

Challenges in Scaling Up VL in Resource Limited Settings

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Outline

□ Background

- VL role in HIV treatment monitoring
- VL testing situation in Kenya
- Barriers to VL scale-up

□ Strategies for scale-up

- DBS
 - Kenya experience
 - Meta analysis
 - DBS challenges
- POC
 - Kenya evaluation

□ Considerations and conclusions

New WHO Recommendations: VL

- Viral load (VL) recommended as the preferred approach to monitor treatment success and diagnose ARV treatment failure in adults and children (Strong recommendation, low quality of evidence)**
- Viral load should be monitored at 6 months, 12 months, then 12 monthly**
- Treatment failure is defined by persistently detectable VL above 1,000 copies/ml**
- Where viral load monitoring is unavailable, the use of clinical and CD4 monitoring is recommended.**

Viral Load Capacity in Kenya

- ❑ Rapid ART scale-up since 2004
 - ~ 800,000 patients on ART in Kenya
- ❑ Clinical/ Immunologic monitoring were mostly used
- ❑ Viral Load testing was based on priority (targeted)
- ❑ VL testing made available to confirm treatment failure prior to ARV switch
 - Currently moving from targeted VL to routine VL testing



Barriers to VL Scale-up in Resource Limited Settings



Barriers of VL Scale-up

- ❑ **High Costs of Equipments & Reagents**
- ❑ **Technical complexities of current platforms**
- ❑ **Limited Quality Assurance systems**
- ❑ **Lack of clear guidelines on VL requests leading to unnecessary or late testing**
- ❑ **Unreliable supply chain for kits/consumables**
- ❑ **Turn around time of results**
- ❑ **Infrastructural challenges**
- ❑ **Transport and cold chain logistics**

Strategies for scale-up

- Dried Blood Spots

Why DBS?

- ❑ **Facilitates sample collection from decentralized settings thereby increasing VL access**
 - ❑ **Stability of RNA in plasma is dependent on freezing after separation, but stable in DBS at ambient temperatures** *(Munoz et al 2005, Reigadas et al. 2009)*
- ❑ **Simpler and cheaper collection**
 - ❑ **Minimum expertise required**
 - ❑ **Relatively low amount of blood is required**
- ❑ **Does not require cold chain & is non-hazardous thereby simplifying shipment to centralized facilities**
- ❑ **Can easily ride on the existing EID infrastructure**

Meta-analysis Methodology

- ❑ Extensive literature review for all studies comparing DBS to plasma for viral load testing using several search engines and terms
- ❑ 38 published/unpublished studies identified met inclusion criteria; primary data included from 27 studies
- ❑ Resulted in >6,500 paired data points for the primary viral load technologies currently available
- ❑ Used a bivariate random effects model to determine bias, accuracy, precision and misclassification to account for between-study variation

Meta-analysis Results

Assay assessed	Sensitivity (mean %)	Specificity (mean %)	<i>n</i>
Abbott Molecular: Abbott RealTime HIV-1 (manual, m24sp and m2000sp) assays with m2000rt platform	95.24 ^a	91.67 ^a	1529
Biocentric: Generic HIV Charge Virale	94.86 ^a	55.16 ^a	531
bioMérieux: NucliSENS EasyQ [®] HIV-1 v2.0	84.37 ^a	94.52 ^a	1062
Roche Molecular Systems: COBAS [®] AmpliPrep/COBAS [®] TaqMan [®] HIV-1 Test, version 2.0 [free virus elution protocol]	81.02 ^b	96.74 ^b	229
HIV-1 RNA 1.0 Assay (kPCR)	90.97 ^a	87.76 ^a	144

Sensitivity, specificity, positive predictive value, and negative predictive value (95% Confidence Intervals) of DBS compared with paired plasma specimen viral load, patient support centers, Nyanza, Kenya

		Plasma viral load			
	DBS viral load	Detectable	Undetectable	Total	
CAP/CTM	Detectable	150	48	198	Sensitivity = 100.0 (97.6 – 100.0) Specificity = 4.0 (0.5 – 13.7) PPV = 75.8 (69.2 – 81.6) NPV = 100.0 (15.8 – 100.0)
	Undetectable	0	2	2	
	Total	150	50	200	
Abbott m2000	Detectable	137	7	137	Sensitivity = 93.9 (88.8 – 97.2) Specificity = 88.0 (82.2 – 92.4) PPV = 100.0 (97.4 – 100.0) NPV = 85.3 (73.8 – 93.0)
	Undetectable	11	52	63	
	Total	148	52	200	

Comparisons between CAP/CTM DBS and Abbott DBS tests at different clinical cut-offs using CAP/CTM plasma as the gold standard

Cut-point (Viral cps/ml)	Test	Sensitivity (%)	Specificity (%)	Correctly classified (%)	LR+	LR-
≥1000	CAP/CTM	100	3.9	75.0	1.04	0.0
≥1000	Abbott	97.3	90.4	95.5	10.1	0.03
≥2000	CAP/CTM	100	17.3	78.5	1.20	0.00
≥2000	Abbott	96.6	90.4	95.0	10.1	0.03
≥3000	CAP/CTM	98.0	36.5	82.0	1.54	0.06
≥3000	Abbott	95.3	94.2	95.0	16.5	0.05
≥4000	CAP/CTM	97.3	54.0	86.0	2.11	0.05
≥4000	Abbott	94.6	98.1	95.5	49.2	0.06
≥5000	CAP/CTM	96.0	82.7	92.5	5.54	0.05
≥5000	Abbott	93.2	98.1	94.5	48.5	0.07

DBS use under field conditions

- **Assess VL performance of DBS prepared in clinical settings using three simplified spotting modalities**
- **Assess diagnostic accuracy of detecting virologic failure (VF) defined as plasma VL ≥ 1000 copies/ml compared to plasma VL**

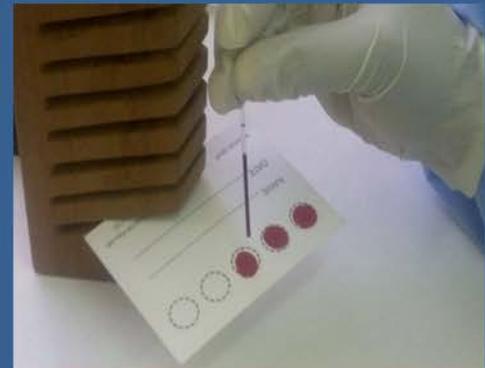
Methods

Venipuncture (Venous) Finger Stick (Capillary)



Venous Blood (V-DBS) Directly

Microcapillar



Results

Table 2. Sensitivity, Specificity, Kappa agreement, and Misclassification by DBS type and threshold compared to plasma on Abbott m2000 platform among adults and children on ART

Threshold (≥ copies/ml) Plasma:DBS	Sample type (n)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Kappa (95% CI)	False positives (%)	False negatives (%)
1000:1000	V-DBS (733)	88.8 (84.2-92.4)	92.6 (89.9-94.7)	0.81 (0.76 - 0.85)	7.4	11.2
	M-DBS (724)	86.9 (82.0-90.9)	94.2 (91.7-96.1)	0.81 (0.77 - 0.86)	5.8	13.1
	D-DBS (732)	85.8 (80.8-89.9)	93.6 (91.1-95.6)	0.80 (0.75 - 0.84)	6.3	14.2
1000:3000	V-DBS (733)	84.7 (79.7-89.0)	97.7 (96.0-98.9)	0.85 (0.81 - 0.89)	2.2	15.2
	M-DBS (724)	84.8 (79.7-89.1)	97.1 (95.2-98.4)	0.84 (0.80 - 0.88)	2.9	15.1
	D-DBS (732)	83.3 (78.1-87.8)	97.3 (95.5-98.6)	0.84 (0.79 - 0.87)	2.7	16.7
1000:5000	V-DBS (733)	81.5 (76.1-86.1)	98.1 (96.5-99.1)	0.83 (0.78 - 0.87)	1.8	18.4
	M-DBS (724)	81.6 (76.1-86.2)	98.1 (96.5-99.1)	0.83 (0.78 - 0.87)	1.9	18.4
	D-DBS (732)	79.3 (73.7-84.2)	98.6 (97.1-99.4)	0.81 (0.77 - 0.86)	1.4	21.0

Challenges using DBS

- Among treated patients contribution of cell-associated & pro-viral DNA leading to low specificity which may lead unnecessary treatment switch
- Variation of results in different assay
 - Lower limit of detection
 - Extraction and amplification technologies
 - Target region for amplification
- Turn around time

Strategies for scale-up

- Point of care devices**

Benefits of viral load POC devices

- ❑ Portability: Increasing accessibility to rural areas**
- ❑ Low cost increasing affordability**
- ❑ Simplicity of use enhancing task shifting from highly skilled laboratory technicians**
- ❑ Limited infrastructure needs e.g. electricity**
- ❑ Fast turn-around time with immediate results**
 - ❑ Leads to reduction in loss to follow-up**
 - ❑ Reduction in patient time and costs-return visits of the results**
 - ❑ Improves care due to fast clinician decision making**

POC Technology Pipeline - Viral Load

Liat™ Analyser

IQuum



Alere Q

Alere



EOSCAPE HIV™
Rapid RNA Assay
System

Wave 80
Biosciences

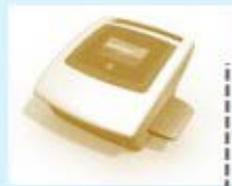


Gene
Xpert



RT CPA HIV-1 Micronics

Viral Load
Ustar



Gene-
RADAR

ALL

Nanobiosy
m



Cavidi AMP



BioHelix



SAMBA VL
DDU/Cambridg
e



Truelab PCR
Molbio/bigTe
C

LYNX Viral Load
Platform
NWGHF



Viral Load
Assay
with BART
Lumora



2012 2013 2014 2015 2016

* Estimated as of March 2013 - timeline and sequence may change. Dotted line indicates that no market launch date has been set by the company.



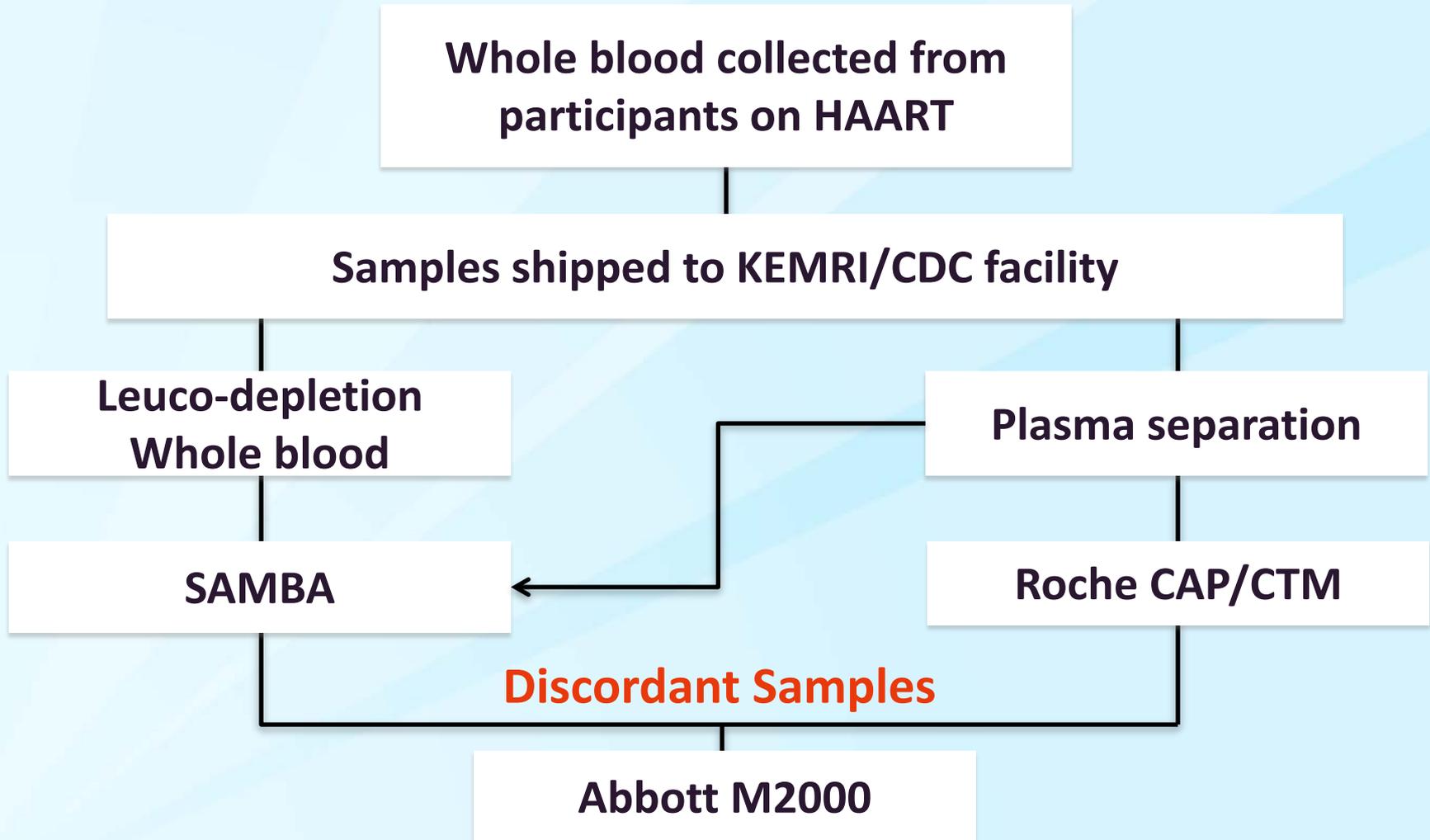
SAMBA background

- **Simple AMplification Based Assay (SAMBA) nucleic acid-based point of care (POC) platform**
 - Qualitative EID test (Positive/Negative)
 - Semi-quantitative viral load monitoring test (>1000 copies)
 - Plasma
 - Leuco-depleted whole blood, without venous puncture and centrifugation

Primary Objectives

- ❑ **Phase 1: Validate in-laboratory performance of the POC SAMBA for country product approval**
- ❑ Phase 2: Feasibility of using POC SAMBA system among clinical site staff at selected health facilities
- ❑ Phase 3:
 - Impact at 6 weeks of life on time to ART initiation
 - Impact on patients retention in care and treatment
 - Cost-effectiveness

SAMBA VL Whole Blood/Plasma Evaluation



VL Results

Plasma VL SAMBA vs. Roche + Abbott (Combined Gold Standard)

Copies/ml	Combined Gold std ≥ 1,000	Combined Gold std <1,000	Total
SAMBA ≥1,000	91	2	93
SAMBA <1,000	6	98	104
Total	97	100	197

Sensitivity at Clinical cutoff of 1000 copies: **93.8% (CI; 87.0- 97.7)%**

Specificity at Clinical cutoff of 1000 copies: **98.0 % (CI; 93.0- 99.8)%**

**Concordance: SAMBA vs Roche + Abbott = 95.9%
(189/197)**

Leuco-depleted Whole blood VL SAMBA vs. Roche + Abbott (Combined Gold STD)

Viral Load(cp/ml)	Roche > 1,000	Roche <1,000	Total
SAMBA >1,000	35	8	43
SAMBA <1,000	0	162	162
Total	35	170	205
Sensitivity	100.0% CI (90.0%, 100.0%)		
Specificity	95.3% CI (90.9% 97.9%)		

Overall concordance: SAMBA vs Roche + Abbott = 96.1% (197/205)

Findings

- **High sensitivity and specificity obtained with SAMBA VL assays**
- **Comparable results obtained from different countries**
- **SAMBA device is much easier to handle and simpler sample processing**
- **SAMBA reagents do not require cold chain transport or cold storage**

Integrated approach (Centralized vs POC)

- Potential limitation for POC's and centralized systems calls for an integrated approach that ensures a greater impact, quality and effective use of both systems**
- Laboratory systems are most preferred in areas with high test needs due to higher throughput as compared to POCs**
- POC's however are likely to leverage turn around time and increase patient retention to care and can be most suitable in outreach clinics**

Conclusion

- ❑ **Need for comprehensive integrated approach on VL testing in RSL**
- ❑ **Plasma use, preferred on sites near centralized systems, while DBS and POC's can be used in remote and far areas**
- ❑ **Need for establishment of QA guidelines on DBS and POC VL testing**
- ❑ **Need for MOH driven in-country VL testing**

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