Xpert for PLHIV: Scaling Up Through a Joint TB and HIV Services Platform

6th Global Laboratory Initiative Partners Meeting
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World Health Organization

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Outline

- Value of Xpert in diagnosing TB in people living with HIV (PLHIV)
- HIV scale up and laboratory services
- Challenges to existing approaches
- Way forward and conclusions

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HIV-Associated TB

- People living with HIV (PLHIV) have a 30-fold increased risk of TB compared to HIV-uninfected people
- Diagnosing TB is challenging among PLHIV
- This causes delays in detection and treatment of TB
- High mortality for HIV-associated TB

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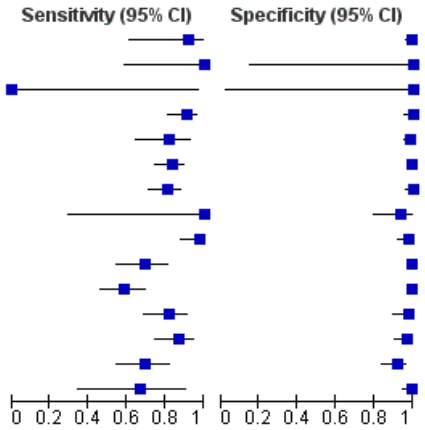
WHO Recommendation

Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test for pulmonary and extrapulmonary TB in both adults and children living with HIV

Xpert MTB/RIF for the diagnosis of pulmonary TB in PLHIV

HIV positive

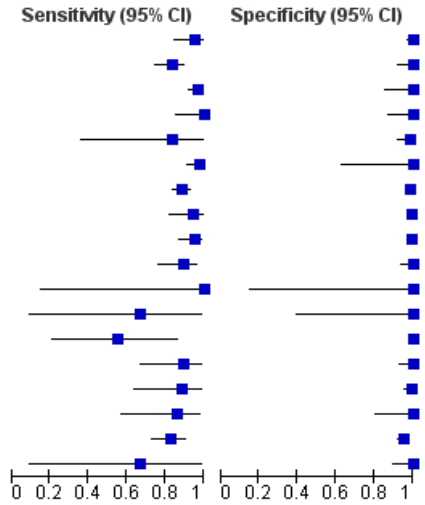
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Boehme 2010a	7	0	0	2	1.00 [0.59, 1.00]	1.00 [0.16, 1.00]
Boehme 2010b	0	0	1	1	0.00 [0.00, 0.97]	1.00 [0.03, 1.00]
Boehme 2010c	60	0	6	81	0.91 [0.81, 0.97]	1.00 [0.96, 1.00]
Boehme 2010d	27	2	6	141	0.82 [0.65, 0.93]	0.99 [0.95, 1.00]
Boehme 2011c	90	1	18	263	0.83 [0.75, 0.90]	1.00 [0.98, 1.00]
Boehme 2011d	80	0	19	88	0.81 [0.72, 0.88]	1.00 [0.96, 1.00]
Boehme 2011e	3	2	0	31	1.00 [0.29, 1.00]	0.94 [0.80, 0.99]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Hanrahan 2013	36	2	16	325	0.69 [0.55, 0.81]	0.99 [0.98, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Rachow 2011	41	1	9	49	0.82 [0.69, 0.91]	0.98 [0.89, 1.00]
Scott 2011	45	3	7	84	0.87 [0.74, 0.94]	0.97 [0.90, 0.99]
Theron 2011	32	7	14	77	0.70 [0.54, 0.82]	0.92 [0.84, 0.97]
Van Rie 2013	8	1	4	99	0.67 [0.35, 0.90]	0.99 [0.95, 1.00]



HIV-positive subgroup
Pooled sensitivity = 79% (70,86)
Pooled specificity = 98% (96, 99)

HIV negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	42	0	2	127	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Boehme 2010a	90	0	18	46	0.83 [0.75, 0.90]	1.00 [0.92, 1.00]
Boehme 2010b	142	0	5	24	0.97 [0.92, 0.99]	1.00 [0.86, 1.00]
Boehme 2010c	23	0	0	26	1.00 [0.85, 1.00]	1.00 [0.87, 1.00]
Boehme 2010d	5	1	1	69	0.83 [0.36, 1.00]	0.99 [0.92, 1.00]
Boehme 2010e	75	0	2	8	0.97 [0.91, 1.00]	1.00 [0.63, 1.00]
Boehme 2011a	161	3	20	252	0.89 [0.83, 0.93]	0.99 [0.97, 1.00]
Boehme 2011b	36	1	2	202	0.95 [0.82, 0.99]	1.00 [0.97, 1.00]
Boehme 2011c	62	1	3	232	0.95 [0.87, 0.99]	1.00 [0.98, 1.00]
Boehme 2011d	41	0	5	56	0.89 [0.76, 0.96]	1.00 [0.94, 1.00]
Boehme 2011e	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Boehme 2011f	2	0	1	4	0.67 [0.09, 0.99]	1.00 [0.40, 1.00]
Hanrahan 2013	5	0	4	182	0.56 [0.21, 0.86]	1.00 [0.98, 1.00]
Rachow 2011	17	0	2	53	0.89 [0.67, 0.99]	1.00 [0.93, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	12	0	2	17	0.86 [0.57, 0.98]	1.00 [0.80, 1.00]
Theron 2011	68	9	14	195	0.83 [0.73, 0.90]	0.96 [0.92, 0.98]
Van Rie 2013	2	0	1	33	0.67 [0.09, 0.99]	1.00 [0.89, 1.00]



Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review), Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N, ***The Cochrane Library, 2014, Issue 1***

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Advantages of Xpert for PLHIV

- Xpert MTB/RIF increases detection of HIV associated TB (45-47%)
- Lawn 2011; Taye 2014
- Xpert MTB/RIF improved the quality of TB diagnosis
- Scott 2011; Theron 2011; O'Grady 2012; Yoon 2012
- Xpert MTB/RIF facilitated earlier diagnosis and reduced time-to-initiation of TB treatment
- Yoon 2012; Bygrave 2012
- Modelling show Xpert to be cost-effective in reducing early mortality among PLHIV
- Abimbola 2012; Andrews 2012
- Xpert reduces indirect cost of TB diagnosis
- Antunes 2014
- Xpert projected to reduce TB prevalence and mortality in HIV prevalence settings
- Menzies 2012

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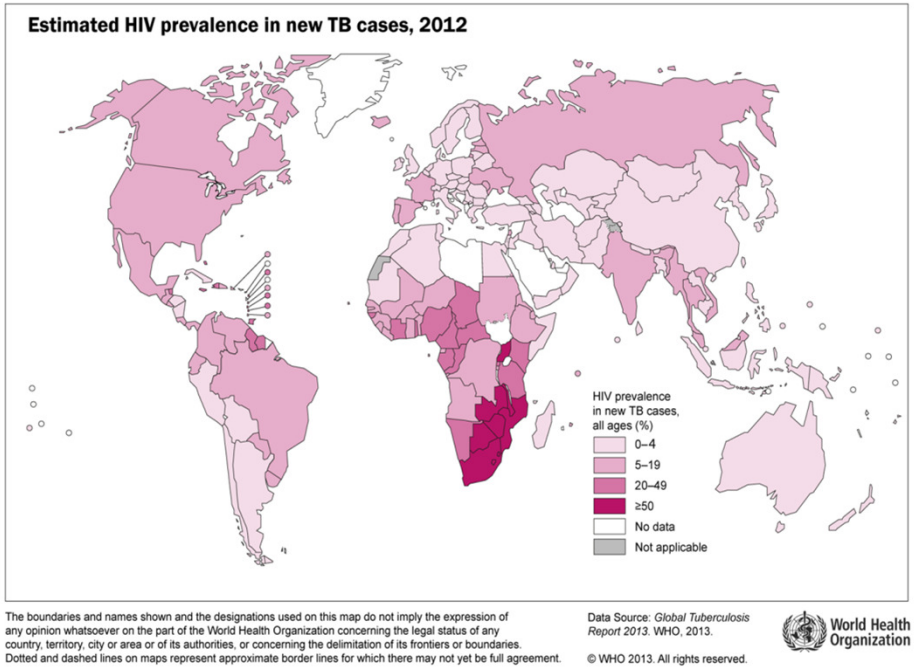
Xpert MTB/RIF is a tool to diagnose HIV-associated TB in addition to MDR-TB

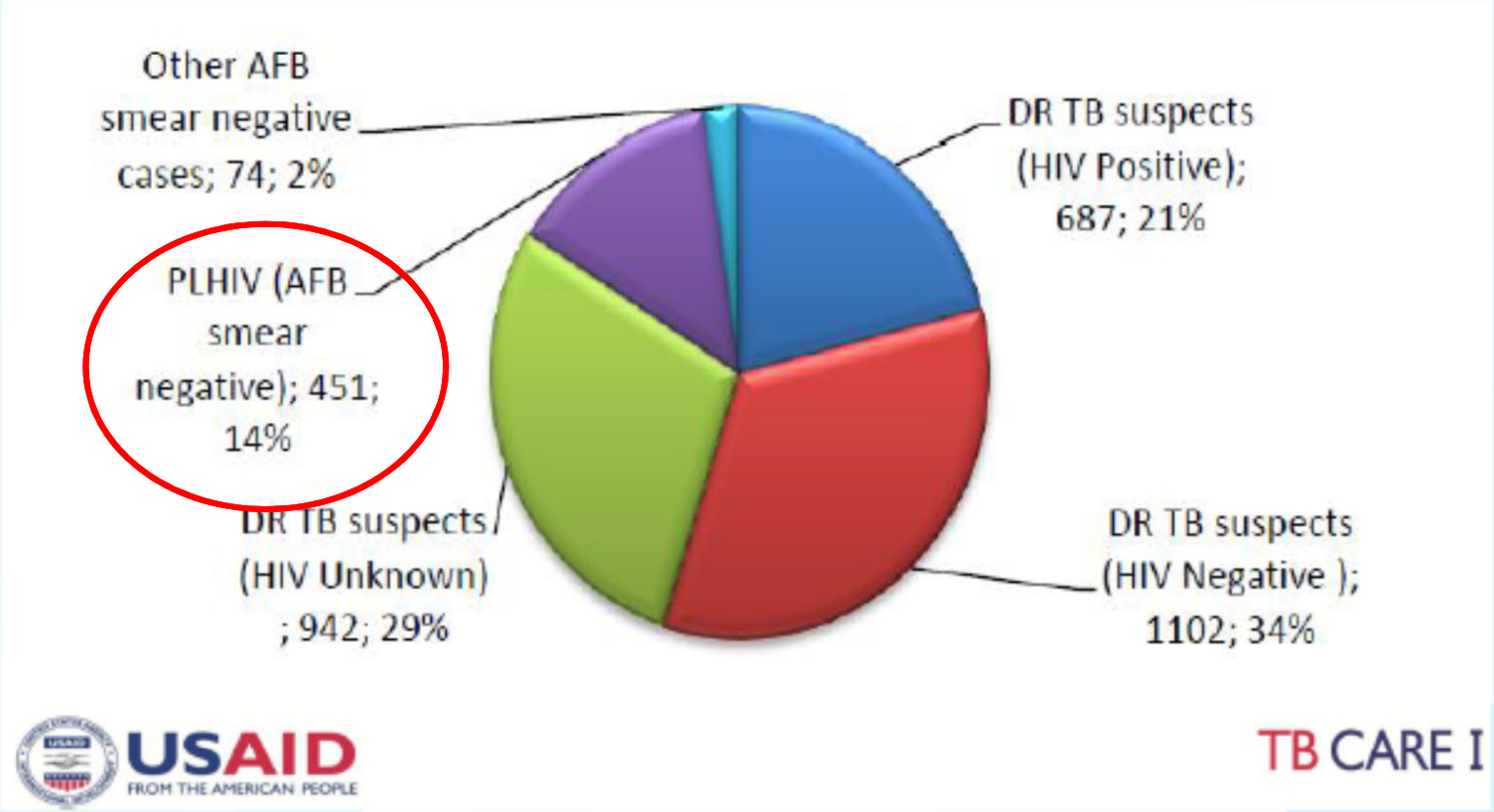
Country	MDR-TB cases*	HIV-associated TB cases**
DR Congo	2,900	16,000
Ethiopia	2,100	23,000
South Africa	8,100	330,000



** Estimates among notified pulmonary TB cases*

*** Estimated incident TB cases in PLHIV*

Initial Testing Algorithms Focused on Presumptive MDR TB Cases



Xpert MTB/RIF testing at 9 sites in Nigeria (January – December 2012)

* www.tbcare1.org/publications/toolbox/tools/lab/TB_CARE_I_GeneXpert_Core_Project_Final_Report.pdf

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Challenges for TB diagnosis in HIV Care Settings

- One patient with 2 parallel care systems
  - Services increasingly integrated, but gaps remain
  - Inadequate referrals and linkages
- Data reporting systems
  - Parallel systems, limited ability to capture Xpert results routinely
  - Intensified TB Case Finding (ICF) activities poorly documented
  - Limited ability to track longitudinal cascade of care
- Coordination among donors, partners, MOH and other stakeholders
- Inefficiency in a resource-constrained environment

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HIV Scale Up and Role of Laboratory Services

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WHO 2013 Consolidated ARV Guidelines

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Clinically relevant

- **Earlier initiation of ART** (CD4 ≤ 500)
- **Immediate ART for children below 5 years**
- **ART for all pregnant and breastfeeding women** (Option B/B+)
- Simplified, fewer, and less toxic 1st-line regimens **(TDF/XTC/EFV)**

Operationally relevant

- Use of **Fixed Dose Combinations**
- Improved patient monitoring with **increased use of viral load**
- Recommend **task shifting, decentralization, and integration**
- **Community based testing and ARV delivery**

Guidance on Operations and Service Delivery

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GUIDANCE ON

OPERATIONS AND SERVICE DELIVERY

09

- Adherence to ART
- Retention across the continuum of care
- Service delivery
  - Integration & linkage
  - Decentralization
- Task shifting
- Laboratory and diagnostic services
- Procurement and supply management

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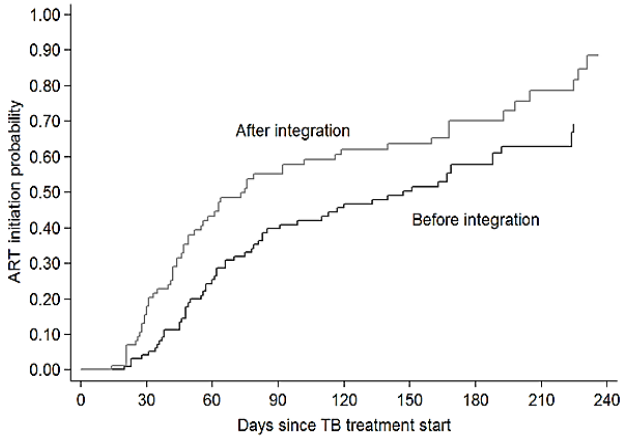
Service Integration: Responding to Co-morbidities and Multiple Needs



WHO 2013 Recommendations:
Initiate and maintain ART in :

- TB care settings
- MCH/ANC settings
- Opioid Substitution Therapy (OST) settings with linkage to continued HIV care and treatment

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Recommendations: Monitoring for ART Response

RECOMMENDATION	STRENGTH
Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure	***Strong recommendation, low-quality evidence*** NEW
If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure	***Strong recommendation, moderate-quality evidence***

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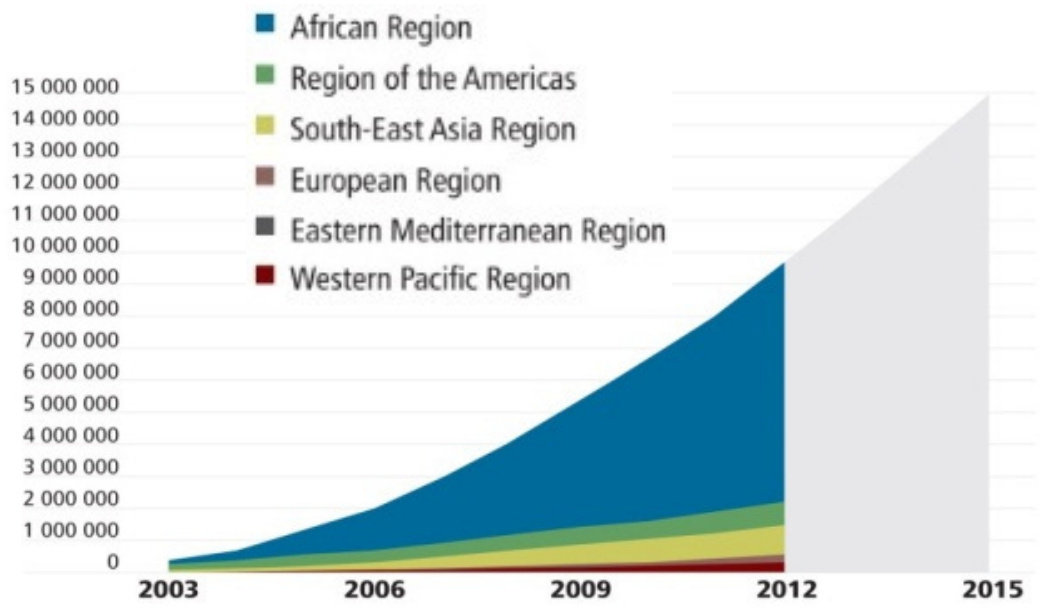
Global Access to Treatment

Actual and projected numbers of people receiving antiretroviral therapy in low-and middle-income countries, and by WHO Region, 2003–2015



- Nearly **10 million** people on ART by end of 2012
- 1.6 million in one year
- Africa region with greatest rate of increase
- Coverage 68% for adults while only 34% for children
- Coverage not uniform - certain regions and populations left behind (key populations)

WHO, Global Treatment Report 2013

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Scale up of HIV services Has Required Scale Up of Lab Systems

Type	Point-of-Care (POC) Available?	Availability
HIV diagnosis (antibody testing)	Yes	Widely available
HIV diagnosis (molecular) Early infant diagnosis (DNA, RNA, TNA, ultrasensitive p24)	In development	Use of dried-blood spots (DBS) has increased availability
Patient monitoring	CD4—yes, PIMA VL—in development	Use of DBS specimens
Toxicity monitoring (Hb, creatinine, chemistry, LFTs)	Needed	Variable
Diagnosis of opportunistic infections	Xpert, syphilis and malaria, rapid tests	Variable
HIV drug resistance surveillance	No	Periodic surveys recommended
Support to lab systems	n/a	Quality assurance, support for national strategic lab plans and a tiered laboratory network, human resource capacity building

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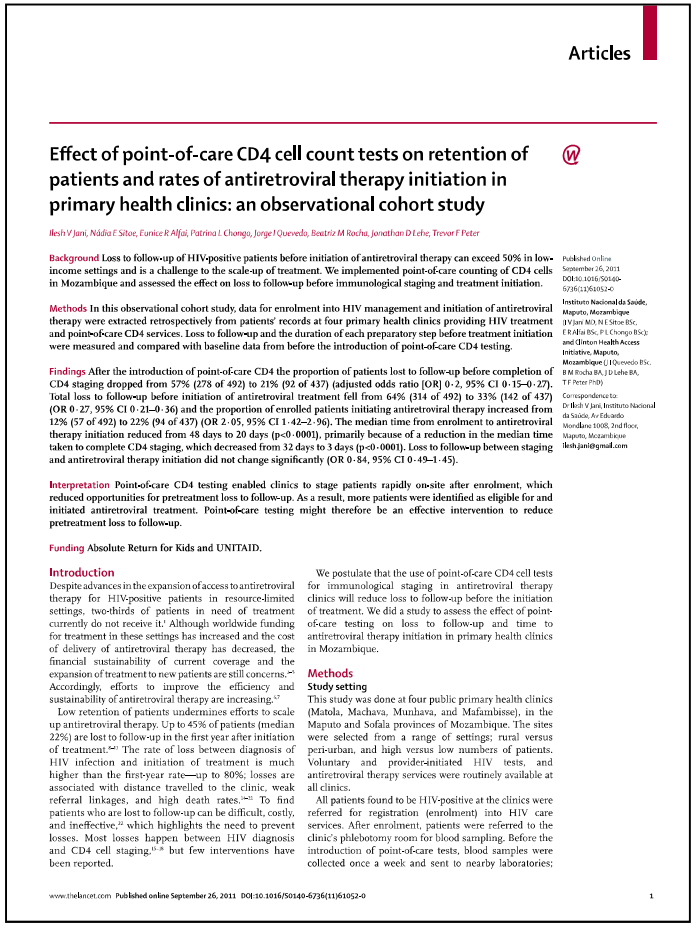
Impact of PoC CD4 on linkage/retention in HIV care



Articles

Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study

Ilesh V Jani, Nádia F Sitoe, Eunice R Alfai, Patrina L Chongo, Jorge I Quevedo, Beatriz M Rocha, Jonathan D Lehe, Trevor F Peter

Background Loss to follow-up of HIV-positive patients before initiation of antiretroviral therapy can exceed 50% in low-income settings and is a challenge to the scale-up of treatment. We implemented point-of-care counting of CD4 cells in Mozambique and assessed the effect on loss to follow-up before immunological staging and treatment initiation.

Methods In this observational cohort study, data for enrolment into HIV management and initiation of antiretroviral therapy were extracted retrospectively from patients' records at four primary health clinics providing HIV treatment and point-of-care CD4 services. Loss to follow-up and the duration of each preparatory step before treatment initiation were measured and compared with baseline data from before the introduction of point-of-care CD4 testing.

Findings After the introduction of point-of-care CD4 the proportion of patients lost to follow-up before completion of CD4 staging dropped from 57% (278 of 492) to 21% (92 of 437) (adjusted odds ratio [OR] 0·2, 95% CI 0·15–0·27). Total loss to follow-up before initiation of antiretroviral treatment fell from 64% (314 of 492) to 33% (142 of 437) (OR 0·27, 95% CI 0·21–0·36) and the proportion of enrolled patients initiating antiretroviral therapy increased from 12% (57 of 492) to 22% (94 of 437) (OR 2·05, 95% CI 1·42–2·96). The median time from enrolment to antiretroviral therapy initiation reduced from 48 days to 20 days (p<0·0001), primarily because of a reduction in the median time taken to complete CD4 staging, which decreased from 32 days to 3 days (p<0·0001). Loss to follow-up between staging and antiretroviral therapy initiation did not change significantly (OR 0·84, 95% CI 0·49–1·45).

Interpretation Point-of-care CD4 testing enabled clinics to stage patients rapidly on-site after enrolment, which reduced opportunities for pretreatment loss to follow-up. As a result, more patients were identified as eligible for and initiated antiretroviral treatment. Point-of-care testing might therefore be an effective intervention to reduce pretreatment loss to follow-up.

Funding Absolute Return for Kids and UNITAID.

Introduction

Despite advances in the expansion of access to antiretroviral therapy for HIV-positive patients in resource-limited settings, two-thirds of patients in need of treatment currently do not receive it.[1] Although worldwide funding for treatment in these settings has increased and the cost of delivery of antiretroviral therapy has decreased, the financial sustainability of current coverage and the expansion of treatment to new patients are still concerns.[2–5] Accordingly, efforts to improve the efficiency and sustainability of antiretroviral therapy are increasing.[5–7]

Low retention of patients undermines efforts to scale up antiretroviral therapy. Up to 45% of patients (median 22%) are lost to follow-up in the first year after initiation of treatment.[8–10] The rate of loss between diagnosis of HIV infection and initiation of treatment is much higher than the first-year rate—up to 80%; losses are associated with distance travelled to the clinic, weak referral linkages, and high death rates.[7–11] To find patients who are lost to follow-up can be difficult, costly, and ineffective,[12] which highlights the need to prevent losses. Most losses happen between HIV diagnosis and CD4 cell staging,[11,13] but few interventions have been reported.

We postulate that the use of point-of-care CD4 cell tests for immunological staging in antiretroviral therapy clinics will reduce loss to follow-up before the initiation of treatment. We did a study to assess the effect of point-of-care testing on loss to follow-up and time to antiretroviral therapy initiation in primary health clinics in Mozambique.

Methods

Study setting

This study was done at four public primary health clinics (Matola, Machava, Munhava, and Mafambisse), in the Maputo and Sofala provinces of Mozambique. The sites were selected from a range of settings; rural versus peri-urban, and high versus low numbers of patients. Voluntary and provider-initiated HIV tests, and antiretroviral therapy services were routinely available at all clinics.

All patients found to be HIV-positive at the clinics were referred for registration (enrolment) into HIV care services. After enrolment, patients were referred to the clinic's phlebotomy room for blood sampling. Before the introduction of point-of-care tests, blood samples were collected once a week and sent to nearby laboratories;

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Instituto Nacional da Saúde, Maputo, Mozambique (I V Jani MD, N F Sitoe BSc, E R Alfai BSc, P L Chongo BSc); and Clinton Health Access Initiative, Maputo, Mozambique (J I Quevedo BSc, B M Rocha BA, J D Lehe BA, T F Peter PhD)

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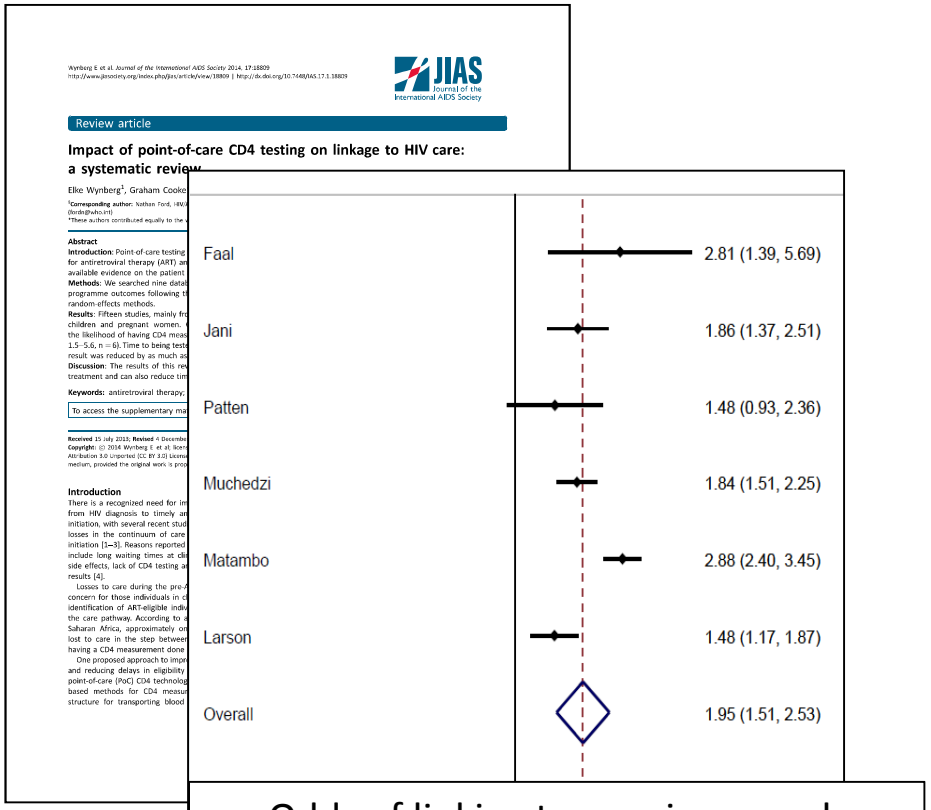

Wynberg E et al. Journal of the International AIDS Society 2014, 17:18809
http://www.jiasociety.org/index.php/jias/article/view/18809 | http://dx.doi.org/10.7448/IAS.17.1.18809

JIAS Journal of the International AIDS Society

Review article

Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review

Elke Wynberg[1], Graham Cooke

Abstract

Introduction: Point-of-care testing

Methods: We searched nine datab

Results: Fifteen studies, mainly fr

Discussion: The results of this re

Keywords: antiretroviral therapy;

To access the supplementary ma

Received 15 July 2013; Revised 4 Decembe

Introduction

There is a recognized need for im

initiation, with several recent stud

losses in the continuum of care

initiation [1–3]. Reasons reported

include long waiting times at cli

side effects, lack of CD4 testing a

results [4].

Losses to care during the pre-A

concern for those individuals in C

identification of ART-eligible indiv

the care pathway. According to e

Saharan Africa, approximately on

lost to care in the step between

having a CD4 measurement done

One proposed approach to impr

and reducing delays in eligibility

point-of-care (PoC) CD4 technolog

based methods for CD4 measur

structure for transporting blood

- Odds of linking to care increased
- Time to testing reduced by 9 days
- Time from testing to receiving the result was reduced by 17 days

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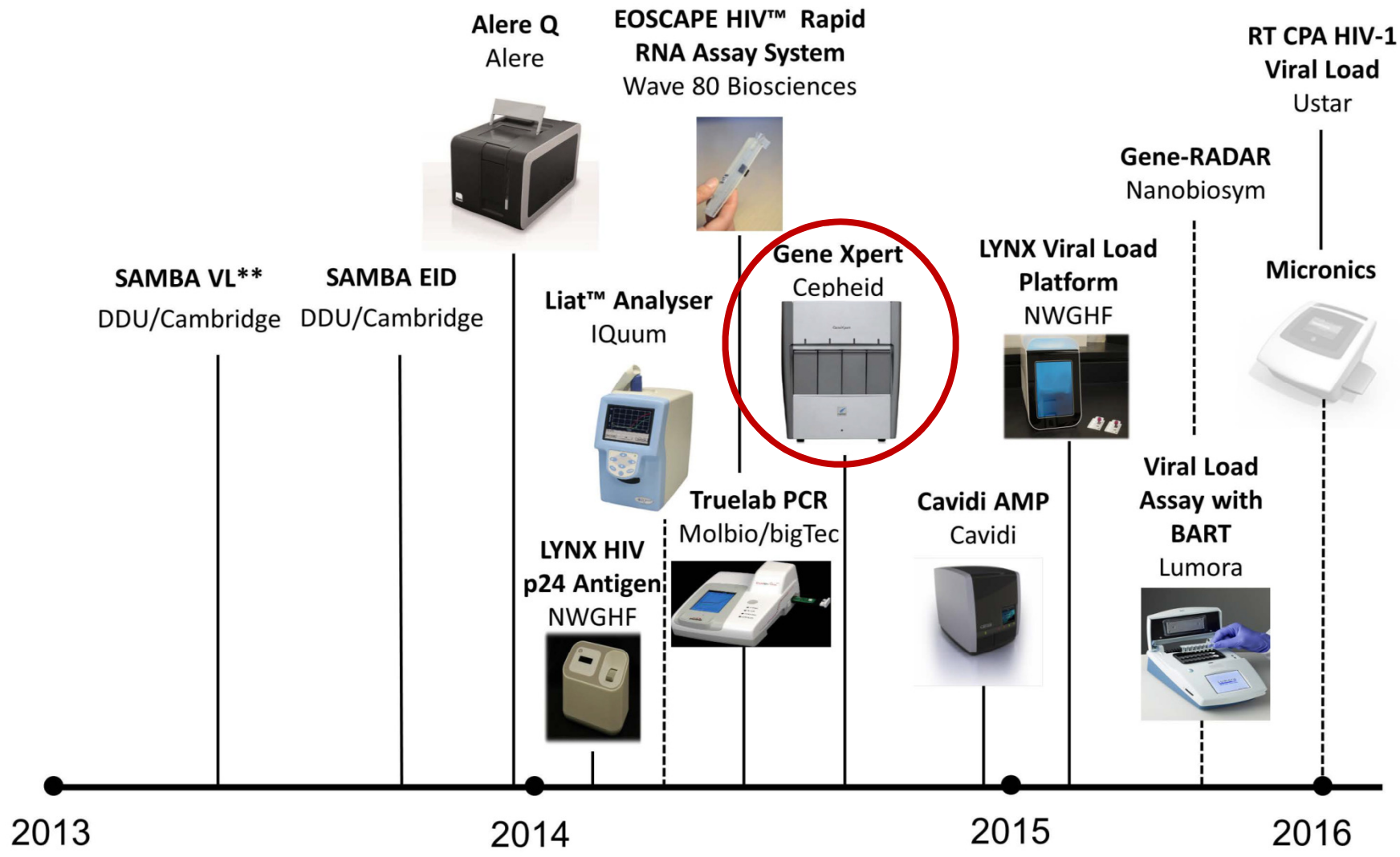
POC viral load & EID products: available and pipeline*



*Estimated as of October 2013 - timeline and sequence may change. ---- No market launch date set by company.
**Available in limited release.

Source: UNITAID, HIV/AIDS Diagnostics Technology Landscape, November 2013

Challenges to existing approaches

Future areas of WHO work

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Operational Challenges

- Low coverage and poor laboratory infrastructure
- Role of point-of-care testing vs. conventional testing
- Poor linkage to treatment services and unclear data on patient outcomes
- Specimen transport and results return
- Quality and reliability of test results
- How to maximize investments and achieve efficiency gains

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Operational Challenges

- Low coverage and poor laboratory infrastructure
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- Quality and reliability of test results
- How to maximize investments and achieve efficiency gains

Programmes, together with WHO and partners are actively working to address these issues

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Way Forward and Conclusions

- Xpert must be seen as essential diagnostic test for PLHIV
- All programs (TB, HIV, Lab) must work together
- Dynamic development of new platforms and strategies offers many new opportunities—single molecular platform for testing in a few years?
- Partnerships and funding

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- Alberto Matteelli

Example from Mozambique—Point-of-care CD4

Where to Place POC Devices?

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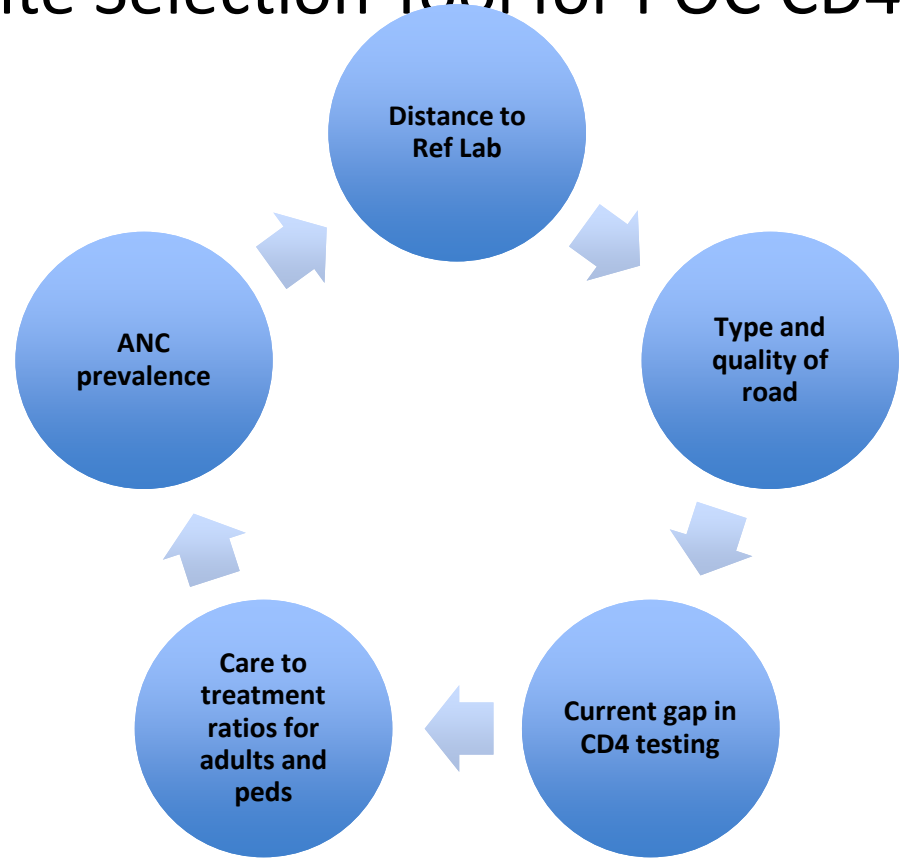
e.g. Site Selection Tool for POC CD4 Devices

Information and metrics from sites are entered into the selection tool in a workshop between national and local authorities, and main stakeholders

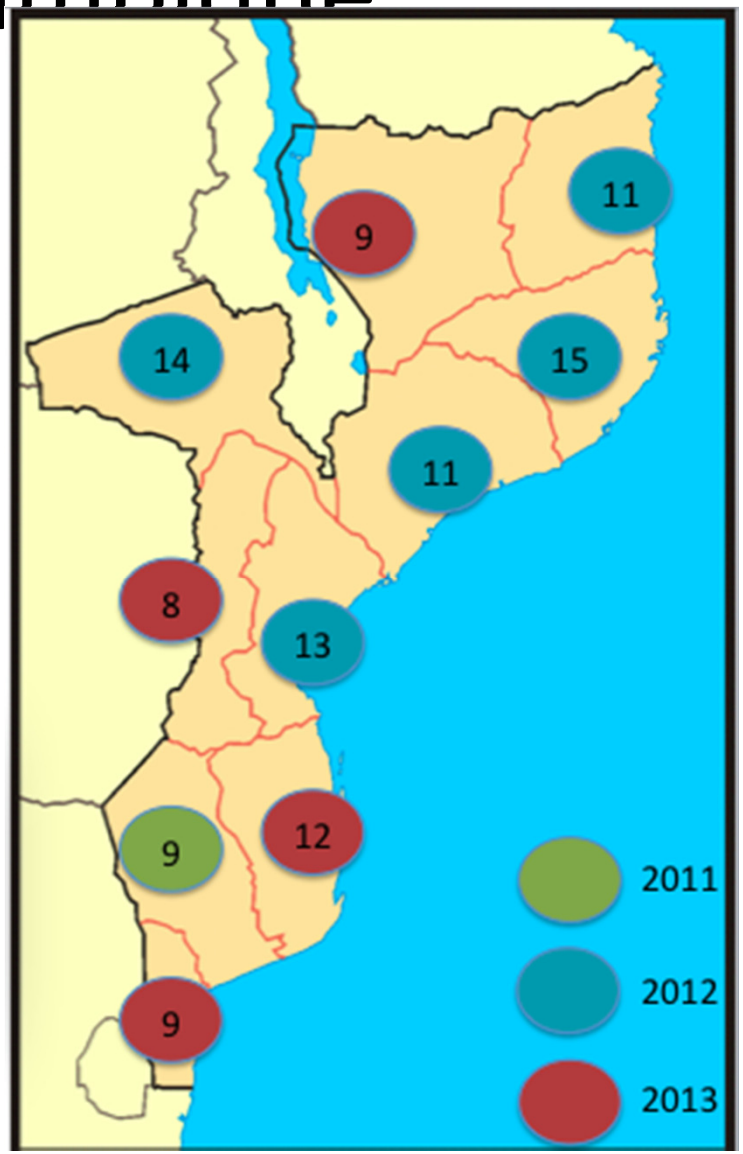


Weak metrics will result in high scores

Score	Site Name
4.00	TSANGANO
4.00	ULÓNGUÈ HR
4.00	ZOBUE
4.00	ZUMBO
3.86	SONGO
3.71	MPHENDE (MAGO¬ê)
3.71	MUCUMBURA
3.71	MUTARARA HR
3.29	MARÁVIA (CS FINGOÉ)
3.14	CHITIMA
3.14	DÓMUE
3.14	FURANCUNGO
3.00	CHIFUNDE
2.86	CHANGARA

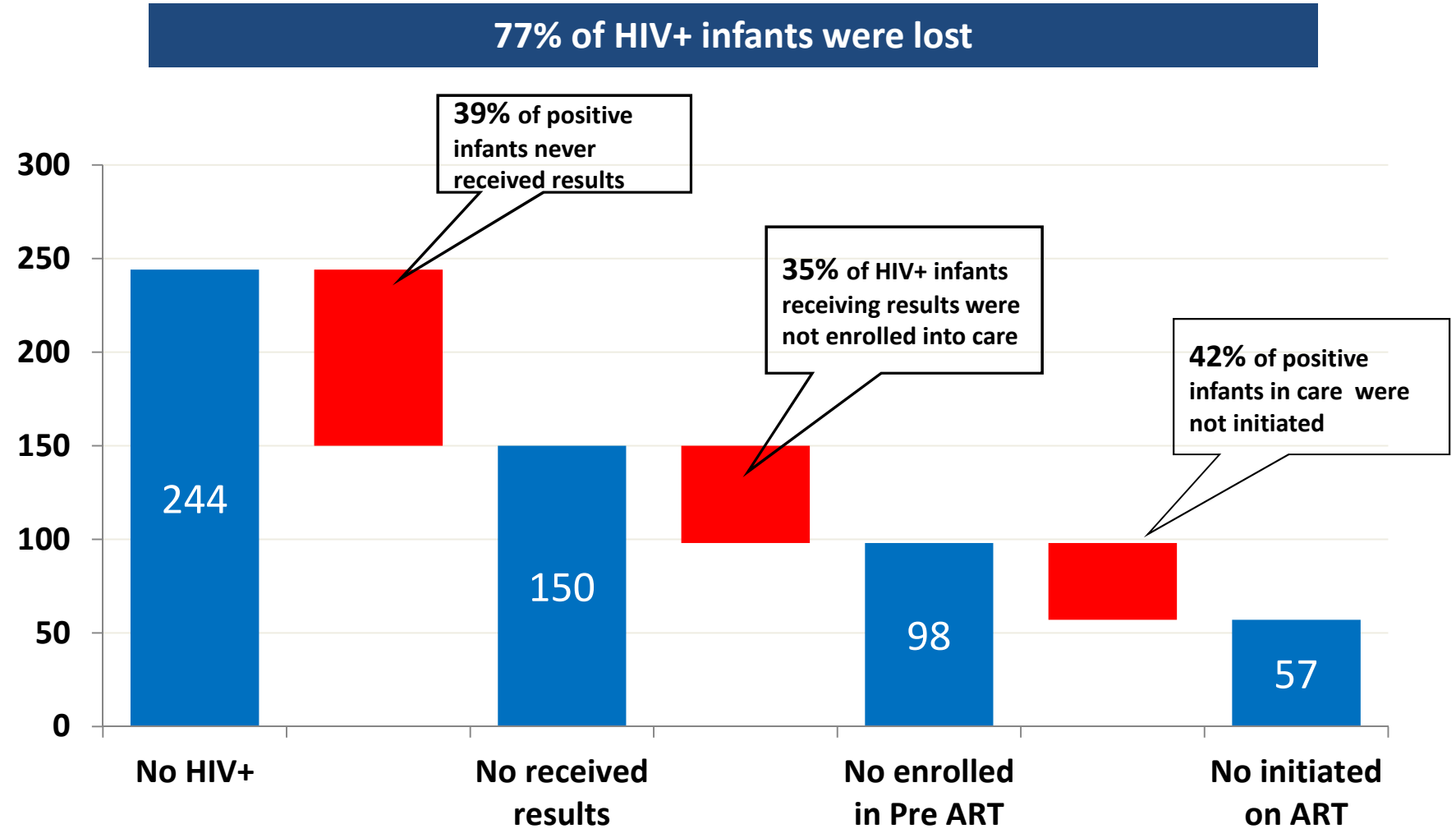
National Scale-Up of POC CD4 Counting in Mozambique

- 2009-2010: selection and evaluation of technology
- 2011: pilot in 1 province
- 2012-2013: ~130 health facilities nationally
- 2013: ~20% of patients in care with access to POC CD4
- Multiple partner effort with national coordination



Example from Uganda—Early Infant Diagnosis

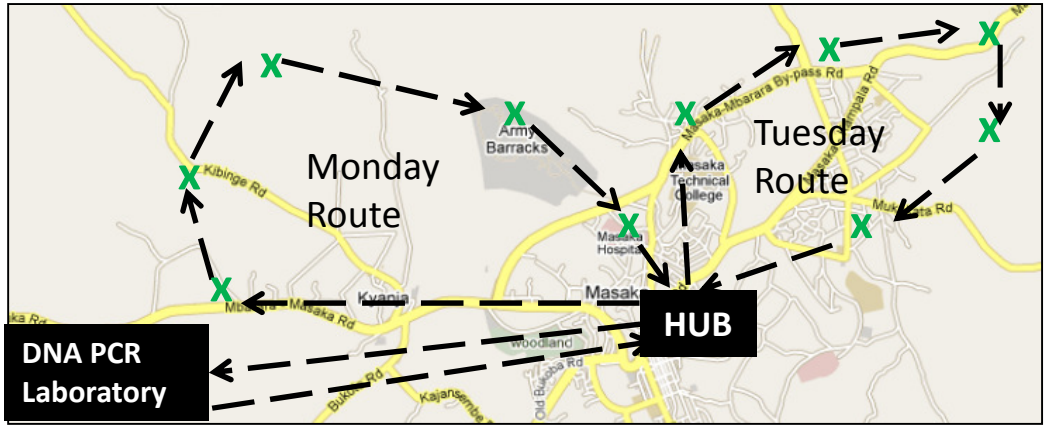
EID Loss to follow up Cascade –Uganda, 2009



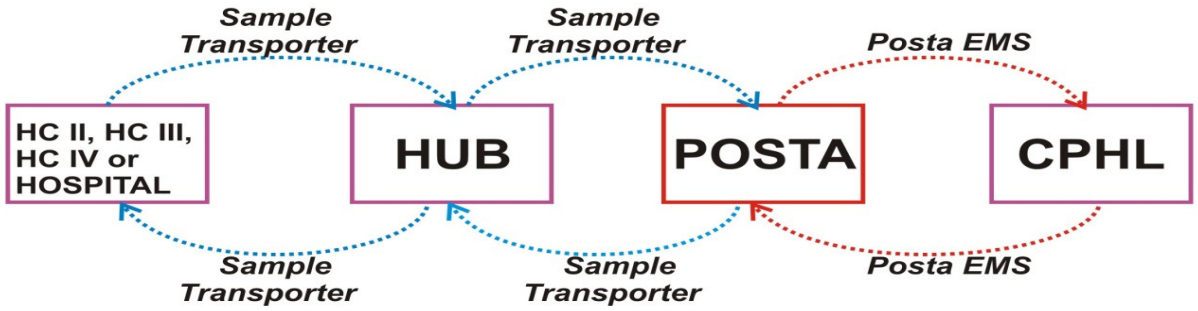
Best Practice--Uganda

3. Improved access through a comprehensive sample transport system

This system involves setting up local networks centered around regional, district hospitals and health facilities, called hubs.



- Each hub is given a motorbike and a sample transporter is assigned to each hub.
- The transporter visits 20-30 health facilities within 20-40km radius around the hub, bringing all referred samples from each facility and delivers results on a weekly basis.
- The hub will then further refer highly specialized tests like DNA PCR to referral labs.



WHO Assessment of Lab Scale up—2013 Survey (2012 data)

Test	Available in country	Market Share (# devices)	# Patients/ machine	Average # tests/ patient	# Tests per machine per day	% with Maintenance Service Contracts
CD4	96%	10	1063 (7-5048)	2 (<1 to 11)	5 per (1 to 22)	39%
VL/EID	81%	5	8706 (51-87,566)	1 (1 to 5)	8 per day (1-123)	39%

- **77 country responses from all WHO regions**

Source: The availability and use of diagnostics for HIV: a 2012/2013 WHO survey of low- and middle-income countries, WHO, in press

Machines Not in Use and Reasons Given

	CD4	VL/EID
% of machines not in use	5%	10%
Reasons Given		
Not installed/deployed	29%	59%
Repair required	54%	4%
Staff training needed	1%	7%
Lack of reagents	16%	31%

Source: The availability and use of diagnostics for HIV: a 2012/2013 WHO survey of low- and middle-income countries, WHO, in press