HIV/AIDS DIAGNOSTICS TECHNOLOGY LANDSCAPE

SEMI-ANNUAL UPDATE

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Glossary of terms and acronyms

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CE/CE-marking	A mark placed on products in the European Economic Area to indicate that a product conforms to the requirements of European Union directives (CE stands for Conformité Européenne [European Conformity])
CT/NG	*C. trachomatis/N. gonorrhea*
DBS	Dried blood spot
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid (a potassium salt that is contained in blood collection tubes and is a strong anticoagulant)
EID	Early infant diagnosis
EQA	External quality assurance
HCV	*Hepatitis C virus*
HPV	*Human papillomavirus*
HIV	Human immunodeficiency virus
IVD	In vitro diagnostics (tests that can detect diseases, conditions or infections)
MRSA	Methicillin resistant *staphylococcus aureus*
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
USAID	United States Agency for International Development
UPS	Uninterruptible power supply
USB	Universal serial bus
WHO	World Health Organization

Overview

The *HIV/AIDS Diagnostics Technology Landscape* is published annually and is prepared as part of a broad and ongoing effort to understand the technology landscape for HIV/AIDS. This document is a semi-annual update on the point-of-care technologies for CD4, viral load, and early infant diagnosis (EID) testing, as well as for the diagnostic pipeline. **The complete *2014 HIV/AIDS Diagnostics Technology Landscape*, together with previous editions and semi-annual updates, is available at: http://www.unitaid.org/resources/publications/technical-reports.**

Methods

The *HIV/AIDS Diagnostics Landscape* is compiled by Maurine M. Murtagh with support from UNITAID. The material in this landscape was gathered by the author from publicly available information, published and unpublished reports and prospectuses, and interviews with developers and manufacturers. The updates in this document were provided by the developers of these diagnostic technologies. If technologies that appear in the *HIV/AIDS Diagnostics Technology Landscape* do not appear in this update, it is because the supplier either did not provide updates or indicated that there were none available at this time. Information in this report is current as of November 2014, unless otherwise specified.

CD4+ T-Cell counting technologies

Update on point-of-care CD4 technologies

BD FACSPresto™ (*BD Biosciences*)

The CE-IVD marked BD FACSPresto™ (Figure 1) was launched on March 28, 2014 and was WHO prequalified as of late September 2014. The price of the instrument is less than US$ 10 000 and the price per test of the assay is less than US$ 10 in resource-limited settings.

Figure 1. BD FACSPresto™ Platform

Daktari™ CD4 counter (Daktari Diagnostics, Inc.)

Daktari reports that independent validation studies on the Daktari™ CD4 system (Figure 2) were completed in Kenya and Uganda in 2013 and in Kenya and southern Africa in 2014. Additional independent studies are expected in several countries in eastern and southern Africa in 2015. The Daktari™ CD4 system is commercially available and is expected to be CE-IVD marked by 2015.

Figure 2. Daktari™ system

Update on laboratory-based CD4 technologies in the pipeline

BD FACSClearCount™ system (BD Biosciences)

BD Biosciences has recently decided not to pursue the development of the BD FACSClearCount system. However, next generation medium- to high-volume CD4 testing remains a priority for BD.

Update on point-of-care CD4 technologies in the pipeline

Merck Millipore® Muse™ (Merck)

Merck Millipore® has delayed the launch of the Muse Auto CD4/C4% system until the second quarter of 2015. In order to further adapt the Muse system for use in resource-limited settings, the company has enhanced the platform. Additions and improvements to the Muse system include a new laser, electronic grounding system, motherboard and software, including an "Extreme Clean" function. In addition, the system will have two new optional battery UPS systems to power the instrument in the field.

Merck Millipore® intends to test these new features in Cameroon. Once the changes are validated, the company will move forward with clinical trials.

Visitect® CD4 (Burnet Institute and Omega Diagnostics Ltd.)

Omega now plans to conduct further trials of its Visitect® CD4 assay in southern Africa, the United Kingdom and the United States in the first half of 2015. The company intends to seek CE-IVD marking for the assay once successful product evaluations have been completed.

ChipCare-CD4 (ChipCare Corporation)

ChipCare Corporation, which is developing a mobile, easy-to-use, laboratory-quality blood testing platform for CD4 testing has provided an image of the proposed platform (Figure 3). The platform is still anticipated to be available in 2016.

Figure 3. ChipCare hand-held platform

Zyomyx CD4 test (Zyomyx, Inc.)

Due to a lack of funding, the Zyomyx CD4 test is no longer on the market, and Zyomyx has closed down as an operating company.

Viral load testing technologies

Update on laboratory-based viral load technologies

VERSANT® 440 Molecular System (Siemens Healthcare Diagnostics)

Siemens Healthcare Diagnostics has announced that it will discontinue manufacturing its VERSANT® HIV-1 RNA 3.0 Assay as of December 31, 2014.

RT-TMA technology (Real-time transcription mediated amplification) for the Panther® system (Hologic)

The Aptima® HIV-1 Quant Dx Assay on the Panther® system is now CE-IVD marked and is available for sale in the European Union and in other countries that observe CE-IVD marking. Hologic has also submitted a dossier for WHO for prequalification and is pursuing FDA approval for the assay. Dried blood spot (DBS) sampling is also being validated for use with the Panther® system. Pricing will be variable and will depend on variables such as instrument purchase, reagent rental and volume-based pricing.

Update on laboratory-based viral load technologies in the pipeline

VERIS^{MDx} (Beckman Coulter)

Beckman Coulter (hereafter Coulter) has introduced its new fully automated random access molecular diagnostics system, the VERIS MDx (Figure 4). This laboratory-based platform is a sample-to-answer system for the quantitative/qualitative analysis of molecular targets. The VERIS MDx system integrates

the extraction, purification, quantification, and results interpretation of infectious disease nucleic acid targets using polymerase chain reaction (PCR). This includes one-step sample introduction, proprietary bead extraction/purification; eluate transfer and reaction set-up; industry-standard real-time quantitative PCR amplification and detection; and results calculation and reporting.

Figure 4. VERIS^{MDx} system

The VERIS MDx accepts several sample containers for plasma, serum and culture tubes; 48 samples can be lined up on 12 racks of four samples each. The time to result for DNA tests is approximately 70 minutes and for RNA tests is approximately 110 minutes. For multiplex analysis, five different detection colors are available with a bandwidth of 505 to 720 mm. The onboard capacity consists of 96 extraction and purification cartridges and reagents are covered for 20 assays with 48 tests per assay. Reagents are stable in the machine for up to 14 days.

Depending on the assay, the VERIS MDx can process up to 450 samples in 24 hours. The system features walk-away time of at least two hours. The system also includes intuitive graphical touch-screen user interface and has laboratory information systems interface capabilities.

The first assay for the VERIS MDx is the Cytomegalovirus, which is CE-IVD marked. Other assays in development for the VERIS MDx system include quantitative HIV viral load, quantitative hepatitis C virus (HCV), viral load and qualitative *C. trachomatis*/*N. gonorrhea* (CT/NG), *staphylococcus aureus* (MRSA), *C. difficile*, and human papillomavirus (HPV).

Update on point-of-care viral load technologies

SAMBA (Diagnostics for the Real World, Ltd.)

In addition to regulatory approval of the SAMBA viral load assay in Malawi, both the SAMBA EID and viral load assays have recently received product approval in Uganda and Kenya. The assays are currently being evaluated in a number of additional countries in sub-Saharan Africa, including Nigeria.

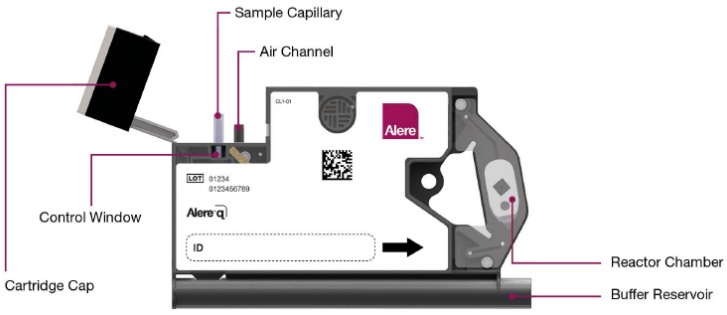
Alere q (Alere)

The Alere q analyser (Figure 5) has been CE-IVD marked since July 2014.

Figure 5. Alere q analyser

The Alere q HIV-1/2 Detect cartridge (Figure 6) is currently undergoing CE-IVD review by an approved notified body per the requirements of the CE marking process. Completion of the review is expected by the end of 2014, with the CE-IVD marked assay for the qualitative detection of HIV-1, including for EID, and HIV-2 available in the first quarter of 2015. The HIV-Detect cartridge and analyser are also currently undergoing the WHO prequalification process.

Figure 6. Alere q test cartridge



The Alere q HIV-1/2 viral load whole blood cartridge is currently available for Investigational Use Only, and is expected to complete CE-IVD marking in 2015.

GeneXpert® system (Cepheid)

The Cepheid GeneXpert® System, which is a fully automated and integrated system for PCR-based nucleic acid testing, currently has 14 FDA-cleared and 19 CE-IVD-approved assays, including tests for enteroviral meningitis, MRSA, *C. difficile*, influenzas A and B, MTB detection and with simultaneous detection of resistance to rifampicin (RIF), CT/NG and group B streptococcus, HPV (simultaneous detection and typing), *Trichomonas vaginalis* and Carba-R (carbapenemase resistance), among others. In addition to the tests listed, Cepheid has 14 tests in active development, including tests for detection and quantification of HIV and quantification of HCV. Any of these tests can be run on virtually all of the more than 7500 GeneXpert® systems placed worldwide.

The GeneXpert® HIV viral load assays are still on track to be launched commercially around the end of 2014. The quantitative HIV-1 assay using plasma and the qualitative HIV-1 assay using either whole blood or DBS are expected to be CE-IVD marked at launch. Clinical studies for the HIV-1 viral load assay have been completed, and the clinical studies for the HIV-1 qualitative assay are in progress.

The company reports that the HIV-1 qualitative assay has a limit of detection of approximately 300 cp/mL for 100 µL of whole blood sample input volume. No special instrumentation or handling is required for the HIV-1 quantitative viral load or the HIV-1 qualitative whole blood assay. A thermomixer is required for the HIV-1 qualitative DBS assay.

The workflow for the HIV-1 quantitative assay consists of: (i) collecting whole blood in acid citrate dextrose (ACD) or EDTA tube; (ii) centrifuging the tube; (iii) transferring 1 mL (pipette provided) directly into the GeneXpert® cartridge; (iv) scanning the cartridge bar code; and (v) loading the cartridge into the GeneXpert® module and closing the door with an approximate 95-minute time to result.

There are two workflows for the HIV-1 qualitative assay. For whole blood: (i) collect whole blood in an EDTA microtainer or tube; (ii) transfer the 750 µl of the sample reagent with the pipette provided directly to the cartridge; (iii) transfer 100 µl with the micropipette provided directly into the cartridge; (iv) scan the cartridge bar code; and (v) load the cartridge into the GeneXpert® module and close the

door with an approximate 95-minute time to result. For DBS: (i) collect DBS with whole blood; (ii) add DBS to the provided sample reagent vial; (iii) place the vial with DBS into a thermomixer and incubate for 15 min at 56°C and rotate at 500 rpm; (iv) transfer all of 1 mL of the mixture (pipette provided) directly into the cartridge; (v) scan the cartridge bar code; and (vi) load the cartridge into the GeneXpert® module and close the door with an approximate 95-minute time to result. An early termination step is included to shorten the time to a positive result for both sample types.

Uptake of the GeneXpert® System via USAID, PEPFAR and other agencies has been escalating rapidly; as of 30 September 2014, a total of 3,504 GeneXpert® instruments (comprising more than 17,000 modules) and more than 8 million GeneXpert® MTB/RIF cartridges have been procured in the public sector in 110 of the 145 countries eligible for concessional pricing. All GeneXpert® tests, including the quantitative and qualitative HIV tests, can be run on the systems placed initially for TB testing.

ZIVA™ (Cavidi)

Cavidi now plans to launch its ZIVA™ system in the 2nd quarter of 2016.

COBAS® Liat System (Roche Molecular Diagnostics)

The COBAS® Liat System is now manufactured by IQuum Inc. for Roche Molecular Diagnostics. The COBAS® Liat System (Figure 7) currently has assays clinically validated and FDA cleared for the detection of influenza A and B strains. Other assays are in development, with the quantitative assay for HIV viral load now anticipated in 2016. Pricing for the platform and assay have not yet been determined.

Figure 7. COBAS® Liat System

NWGHF Savanna viral load test and platform (Northwestern Global Health Foundation and Quidel)

Laboatory evaluations of the Savanna viral load test and platform (Figure 8) are expected to begin in Africa in 2015.

Figure 8. Savanna viral load platform

Early infant diagnostics

Update on point-of-care EID technologies in the pipeline

To date, no point-of-care testing platforms dedicated to early infant diagnosis (EID) have been launched. Below are updates on one of the products in the pipeline.

LYNX HIV p24 antigen assay (Northwestern Global Health Foundation and Quidel)

In 2015, Northwestern Global Health Foundation will: (i) evaluate the laboratory and field performance of the LYNX p24 system with the addition of an automated reader in 2015; (ii) obtain ISO 13485 certification; and (iii) prepare for high volume manufacturing of the LYNX p24 system.

APPENDIX 1: Operational characteristics of CD4, viral load, and early infant diagnosis platforms

Note: Only tables that have been updated from the June 2014 *HIV Diagnostics Technology Landscape* are included here. For a comprehensive catalogue of tables, please see the June 2014 report at: http://unitaid.org/en/resources/publications/technical-reports.

Point-of-care CD4 technologies in the pipeline

BD FACSPresto™	
Type of technology	Small, bench-top, fixed volume cytometer
Output	Absolute CD4, CD4% and Hb
Turnaround time	3–4 minutes reading; plus incubation of cartridge (18 minutes)
Capacity	Maximum of ~60–80 samples per day
Throughput per technician/per day	~50–60 samples per technician per day; flexible throughput capabilities; walk-away operation
Sample needed and stability	~20 µL of capillary (fingerstick) blood wicked directly into BD cartridge or ~20µL of venous blood collected in EDTA anti-coagulant tube. Cartridge must be inserted and tested within two hours of sample application.
Sample preparation and protocol complexity	No sample preparation required. For capillary blood: (i) lancet finger; (ii) apply blood drops to cartridge; (iii) close cartridge; (iv) incubate cartridge; (v) insert cartridge into analyser; (vi) enter patient ID; (vii) read result from LED screen; (viii) print result.
Reagent stability	Dried reagents require no refrigeration. Stable for 12 months at 10–31°C
Cost/test	<US$ 10 in resource-limited settings
Cost/instrument	<US$ 10 000 in resource-limited settings
Regulatory status	CE-IVD marked; U.S. FDA 510(k) will follow; WHO prequalified
Physical dimensions (cytometer only) (L x H x D)	Length: ~26 cm (10.2 inches) Height: ~28.5 cm (11.2 inches) Depth: ~25 cm (9.8 inches)
Weight	~7 kg (~15 lbs) (instrument only)
3rd party supplies	For venous samples: transfer pipette For capillary samples: sterile lancets, alcohol swabs, cotton gauze, Band Aid
Electric Power requirements	100 to 240 V (A/C) at 45–65 Hz mains power Analyser contains on-board rechargeable battery. Can be charged with cigarette lighter.
Environmental requirements	• Operating Temperature: 10–40°C (50–104°F) (ongoing validation) • Humidity: 5–95% (ongoing validation) • Maximum altitude: 2500 meters (8200 feet) (ongoing validation)
Data station	Dedicated CPU integrated into instrument; approximately 1000 test results can be stored on the instrument archive; results can be downloaded via USB. The USB port also can be used to support an external blue tooth or GPRS/GSM module to communicate with SMS printer or the port would be developed but not enabled, providing an option for wireless to be enabled post launch. Potential to install an SMS chip to transmit results or internal calibration data.
Monitor	LED multi-colour screen integrated into instrument
Printer	On board printer (prints on thermal paper)
Bar-code scanner	Integrated into instrument for test cartridges only
Training	Minimal training required. Lay person can be trained in less than half a day. Primary skill required is for correct lancet blood draw.

Table continued on next page

Maintenance	Analyser contains an integrated camera and microscope that might be susceptible to damage if dropped. If damaged, low cost and portability of device allows for direct swap-out replacement rather than on-site repair.
Internal QC	Yes. Instrument will check itself each day and each cartridge will have onboard QC.
External QA	Will be compatible with CD4 EQA programs (ongoing validation)
Infrastructure requirements	Can be used at all levels of health facility, including health centres or in mobile facilities.
User interface	Touch screen keyboard on the device

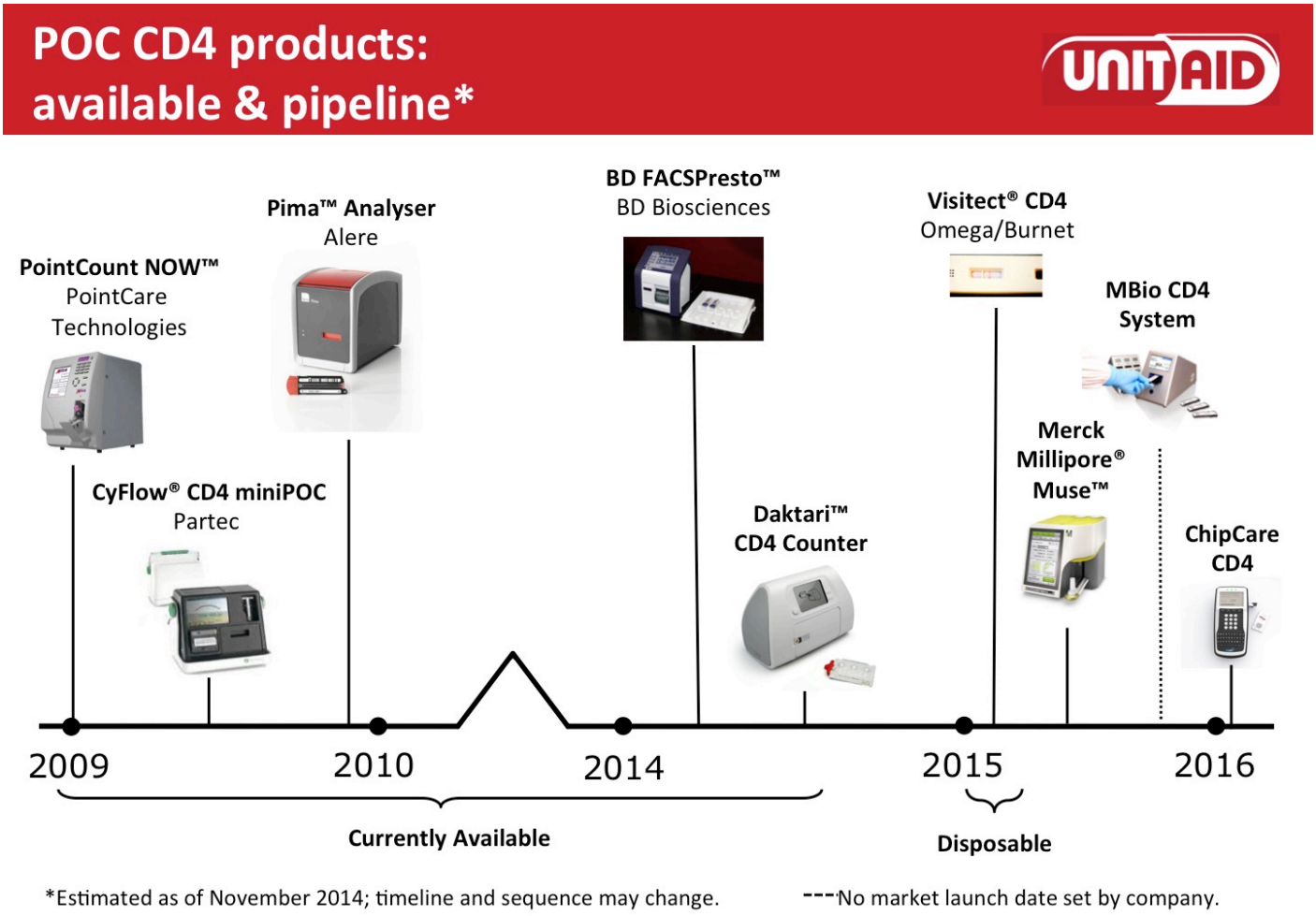
Point of care viral load technologies in the pipeline

NWGHF/Quidel Savanna HIV Viral Load Test and Platform	
Type of technology	A bench-top automated cartridge-based system that extracts, amplifies and detects nucleic acid targets for IVD applications
Output	Quantitative HIV-1
Turnaround time	~60–90 minutes
Capacity	The processor will accommodate 13 tests per 8-hour work day
Throughput per technician/per day	13 tests per 8-hour work day
Sample needed and stability	To achieve 1000 copies/mL of plasma, ~165 µL of whole blood will be converted into plasma with simple sample preparation materials provided by NWGHF
Sample preparation and protocol complexity	(i) Add sample to mini-cartridge; (ii) close sample port and cap to seal mini-cartridge; (iii) place the mini-cartridge into sample prep device for 2–3 minutes; (iv) remove mini-cartridge from sample prep device and attach to cartridge; (v) place cartridge onto the loading/unloading position on the system; (vi) read the results on the screen.
Reagent stability	The shelf life of the assay kit is expected to be 12–18 months at 30–40°C, 70%-90% humidity
Cost/test	<US$ 10 per test
Cost/instrument	<US$ 12 000
Regulatory status	TBD
Physical dimensions (W x H x D)	Width: 24.1 cm (9.5 inches) Height: 59.7 cm (23.5 inches) Depth: 62.2 cm (24.5 inches)
Weight	TBD
3rd party supplies	Blood collection supplies
Electric power requirements	The processor is powered by an external power transformer that connects to either an AC or DC power cable that connects to an AC or DC power socket in the clinic or laboratory. A fully-charged battery will complete the cartridges in the processor.
Environmental requirements	No cold chain or humidity control is required for shipping and transport
Data station	Internal EDGE/3G modem provided upon request
Monitor	Integrated into the instrument
Printer	Optional
Bar-code scanner	Integrated into the instrument
Training	Minimal training required; primary skill required is for correct lancet blood draw.
Maintenance	Minimal maintenance
Internal QC	Yes
External QA	Will be fully-compatible with existing EQA programs
Infrastructure requirements	Can be used at all levels of health facility, including health centres or in mobile facilities
User interface	On-board display

Point-of-care early infant diagnosis technologies in the pipeline

NWGHF LYNX HIV p24 Antigen Test (EID)	
Type of technology	p24 Antigen Assay for EID
Output	Qualitative detection of HIV infection
Turnaround time	51 minutes
Capacity	1 sample tested sequentially
Throughput per technician/per day	~12 samples per day
Sample needed and stability	~80 µL of blood from the infant's heel
Sample preparation and protocol complexity	(i) Prick infant's heel and collect blood; (ii) separate plasma from red blood cells; (iii) add buffer and heat; (iv) insert test strip into sample processor and wait 30 - 40 minutes; (v) read test
Reagent stability	TBD
Cost/test	Estimated to be: US$ 7–15 per test, depending on volume
Cost/instrument	~US$ 700–2 000 for sample processor, depending on volume
Regulatory status	Pending
Physical dimensions (W x H x D)	Width: 202mm (8.0 inches) Height: 156mm (6.1 inches) Depth: 134mm (5.3 inches)
Weight	1.7 kg (~3.7 lbs)
3rd party supplies	None
Electric Power requirements	Sample processor is battery powered with 12 V DC (e.g., solar or car battery) or 100–240 VAC recharging
Environmental requirements	TBD
Data station	TBD
Monitor	None
Printer	No printer provided
Bar-code scanner	None
Training	Minimal training required; primary skill required is for correct lancet blood draw.
Maintenance	Test is disposable; sample processor is expected to last three years with original battery; life can be extended to five years if battery is swapped out
Internal QC	Yes
External QA	In process of determining whether compatible with EQA programs
Infrastructure requirements	Can be used at all levels of health facility, including health centres or in mobile facilities.
User interface	Display with timer and battery indicator

APPENDIX 2: Point-of-care CD4 technologies in the pipeline



APPENDIX 3: Point-of-care viral load and EID technologies in the pipeline