
Use description: A test to identify recent HIV infection to provide population-level information (national, regional, or sub-population) for countries with generalized epidemics or for key or sub-populations with high burden of disease. TPP characteristics listed here apply to all use cases listed in Table 1.

Characteristic	Minimal	Optimal
Scope		
Target user	Moderately trained laboratorian (e.g., 1 year certificate)	Same as Minimal Requirement
Infrastructure level	Level 3[1]	Level 1[2]
Assay design, performance and functionality		
Test performance (MDRI/FRR)	Any MDRI/FRR pair that satisfies the maximal allowable sample size to obtain minimal requirements for each use case (see Tables 3 & 4)	Any MDRI/FRR pair that satisfies the maximal allowable sample size to obtain optimal requirements for each use case (see Tables 3 & 4)
Test performance with various HIV subtypes and circulating recombinant forms (CRFs)	Test performance requirements (MDRI/FRR) met for subtypes B & C (does not require subtype identification)	Test performance requirements met for subtypes A, B, C and D and major CRFs including CRF01_AE, CRF02_AG, and other CRFs present in more than 10% of the target population
Supplemental tests in a recent infection testing algorithm (RITA) to achieve desired FRR	Acceptable if other tests are required. Maximum of 3 additional tests, considering preference for lowest cost of the RITA and easy to collect specimens. Preference for supplemental tests that also provide useful information for HIV monitoring (e.g., VL)	Single test for recency determination, no supplemental tests are required.
Specimen handling		
Specimen type	Any of the following are acceptable: whole blood, plasma, serum, DBS (fingerprick), urine, saliva, PBMC OR stool depending on analyte	Easy-to-collect specimen requiring minimal training (e.g., fingerprick blood, DBS)

Characteristic	Minimal	Optimal
Specimen volume	TBD, depending on specimen type and test format, but not to exceed 1 ml. For example, 1 ml for whole blood; 100 - 1000 µl saliva or oral fluid captured via swab, sorbette, or other wicking device; 50 - 1000 µl urine	TBD, depending on test. For example, 10 - 100 µl whole blood from fingerprick or heel stick
Specimen preparation at point of collection	TBD depending on test; requiring maximum of two user-performed steps at point of collection. No quantitative liquid handling steps	No specimen preparation required
Specimen preparation in the laboratory	TBD depending on test. Steps performed in lab procedure amenable to automation to support required throughput (see throughput requirements below)	Same as Minimal Requirement
Stability of specimen between collection and arrival at laboratory	Stable in collection format for 24 hours before arrival at lab. Stabilization at 4°C acceptable	Stable in collection format at ambient temperature for 48 hours before arrival at lab.
Specimen storage conditions at laboratory	- 20°C	Ambient temperature
Time analyte must be stable in specimen storage format	1 year (e.g., specimen storage format such as frozen aliquots or DBS)	~ 10 years
Device characteristics (if instrument is needed)		
Platform design considerations	Dedicated[3] platform/instrument. Design should consider importation, operation, service and support, and waste disposal in sub-Saharan Africa	Multi-purpose[3] platform/instrument. Design should consider importation, operation, service and support, and waste disposal in sub-Saharan Africa
Throughput	Up to 100's per day, with flexibility for smaller batches when needed	Same as Minimal Requirement
User interfaces		
Data input by user	Must support simple method for user to enter data such as specimen/patient identifying information (e.g., alphanumeric keyboard). Must support use of bar codes.	Same as Minimal Requirement

Characteristic	Minimal	Optimal
Data export to user / result interpretation	Reader/instrument required for result interpretation. Data export via USB (e.g., to printer) and via wireless (e.g., to computer, server)	No reader/instrument required for result interpretation. Access to raw data to enable research for alternative data analyses
Other data export (not to user, e.g., performance information for service and maintenance)	Supports local export (e.g., at repair shop) via USB of reports, error messages, or performance information onto memory stick, printer, communication "smart hub" or another device	Real-time connection
Distribution, support and training		
Reagent stability	12 months at 4^0 C or -20°C	18 months with no cold chain required
Shipping conditions	4°C or -20°C (frozen, but no dry ice required). Packaging/shipping provisions should be made for transport stress (e.g., 72 hours at 50°C and uncontrolled humidity)	No cold chain required. Packaging/shipping provisions should be made for transport stress (e.g., 72 hours at 50°C and uncontrolled humidity)
Cost considerations		
Target cost per test (recency test only)	< $10 USD/test	< $5 USD/test
Target instrument/system cost (if required)	Instrument cost <$30,000 USD	Instrument cost <$5,000 USD
Regulatory considerations		
Product registration/regulatory path	Research Use Only (RUO), developed and manufactured per ISO 13485. Standard evaluation of product performance by CEPHIA or other independent body (e.g., CDC ILB) required	CE Mark; approvals in target countries. Standard evaluation of product performance by CEPHIA or other independent body (e.g., CDC ILB) required

[1] Level 3 laboratory – Well equipped laboratory within the developing world with access to automated and advanced equipment, reliable access to electricity and clean water (e.g., national clinical laboratories).
[2] Level 1 laboratory – Not all facilities have a dedicated laboratory. If present, only basic equipment (e.g., microscope, centrifuge) are available, access to electricity or clean water not reliable (e.g., health centre).
[3] Dedicated platform is an instrument for a particular assay, single use application. Multi-purpose platform would allow different assays to be run on the same instrument commonly found in a level 3 laboratory (e.g., plate reader).

Test performance characteristics for tests for recent infection are the mean duration of recent infection (MDRI) in days and the false recent ratio (FRR) as a percentage. Parameters (MDRI/FRR pairs) were identified that achieved maximum feasible sample sizes required to obtain incidence estimates for each use case. Table 3 summarizes the acceptable sample sizes for the minimal and

optimal test performance characteristics by use case. ***Any combination of MDRI/FRR pairs that satisfies the sample size criteria is acceptable.*** Note that the MDRI/FRR pairs listed are examples. A tool is available online to enable calculations of test performance based on the sample populations of interest (http://www.incidence-estimation.org/page/tools).

Table 3: Test performance requirements for use case to obtain incidence estimates

	Incidence Point Estimates			Impact Assessment	
Use case	**National surveillance[1]**	**Program, prevention or trial planning[2]**	**Key or sentinel populations[3]**	**National surveillance[4]**	**Key or sentinel populations[5]**
Use case description	To provide national estimate of incidence; may be part of a broader demographic study	To provide incidence estimate in sub-populations for planning, prioritizing, or other instances when an estimate of incidence is required. Often may be for only a city or region	To provide incidence estimates in special (high incidence) sub-population using targeted sampling methods	Comparing a reduction in incidence before and after an intervention to assess the impact of interventions	
Minimal Criteria					
Maximum sample size	≤ 30,000[6]	≤ 10,000[6]	≤ 1,000	≤ 30,000[6]	≤ 2,000
Test performance MDRI (days) / FRR (%)	120 d / 0.5%[7] 180 d / 1.5% 240 d / 3.0%	180 d / 0. 5% 240 d / 1.5%	150 d / 1.0% 180 d / 3.0%	Not feasible	300 d / 1.25% 330 d / 3.0%
Optimal Criteria					
Maximum sample size	≤ 10,000[6]	≤ 5,000[6]	≤ 500	≤ 10,000[6]	≤ 1,000
Test performance MDRI (days) / FRR (%)	300 d / 0.75% 365 d / 1.0%	330 d / 0.5% 365 d / 1.25%	270 d / 0.25% 300 d / 2.0%	Not feasible	Not feasible

[1] Criteria were established to obtain an estimate of incidence (with RSE 30%) in a population with annual HIV incidence 0.3%, prevalence 5%, design effect for both prevalence of HIV infection and recent infection among positives 1.3. RSE on MDRI estimate: 5%, RSE on FRR estimate: 20%.
[2] Criteria were established obtain an estimate of incidence (with RSE 40%) in a population with annual HIV incidence 0.3%, prevalence 5%, design effect for both prevalence of HIV infection and recent infection among positives 1.3. RSE on MDRI estimate: 5%, RSE on FRR estimate: 20%.
[3] Criteria were established to obtain an estimate of incidence (with RSE 30%) in a population with annual HIV incidence 5%, prevalence 15%, which is on the higher end of most key populations, design effect for both prevalence of HIV infection and recent infection among positives 1.3. RSE on MDRI estimate: 5%, RSE on FRR estimate: 20%.
[4] Criteria were established to detect a change in incidence of 50% in a test population (alpha = 5%, power = 80%, corresponding to a RSE of 35.69%) with 0.3% incidence, 5% prevalence, design effect for both prevalence of HIV infection and recent infection among positives 1.3. RSE on MDRI estimate: 5%, RSE on FRR estimate: 20%.
[5] Criteria were established to detect a change in incidence of 50% in a test population (alpha = 5%, power = 80%, corresponding to a RSE of 35.69%) with 5% incidence, 15% prevalence, which is on the higher end of most key populations, design effect for both prevalence of HIV infection and recent infection among positives 1.3. RSE on MDRI estimate: 5%, RSE on FRR estimate: 20%.
[6] This is the total population screened, assuming the reported incidence only pertains to the 15-49 age group, since 73.5% of the population was considered as the maximal sample size possible.
[7] For all MDRI/FRR pairs shown, only pairs with an FRR ≤ 3% and/or an MDRI ≤ 365 days were considered feasible.

Table 4 summarizes use cases that provide population-level information on recent infections, which are not used to calculate incidence estimates. For these applications, a longer MDRI is recommended, so that a larger number of recent infections are identified in a population as compared to a shorter MDRI. However, since sample sizes vary widely by application, they are not listed here.

Table 4: Test performance requirements for Use Cases not relating to incidence estimation

	Population level use	
Use Case	**Case-based surveillance[1]**	**Targeted prevention planning**
Use Case description	To provide national or regional population-level information on recent infections via case-based reporting of newly identified HIV+ individuals	To provide population-level data on recent infections to enable risk factor analysis or identify hot-spots to inform targeted prevention planning (no incidence estimate is obtained)
Test performance MDRI (days) / FRR (%)	Any MDRI/FRR values that satisfy minimal criteria of national surveillance use case	

[1]Note – testing alone is not used to obtain incidence estimates, though recency test results incorporated into modeling have been used to extrapolate incidence estimates and methodologies vary greatly by country

References

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4. Morrison C, Homan R, Mack N, Seepolmuang P, Averill M, Taylor J, Osborn J, Dailey P, Parkin N, Ongarello S, Mastro TD (2016). Assays for Estimating HIV Incidence: Updated Global Market Assessment and Estimated Economic Value. HIV Research for Prevention (HIVR4P) Conference: Chicago, Ill, Oct 17-21, 2016.

Reference materials

Table 5: Definition of health system infrastructure levels

Characteristics	Level 0	Level 1	Level 2	Levels 3 & 4
Description	In the community or home	Lowest level of healthcare system with a laboratory	First level of referral healthcare & laboratories	Second and higher levels of referral healthcare & laboratories
Examples of locations	In homes, health fairs, health posts, clinics with no lab, pharmacies	Health centres (Africa); rural health centres (Asia and Latin America)	Hospitals (Africa); urban health clinics (Asia and Latin America), clinical labs in developed world	Hospitals (Latin America and Asia) National Clinical Laboratoires (Africa), surveillance laboratories, research laboratories
Electricity	Not reliably available	Not reliably available	Available Expected to have refrigeration	Available
Clean water	Not reliably available	Not reliably available	Available	Available
Physical lab infrastructure & lab equipment	No laboratory	Not all facilities have labs. If present, minimal lab (e.g., microscope, centrifuge) or moderate lab (see Level 2 description)	Moderately equipped lab (e.g., additional equipment for basic chemistry and manual immunoassays)	Well-equipped laboratories (e.g., automated and advanced equipment)
Personnel	Community health-care worker, nurse, family member, pharmacist, traditional medicine practitioner	Nurses, sometimes physicians, laboratorians with a range of training	Nurses, physicians, moderate and well-trained laboratorians	Nurses, physicians, well-trained laboratorians

Appendix A: Participants list

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Appendix B: Glossary

Terms	Definition
Acute HIV infection	The phase of HIV disease immediately after infection during which an initial burst of viremia occurs; anti-HIV antibodies are undetectable at this time while HIV RNA or p24 antigen are present
Avidity	A measure of the strength of a binding reaction, for example between an antibody and an antigen
Biomarker	A measurable biological analyte or variable
Chronic infection	Infection for a period of time longer than *T*
Detuned assay	Modification of an antibody detection assay designed to allow for discrimination between recent and chronic infection (e.g., high dilution, reduced incubation periods, high cutoff)
Delphi-like survey	The Delphi technique is a quantitative option aimed at generating consensus. It solicits opinions from groups in an iterative process of answering questions. After each round the responses are summarized and redistributed for discussion in the next round. Through a process of convergence involving the identification of common trends and inspection of outliers, a consensus is reached. Our process was originally outlined to use the Delphi technique. However, given that high consensus was achieved after a first round, the iterative consensus-building process was not necessary.
Elite controller	HIV-infected (antibody positive) individuals who are able to control infection, reflected by undetectable viral RNA in plasma, without ART
False recent rate	The proportion of individuals in a particular population at a particular time infected for longer than an explicitly specified time cut-off (*T*) with a recent test result
Fiebig stage	Serial stages of acute infection, as defined by the results of an array of readily available (in 2003) laboratory assays for HIV viremia and antibodies
HIV incidence assay	A laboratory procedure that can be used to estimate the incidence of HIV in a defined population
HIV incidence	The number of new HIV cases occurring in a population per person-time at risk, often expressed as an annual rate.
Less sensitive assay	Modification of an antibody detection assay designed to allow for discrimination between recent and chronic infection (e.g., high dilution, reduced incubation periods, high cutoff). Also referred to as “detuned” assay.
Mean duration of recent infection	The average time which individuals spend being classified as ‘recently infected’, while also infected for less than an explicitly specified time cut-off (*T*)
Prevalence	The proportion of individuals in a population who are infected at a given time
Recent infection	A transient period soon after HIV infection. The rate at which the susceptible population enters this transient state is the incidence of HIV infection. Its duration varies between individuals and depends on the method used for detection. Operationally, for the purposes of assay development and calibration, infection for a period of time less than *T.*
Recent infection testing algorithm	A combination of laboratory tests, or combination of test(s) and clinical information, intended to classify individuals as recently or not recently infected, for the purposes of estimating HIV incidence.
Shadow period	A statistical measure of how far back into the past (from the point that the samples were collected) HIV incidence can be estimated using an incidence assay or RITA; or, the expected duration that a person who is classified by an incidence assay or RITA as recently infected has actually been living with HIV infection

Terms	Definition
T	A variable used to denote post-infection time cut-off, separating 'true-recent' from 'false-recent' results; often set at 2 years
Target Product Profile	A set of assay performance characteristics that define minimum acceptable and optimal criteria for a given use case
Test for Recent Infection	A laboratory procedure that reports whether a particular individual was infected within a defined time period or not
Use Case	Description of intended application of an assay
Viral Load	The amount of virus measured as copies of viral RNA per ml plasma. Different assays have different lower limits of detection (e.g., <20 or <40 copies/ml)
Window period	Time between infection and detection of anti-HIV antibodies