Amsterdam Institute for Global Health and Development

Academisch Medisch Centrum
Universiteit van Amsterdam

Monitoring HIV Drug Resistance in Africa and Asia

Pan-African (PASER) and TREAT Asia (TASER) Studies to Evaluate Resistance

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Disclosures

- The speaker has no conflict of interest to report

HIV Drug Resistance Program - Objectives

To evaluate HIVDR and build capacity on the monitoring and surveillance of HIVDR in Africa and Asia by

- Network development, training and mentoring
- HIVDR observational surveys
- Centralized clinical and HIV sequence databases
- Laboratory Quality Assurance Network

To provide support to policy makers

- Coordinated with WHO/HIVResNet

HIV Drug Resistance Program – Organization

Supported by:

- The Ministry of Foreign Affairs of The Netherlands/Aids Fonds (€ 10.2 million, 2006-2011)
- PharmAccess Foundation
- amfAR
- US National Institutes of Health (NIAID, NICHD)

LAASER-HIV/AIDS
Enhancing Africa's and Asia's Response to AIDS

- TREAT Asia Studies to Evaluate Resistance (TASER)
- Pan-African Studies to Evaluate Resistance (PASER)
- International Civil Society Support (ICSS)

Cohort Profile: The PharmAccess African (PASER-M) and the TREAT Asia (TASER-M) Monitoring Studies to Evaluate Resistance—HIV drug resistance in sub-Saharan Africa and the Asia-Pacific

Int J Epidem 2012

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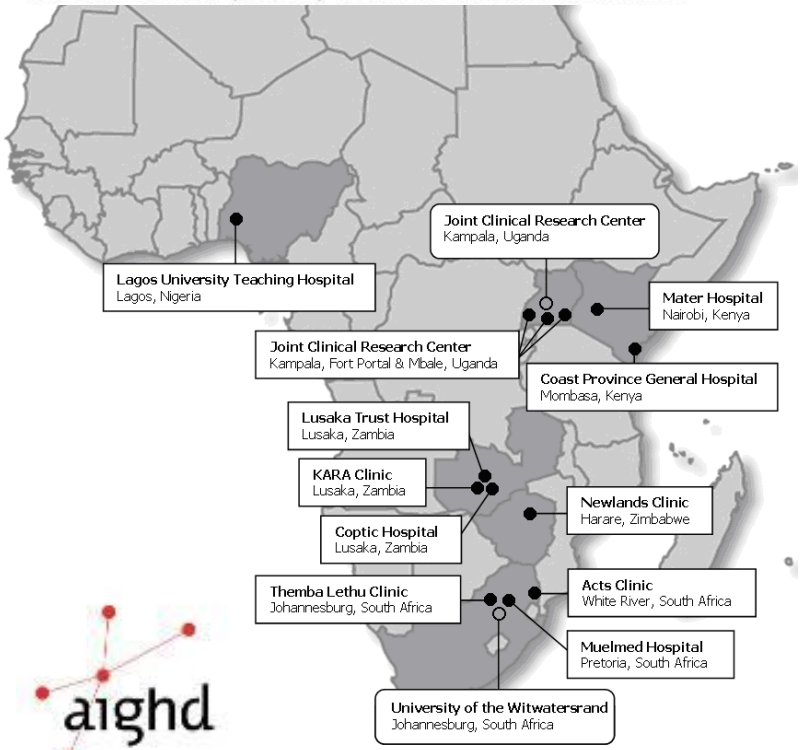

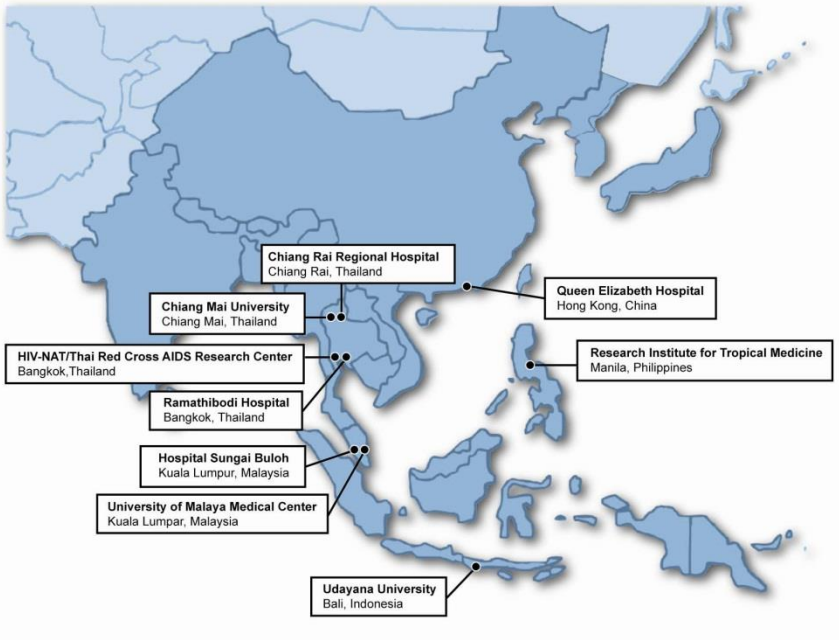

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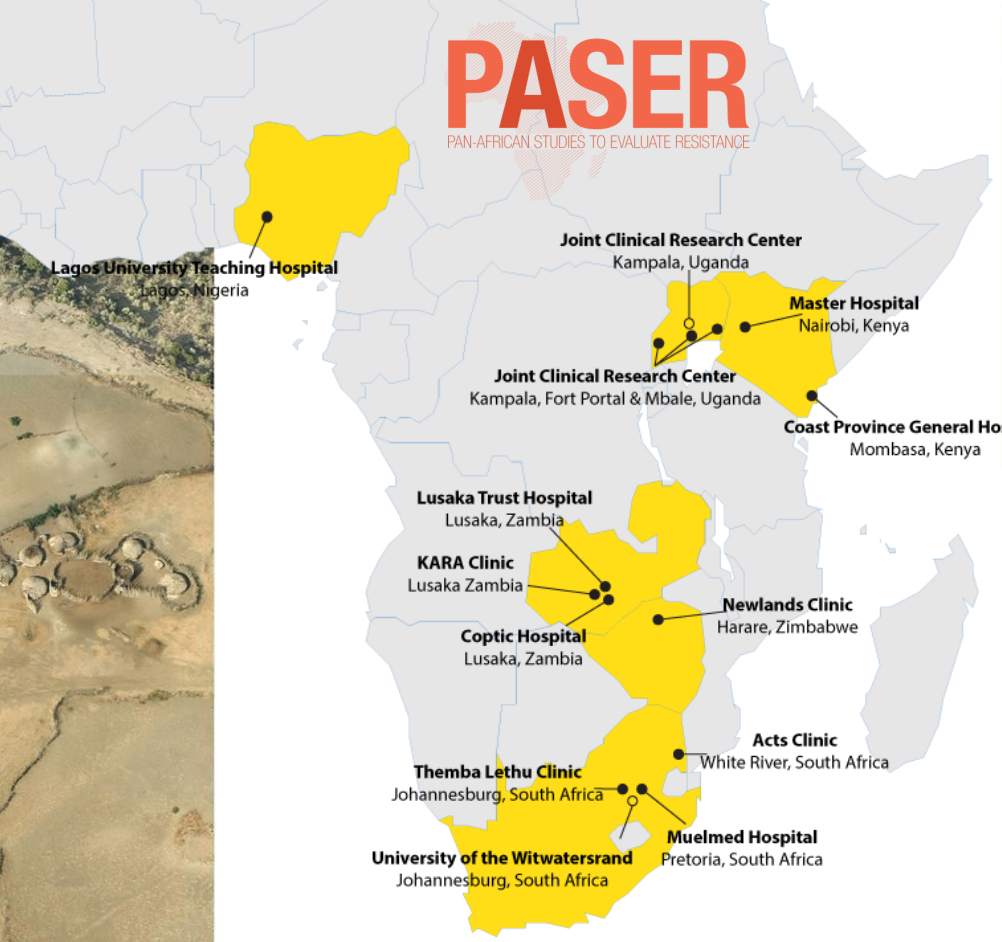
PharmAccess FOUNDATION

Therapeutics Research • Education • AIDS Training
TREATASIA

PASER

PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE



Monitoring	Surveillance
PASER M	**PASER S**
HIV treatment centers	VCT sites
Prospective cohort study	Cross-sectional survey
Patients on HAART	Newly HIV+, ARV naïve
Acquired HIVDR	Transmitted HIVDR

2733 patients initiating 1st line followed up for 24 month

250 patients enrolled at 2nd line switch followed up for 24 months

2 surveys

81 patients in Mombasa (2008/9)

77 patients in Kampala (2009)

- Surveillance and monitoring studies built local and regional capacity for HIVDR
- 2007-11, ~3000 patients
- Retrospective VL and *pol* genotyping
- 13 clinical sites, 2 ref labs, 6 countries
- Central clinical and sequence database and sample repository (DBS+plasma)
- Genotyping EQA in collaboration with NRL Australia (TAQAS)
- Clinical ART provider and lab staff trainings

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TASER experience

- Surveillance and monitoring studies built local and regional capacity for HIVDR
  - 2007-12, ~2500 patients, 12 sites, 5 countries
  - Patient data integrated into NIH IeDEA collaboration
- Genotype EQA in collaboration with NRL Australia (TAQAS)
  - 2005-present, up to 23 labs, 13 countries (currently 8 labs)
- Clinical provider and lab staff trainings
- Subsequent studies on pediatric and adult 2nd-line
  - TASER-Pediatrics (monitoring) completed in 2014
  - TASER-2 (cross-sectional) adult 2nd line VF+HIVDR (2016-2018)

Therapeutics Research•Education•AIDS Training
TREATASIA

TASER
Studies to Evaluate Resistance

1. First evidence of rising PDR prevalence in ARV-naive populations in Africa, after ART scale-up

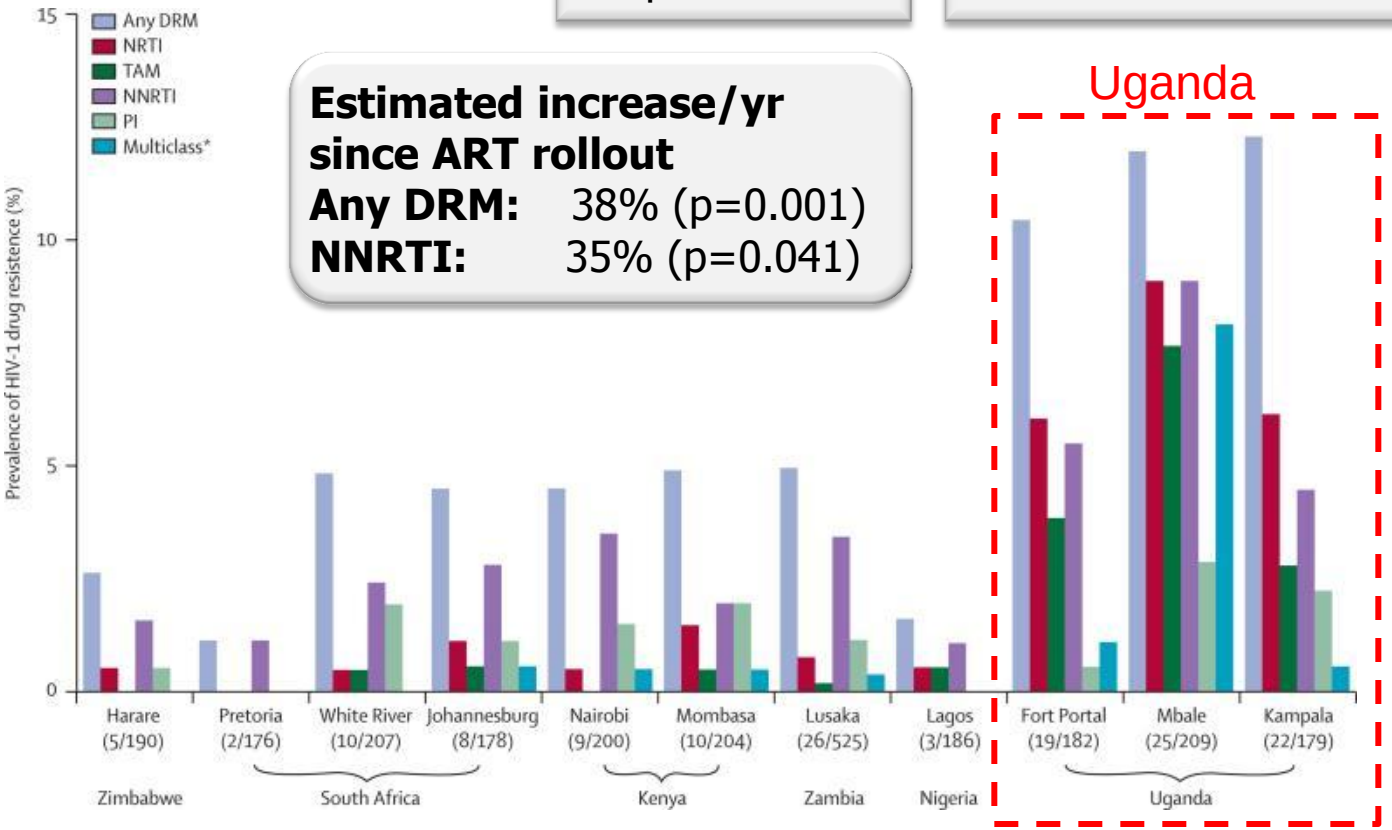
PASER
PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE

2590 participants
2436 *pol* sequences
2007-2009

PDR prevalence
Overall: 5.6%
Pretoria: 1.1%
Kampala: 12.3%

NRTI 2.5%
NNRTI 3.3%
PI 1.3%
Dual class 1.2%

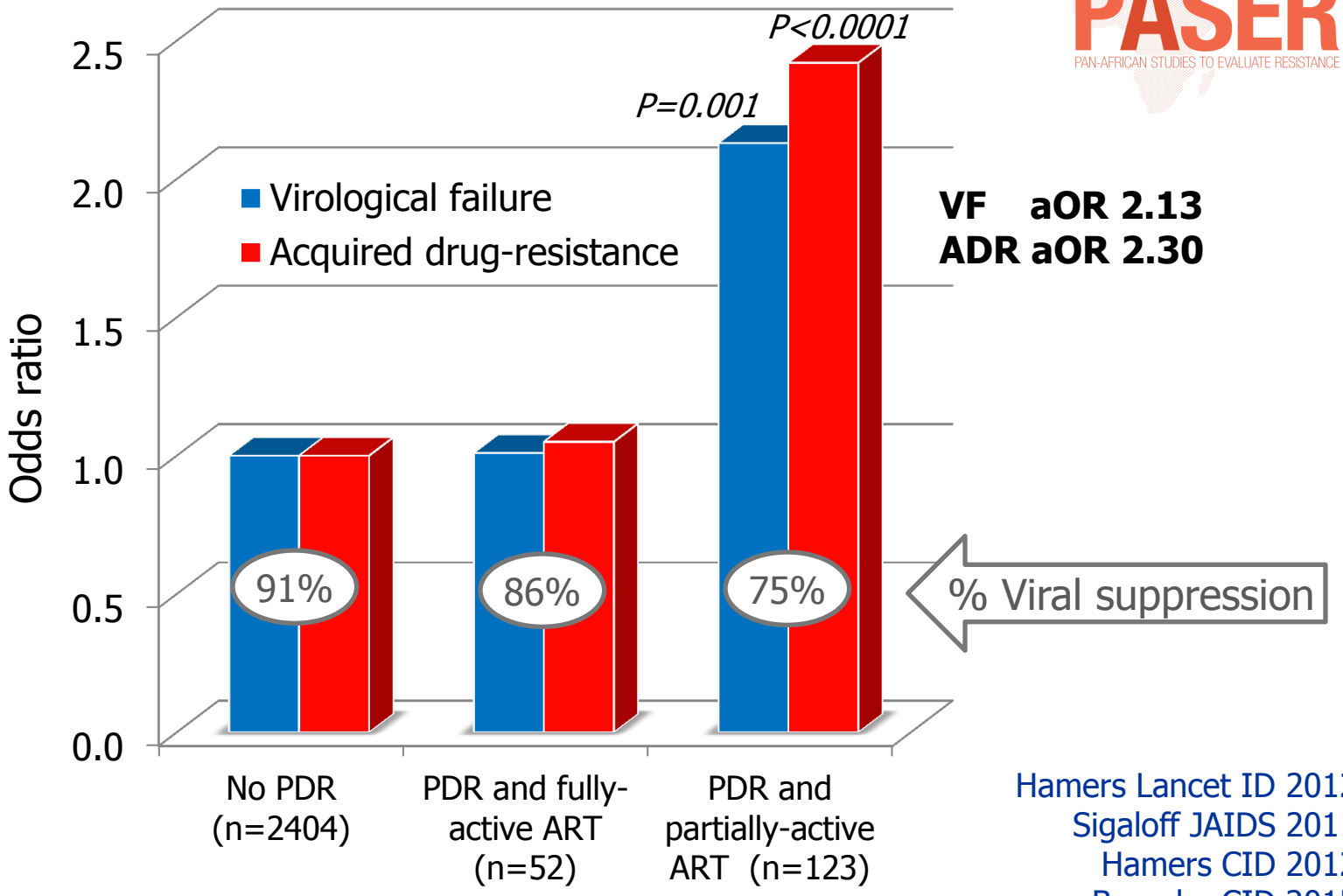
Estimated increase/yr since ART rollout
Any DRM: 38% (p=0.001)
NNRTI: 35% (p=0.041)



Hamers The Lancet Inf Dis 2011;
Ndembi AIDS 2011; Sigaloff Aids Res Hum Retro 2011

2. PDR compromises impact of standard first-line ART

- Virological response, immunological recovery, DRM accumulation, increased regimen switching
- No effect on survival/aids in first 3 yrs



Hamers Lancet ID 2012;
Sigaloff JAIDS 2011;
Hamers CID 2012;
Boender CID 2015;

3. Longitudinal analyses of VF+DRM patterns in 1st+2nd line failures

Adults failing LPV/r-based 2nd line (up to 36mo followup)

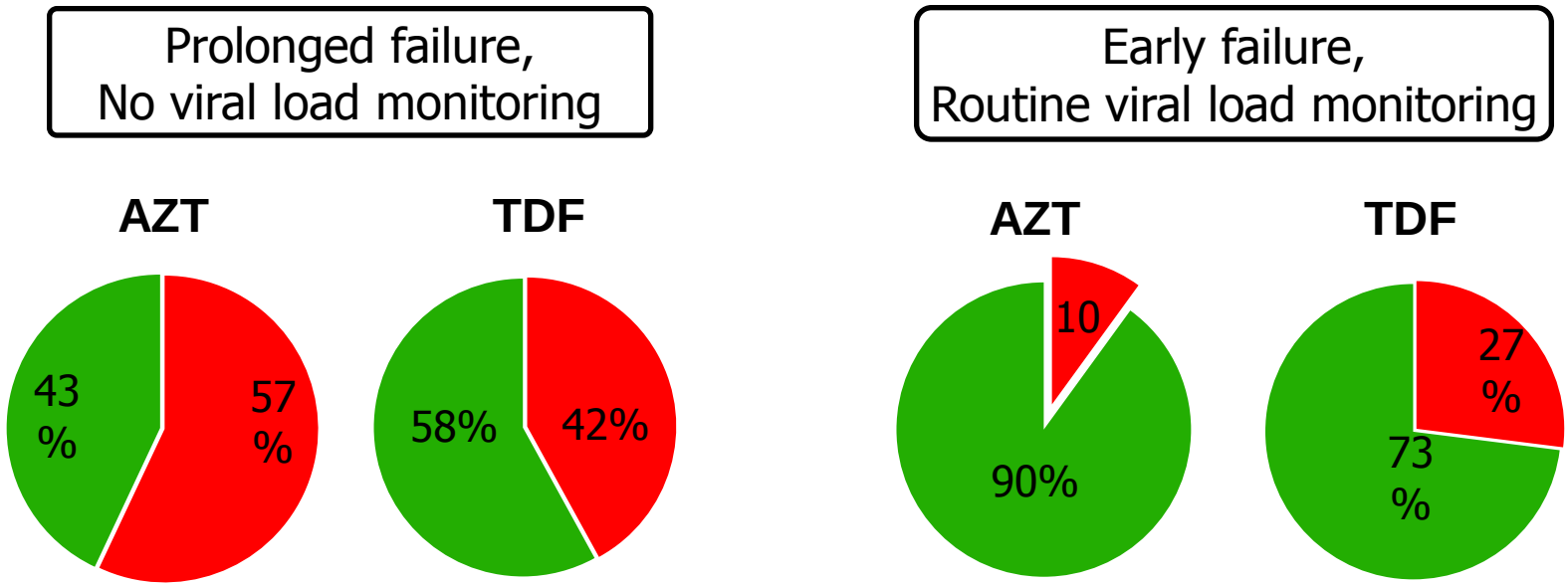
	VL<400 cps/ml	PI mutation
12 months	175/205 (85%)	2/17 (12%)
24 months	150/177 (85%)	6/21 (29%)
36 months	80/90 (89%)	2/3 (67%)

- 7/32 (22%) PI resistance in those with VL>1000 cps/ml and GRT available
  - M46I, V82A, L76V, I50V, L90M
- 7/227 (3%) of all who started 2nd-line acquired major PI-DRM

Boender submitted

4. Clinical benefits of routine viral load monitoring

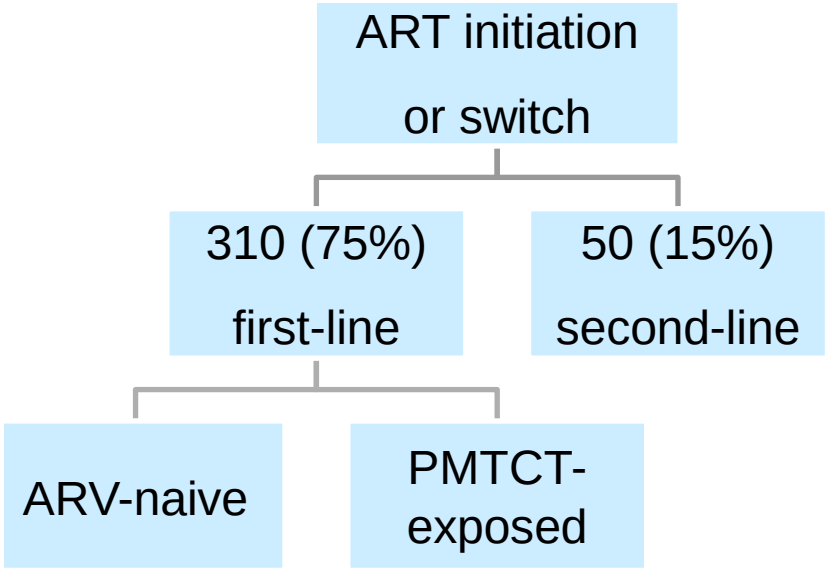
1. Averts accumulation of DRMs, preserving ARV drug susceptibility
2. Averts unnecessary regimen switching
3. May lead to cost savings



Sigaloff et al. J Inf Dis 2012; Hamers et al. Clin Inf Dis 2012; Hamers et al. AIDS 2012

MARCH-Uganda study
Monitoring ARV Resistance in Children

- Prospective cohort study of 360 children in Uganda on ART
- Initiated in January 2010
- Funded by EDCTP, NACCAP



Sigaloff ARHR13, Kityo ARHR16

Affordable HIV Resistance Test for Africa 2007-2011

ARTA
AFFORDABLE RESISTANCE TEST FOR AFRICA

Current:
↓
Plasma

- Cold Chain required
- Expensive Assays (commercial kits)
- Infectious

Patient Sample:
Plasma / DBS

Nucleic Acid Extraction

Virological Failure Assay
Qualitative PCR

Cut-off >5,000 HIVRNA c/ml

Negative → Effective viral suppression

Positive

Single-round HIV-1 RT Genotyping

"ART-A" Genotyping (GT)

No resistance mutations → Consider alternative reasons for failure e.g. non-compliance

Positive for mutations

Report
Decide on future treatment strategies

ART-A:
↓
DBS

- Ambient temperature
- Stable
- Non-infectious
- Set of Compatible non-commercial Assays

WiTS HEALTH CONSORTIUM
Universitair Medisch Centrum Utrecht
crp SANTÉ CENTRE DE RECHERCHE PUBLIC
Johnson&Johnson
CLS CONTRACT LAB SERVICES
aighd

Struck JCV12; Bronze J Virol Meth13; Aitken JCV12, JCM13, PLoS ONE15

PASER continuation grants (2012-2016)

ART-A field evaluations and PASER-M extended patient follow-up

Heineken Africa Fund € 333,000
PASER-M + MARCH Nigeria 3Y

AIDS Fonds € 200,000
PASER-M Zimbabwe 1Y

Uganda	**Baseline** Jan '08-Oct '08	Month 24	**Month 72** Oct '14
Nigeria	**Baseline** Sept '08-Jun'09	Month 24	**Month 60** Oct '14
Zimbabwe	**Baseline** Sept '08-Sep '09	Month 24	**Month 60** Oct '14
Zambia	**Baseline** May '07-Nov'07	Month 24 / Month 60-74 Feb '13	**Month 72** March '14
South Africa	**Baseline** May '07-June '08	Month 24 / Month 60-74 Feb '13	**Month 72** Nov '14
Kenya	**Baseline** Oct '08-June '09	Month 24	

oundation € 125,000
R-M Uganda 1Y

IACCAP € 1.4 million
-M Uganda, 3Y

retoria € 1.2 million
R-M Zimbabwe,
a, South Africa, 3Y

University of the Witwatersrand
Johannesburg, South Africa

Capacity building

Regional workshops and on-site trainings for clinical ART providers and lab staff

- 2006, Johannesburg: PASER Network meeting
- 2007, Dar es Salaam: Advanced Medical Training
- 2008, Kampala: PASER Network meeting
- 2008, Nairobi: PASER/ARTA Network meeting
- 2009, Lusaka: PASER/ARTA Network meeting
- 2010, Entebbe: PASER/ARTA Network meeting
- 2012, Kampala: ARTA/PASER Policy workshop
- 2013, Bloemfontein: PASER/SATuRN Medical Training

WHO HIVDR Global Report 2012

PASER data account for
11% overall and
25% from Africa

www.who.int/hiv/pub/drugresistance/report2012

Data-sharing and secondary analyses

- **Aggregated analyses on TDR, PDR, ADR, viral suppression**
  - WHO HIVDR Global Report 2012, Gupta Lancet 2012, Tang JID 2013, Boender CID 2015, Rhee Plos Med 2015, TenoRes Lancet Inf Dis 2016, Boerma (under review)

- **Mathematical modelling**
  - Costeffectiveness of VLM (Hamers Aids 2012)
  - Early ART and TDR (Nichols Aids 2014)
  - Costeffectiveness access 2nd-line and TDR (Nichols JIAS2014)
  - RDI's HIV-Treatment Response Evaluation System (HIV-TRePS) (Revell JAC 2013 and 2014)

- **Phylogenetic studies on HIV spread**
  - HIV transmission MSM-HSX Coastal Kenya (Bezemer ARHR2014)
  - Comparative phylogeography of HIV-1 subtypes in central and eastern Africa (Faria, in prep)

Conclusions – PASER-TASER

- HIVDR is an emerging public health problem in LMICs
  - PDR/TDR: on the rise, in adults and children, compromising first-line
  - ADR: NNRTI/NRTI patterns as expected, PI-resistance limited but emerging
  - Clinical benefits of routine VL monitoring
  - Children: underrecognized challenges

- Pioneering HIVDR capacity building, assessment and advocacy in sub-Saharan Africa and Asia, early during ART scale-up

- Paired clinical-genetic regional databases important data source for scientists and policy makers (WHO) to help shape ART policies

- Networks and operational systems in place to strengthen local capacities and undertake HIVDR surveys

Conclusions

- Long-term HIV treatment will become increasingly complex, need for access to affordable HIVDR diagnostics and 3rd line drugs – with appropriate education

- More than ever, need for HIVDR research and surveillance framework to protect and sustain ART impact in LMICs

- Future directions?
  - Completion of PASER-M long-term data analyses
  - TASER-2 2016-2018 - supported by ViiV Healthcare, NIH IeDEA
  - Exploring opportunities for future studies

Funding

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Ministry of Foreign Affairs of The Netherlands (2006-2011)

The Netherlands Organization for Scientific Research (NWO) -
WOTRO under the Netherlands African Partnership for Capacity Development and Clinical Interventions against Poverty related Diseases (NACCAP) (2007-2016)

Stichting AidsFonds (2006-2011)

De Grote Onderneming (2008)

Jura Foundation

Royal Netherlands Embassy in Pretoria (EKN)

European & Developing Countries Clinical Trials Partnership

Heineken Africa Foundation

amfAR

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Nicaise Ndembi

PASER
PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE

ARTA
AFFORDABLE RESISTANCE TEST FOR AFRICA

MARCH
MONITORING ANTIRETROVIRAL RESISTANCE IN CHILDREN