Global Spread of HIV-1 Drug Resistance: Meeting the Challenge

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Outline

- **Refresher on HIV Drug Resistance**
  - Principles, types, major vs. minor
- **Drivers of HIV resistance**
  - PrEP vs ART
- **What can we do to minimize resistance?**
  - Multiple improvements required
- **Take home message**
  - We need to meet the challenge!

Principles of Resistance

- HIV-1 can develop resistance to any ARV

HIV Replication + One or Two ARV = RESISTANCE

NO REPLICATION (3 Drug ART) = NO RESISTANCE

- Remove drug, resistance decays, but it depends on mutation and drug
  - M184V (3TC/FTC) = fast
  - K103N (NNRTI) = slow

Types of Resistance

ACQUIRED

- Infected with wildtype virus
- Resistance selected by sdNVP, ART or PrEP
- Can infect partner with resistant virus

TRANSMITTED

- Infected with resistant virus
- Never exposed to ARVs
- Partner received ART, sdNVP or PrEP
- Or partner infected with resistant virus (2° transmission)

Major vs. Minor

MAJOR

- **≥ 25%** of virions in a person are resistant
- Detected by standard population genotype

MINOR

- **< 25%** of virions in a person are resistant
- Missed by standard genotype
- Detected by sensitive methods (ASPCR, SGS, Deep Sequencing)

What drives drug resistance?

Resistance in PrEP Trials

Infected Post-Enrollment

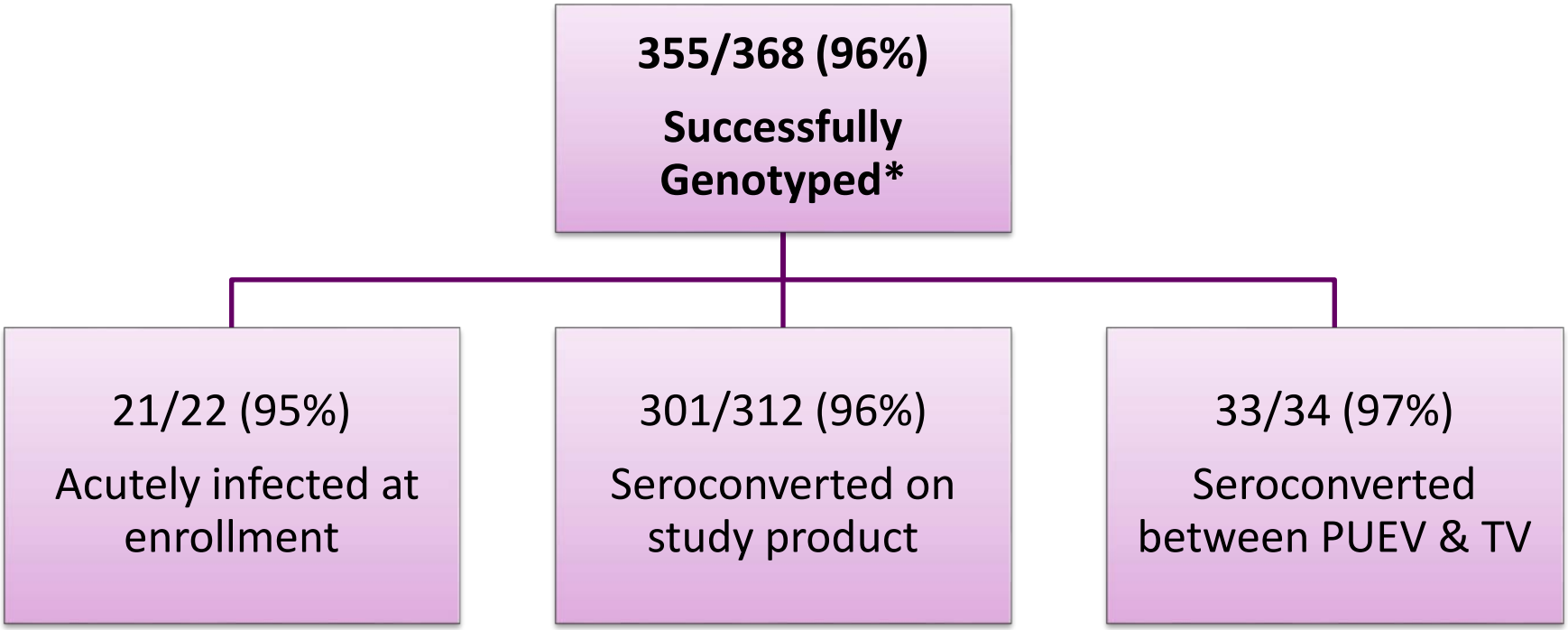
Study	# Sequenced		# Resistant to TDF or FTC
	Placebo	Active	
Bangkok Tenofovir	35	15	0
CAPRISA-004	0	35	0
Fem-PrEP	35	33	1 Placebo (M184V) 4 TDF-FTC (M184V/I)
iPrEX	64	36	0
Partners in PrEP	51	27	0
TDF2	24	9	1 Placebo (K65R <1%)
VOICE/MTN-003	128	173	1 TDF/FTC (M184V)
TOTAL	**665**		**7 (1%)**

Resistance in PrEP Trials

Enrolled during Acute Seroconversion

Study	# Infected at Enrollment	# Resistant to TDF or FTC
Bangkok Tenofovir	2	0
Fem-PrEP	5	0
iPrEX	10	3 (M184I/V)
Partners in PrEP	8	2 (1 K65R + 1 M184V)
TDF2	1	1 (K65R/M184V)
VOICE	9	2 (M184I/V)
TOTAL	**35**	**8 (23%)**

Drug Resistance in VOICE



*No result (n=13) due to:

- No stored plasma (n = 1)
- Insufficient copies of HIV-1 RNA for extraction (n = 11)
- PCR amplification failure (n = 1)

VOICE Standard Sequencing

No resistance to TFV

- **<u>TFV oral or gel arms (K65R or K70E)</u>**
- 0/173 infected after enrollment
- 0/18 acutely infected at enrollment

3 cases of FTC Resistance

- **<u>Oral Truvada arm (M184V/I)</u>**
- 1/55 infected after 309 days on product
- 2/9 acutely infected at enrollment; on product 26 & 29 d

8 cases of NNRTI resistance (transmitted)

- **<u>All arms (K103N/V106M and/or Y181C)</u>**
- 8/355 (all seroconverters)
- 2009 WHO TDR mutations (n=34)

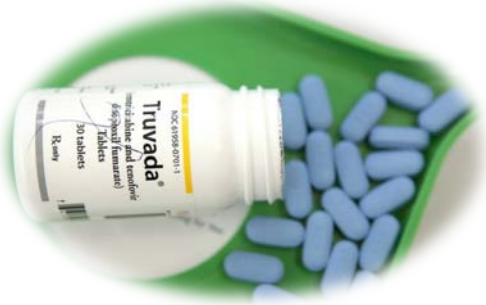
Drivers of Resistance from PrEP

- Use of product by acutely infected individuals pre-seroconversion
  - Need better point-of-care tests that can detect infection earlier
- Incomplete protection by product
  - Rare so far
  - Resistance may increase with better adherence
- Product does not protect against transmitted resistance from partner

ART in Africa

First line

2 NRTI + 1 NNRTI



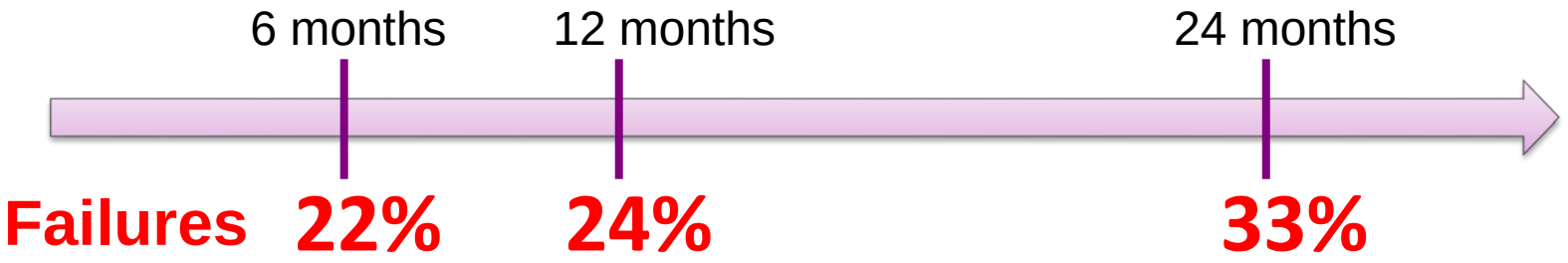
Second line

2 different NRTI + PI

Resistance from 1st Line ART

Virological efficacy and drug-resistance outcomes for 13,288 patients from sub-Saharan Africa on first line ART

How effective was ART?



Resistance found in failures: M184V (65%), K103N (52%), TAMS (5-20%), K65R (5%)

Barth et al. *Lancet Infect Dis* 2010

PASER

PharmAccess African Studies to Evaluate Resistance

- Multi-country 13-site cohort study
- 70% of patients achieved HIV RNA suppression
- **71%** resistance among failures; **21% of all on ART!**
  - 96% of cases were acquired resistance
  - 4% of cases were transmitted resistance
  - Predominant mutations: K103N, M184V, TAMS, K65R

Hamers *Int J Epidemiol* 2012

Resistance to Second Line Therapy

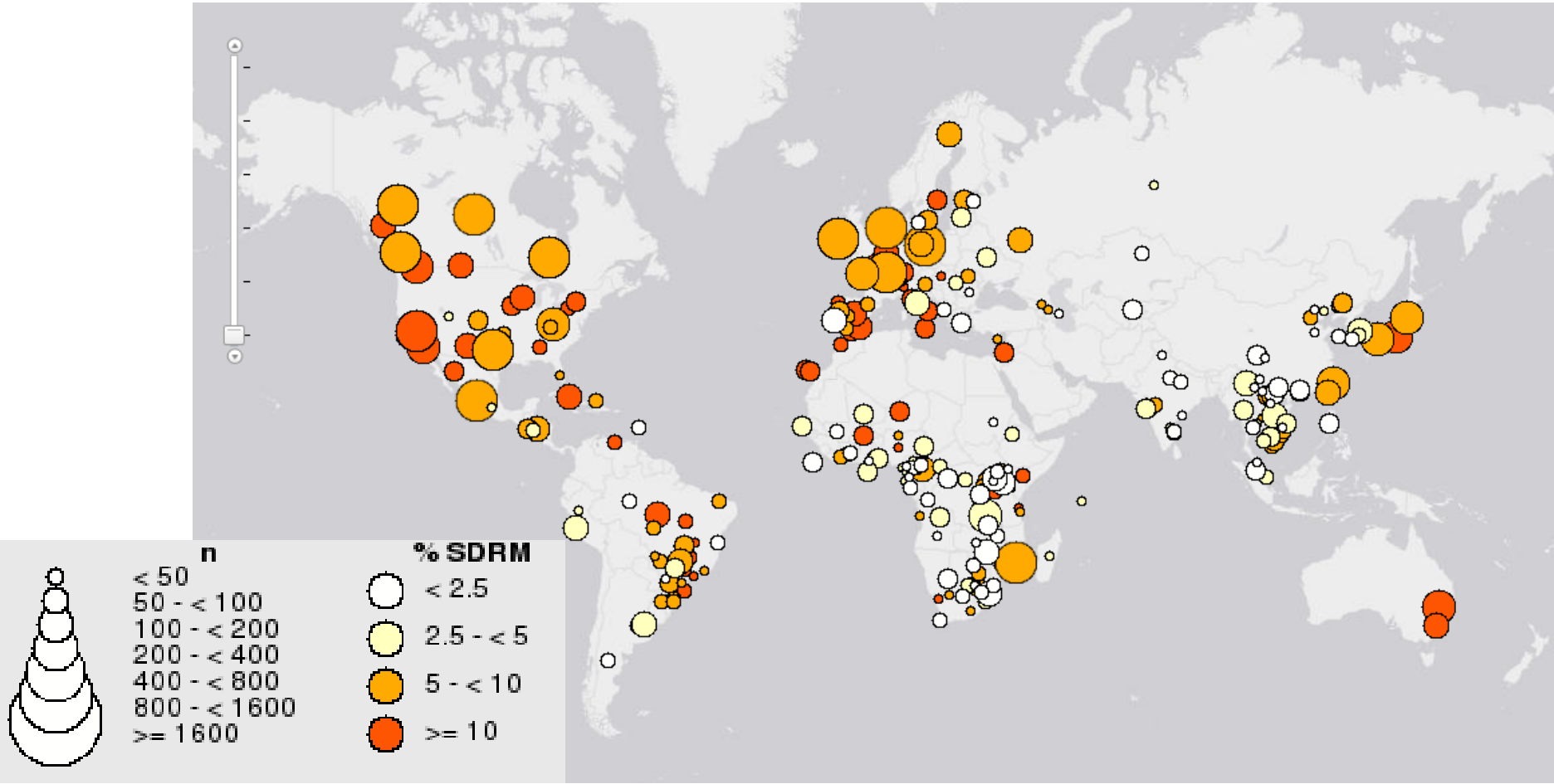
- 22% fail second-line therapy (HIV RNA not suppressed by 6 months)
  - Major cause: poor adherence
  - PI Resistance is infrequent
- Low level resistance to PI may be caused by mutations in *env*?

Hosseinipour *JID* 2013; Stray *JV* 2013

Transmitted Drug Resistance (TDR)

Stanford Resistance Database HIV-1 Drug Resistance in ARV-naive Populations

Compendium of published virus sequences from 46,765 persons, 264 studies



Increasing TDR!

- Assessment of published studies and WHO surveys of HIV drug resistance in 26,102 untreated persons in 42 countries showed:

Region	Rate of Increase of TDR/year since ART roll-out (95% CI)	P-value
East Africa	**29% (15 – 45)**	0.0001
Southern Africa	**14% (0 – 29)**	0.054
West/Central Africa	3% (-0.9 – 16)	0.618

Hamers *Curr Opin HIV AIDS* 2013

Transmitted Resistance in MTN-009 & VOICE

MTN-009 (Women screening for PrEP Trials)

- 26/352 (7.4%) with resistance
  - 62% had single-class NNRTI resistance
  - 19% had dual-class NRTI/NNRTI

VOICE/MTN-003

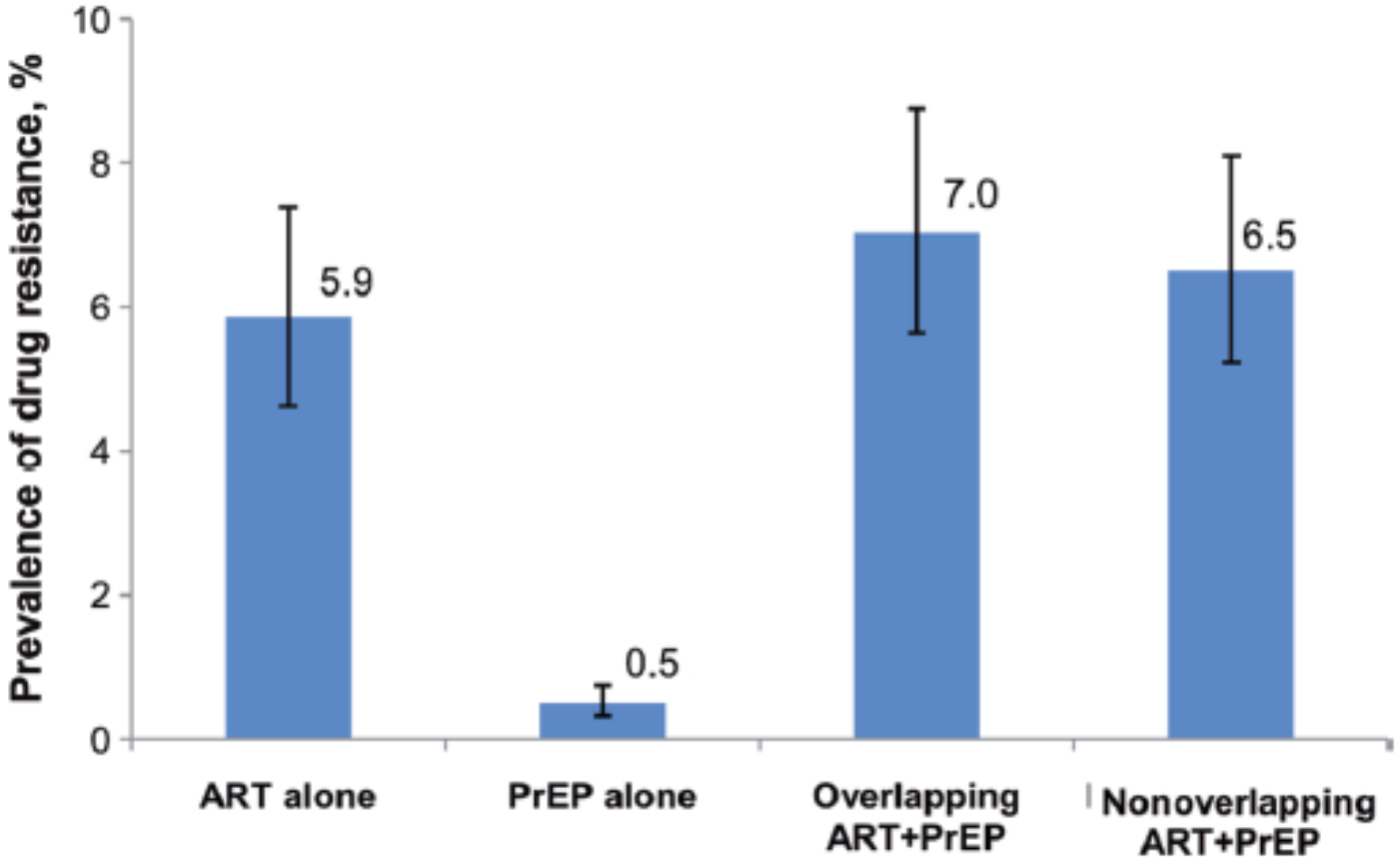
- 8/355 (2.3%) NNRTI-R (K103N/V106M/Y181C)
- 34/355 (9.6%) WHO TDR mutations

Drivers of resistance from ART

- Lack of viral load monitoring
- Loss to follow-up
- Inconsistent access to ART
- Adherence
- Treatment failure

Drivers of Drug Resistance

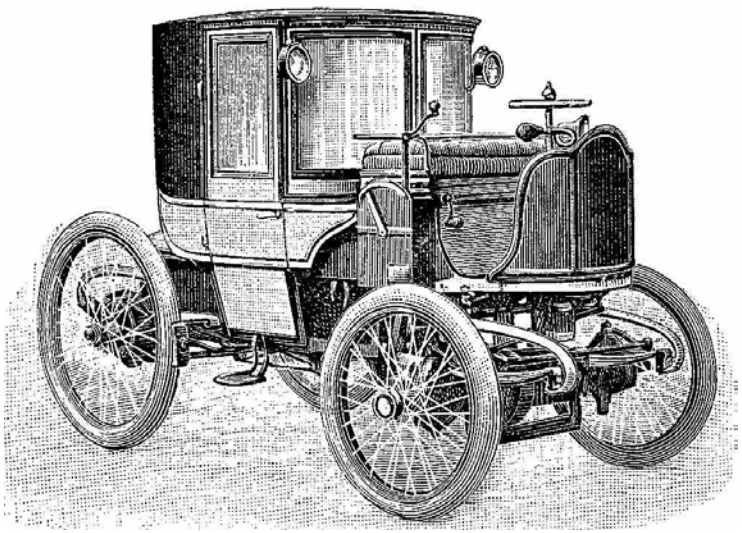
PrEP won't drive resistance – THERAPY will



Abbas *JID* 2013

Drivers of Drug Resistance

PrEP



ART

What can we do to minimize resistance from PrEP?

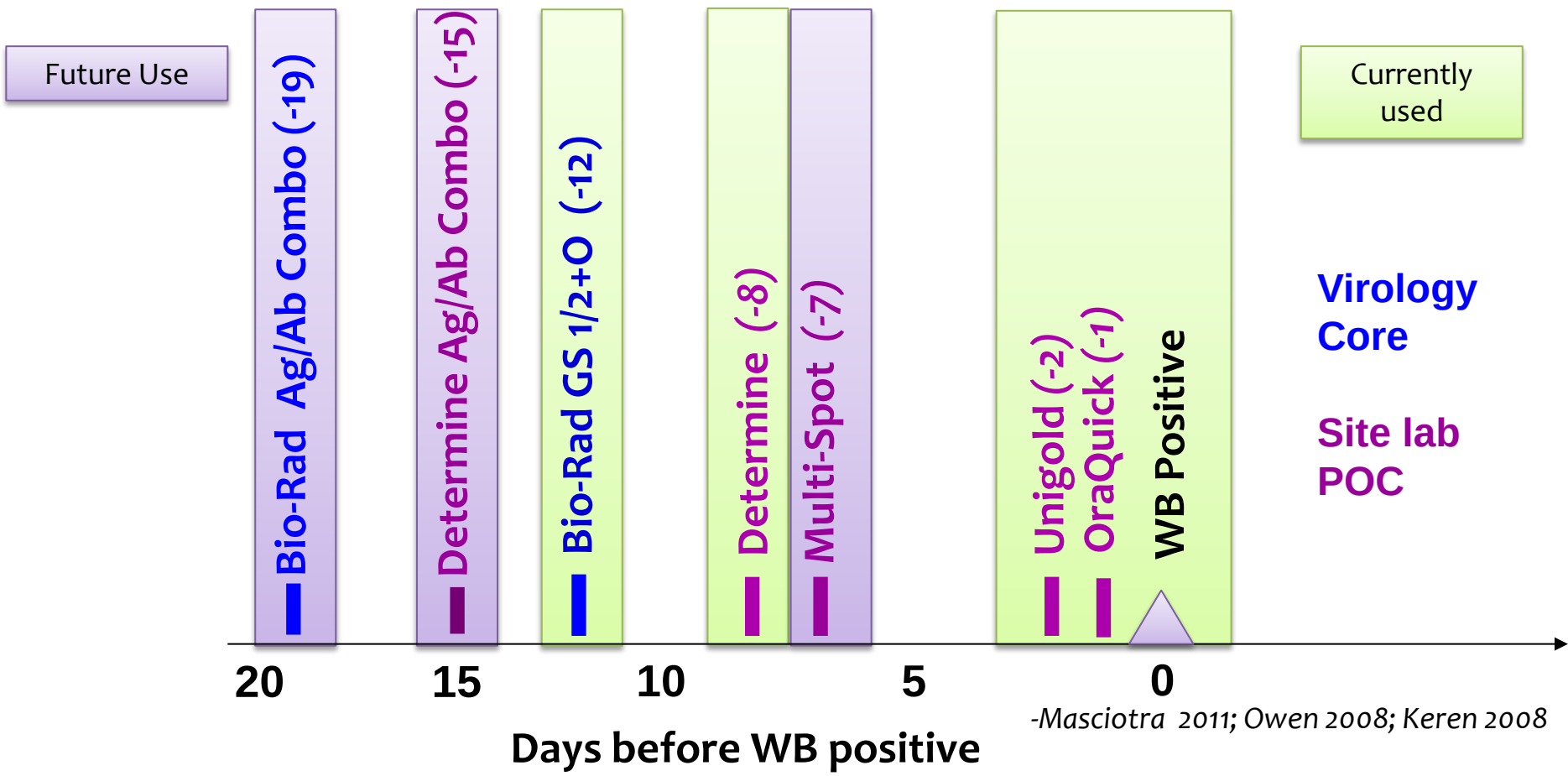
- Earlier detection of HIV infection
  - "Close the window"
- Detect low frequency mutants that can be transmitted or affect response to ART
- Better understand cross-resistance between PrEP and ART – avoid collisions!
  - NNRTI: efavirenz, nevirapine, rilpivirine, dapivirine

Earlier HIV Detection

- 31 acute infections in VOICE were missed by current rapid tests (22 @ enrollment; 9 @ PUEV)
- High rate of resistance (8/28; 29%) in subjects acutely infected at enrollment assigned to active product arms (iPrEx, Partners, TDF2, VOICE)
- Highest risk of resistance for PrEP is from acutely infected persons using active product

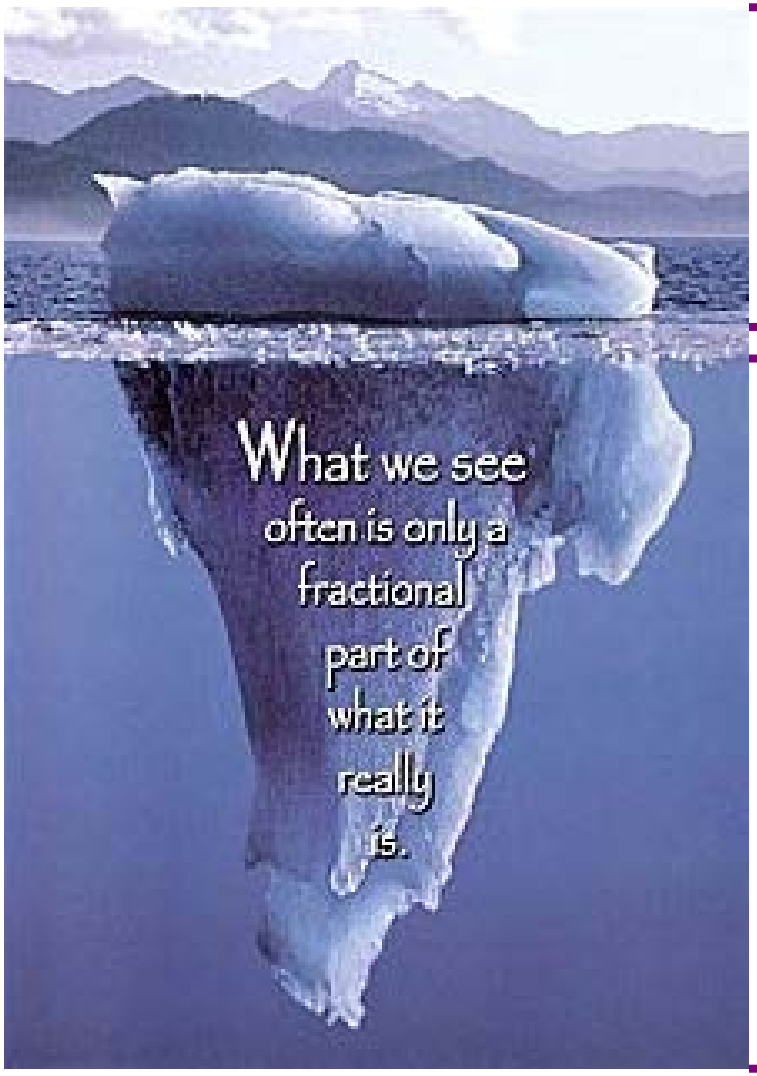
HIV Replication + One or Two ARV = RESISTANCE

Close the "Window Period" with New Diagnostic Tests



VIROLOGY CORE GOAL: Evaluate new HIV diagnostic tests and redesign endpoint algorithm for future studies

Detect Low Frequency Mutants



Standard
Resistance Testing

Sensitive
Resistance testing
(ASPCR)

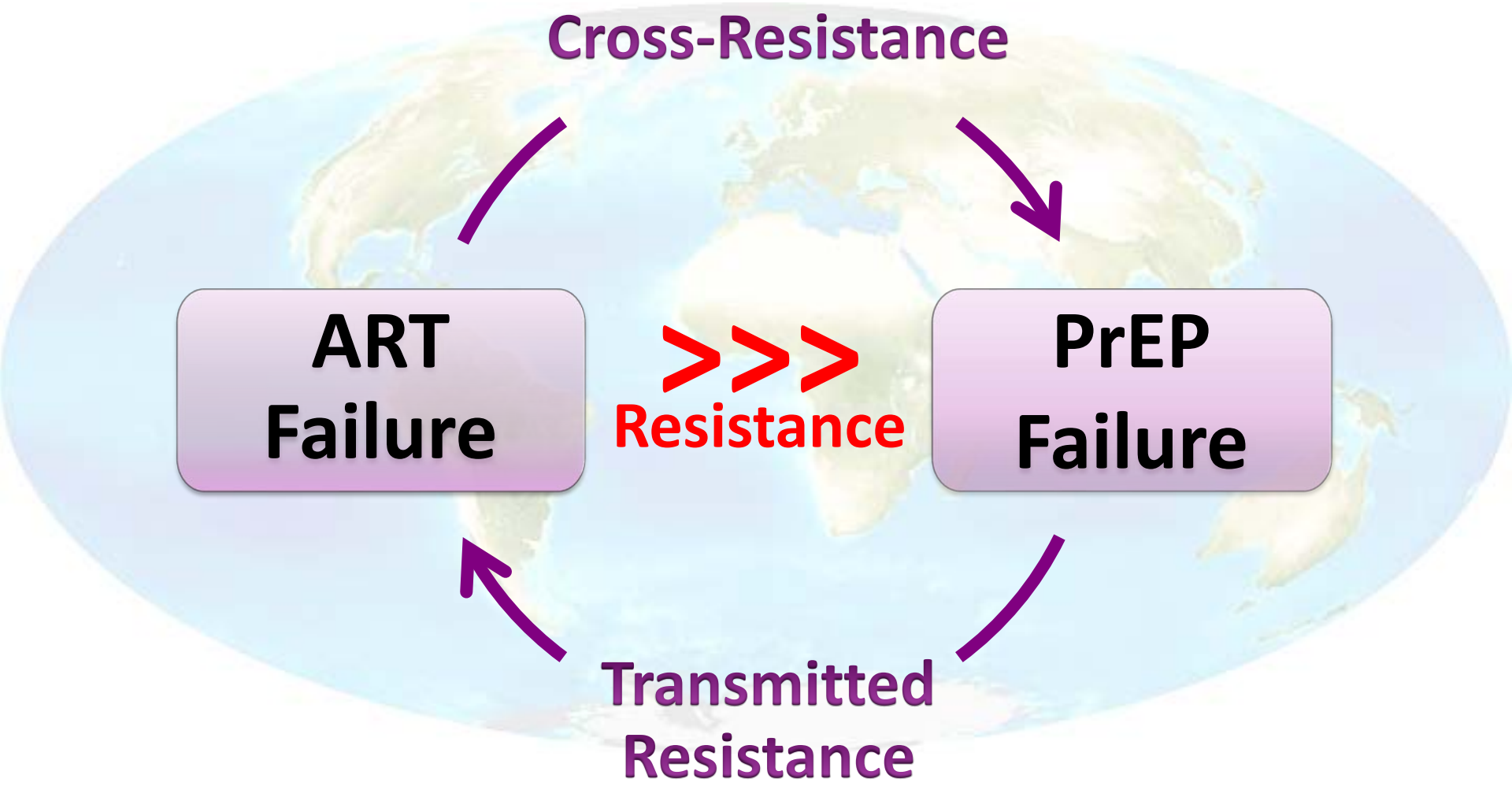
Necessity of AS-PCR

- NVP-resistant mutant frequencies >1% are significantly associated with increased risk of NVP-containing ART failure (A5208/Octane).
- No data on the impact of low frequency **NRTI** mutations on response to future ART
  - Tenofovir and 3TC/FTC used as 1st line therapy in Sub-Saharan Africa
- **Will seroconverting on product select for low-frequency resistance mutations?**
  - **In ASPIRE?**

What can we do to minimize resistance from ART?

- Individual monitoring of ART for viral breakthrough/treatment failure
  - POC HIV-1 RNA assays
- Differentiate non-adherence from HIV-1 drug resistance as cause of breakthrough/failure
  - POC tests for ARV levels or common drug resistance mutations
- Better access to 2nd line therapy for first-line resistance
  - 2nd line may become first-line in specific regions
- Real-time global surveillance for HIV-1 drug resistance
  - When to switch first-line regimen?
- Strengthen ARV supply chain
  - Prevent stock outs

Global Threat of Resistance



We can meet the challenge by…

- Improved individual and epidemiological monitoring for ART failure and drug resistance using standard and sensitive methods for detection
- Simplified single tablet regimens for 1st, 2nd, 3rd ART with a strong supply chain
- Improving HIV diagnostic tests to close the window period during which PrEP could cause resistance
- Gaining a better understanding of cross-resistance between ART and PrEP through analysis of patient-derived viruses, thus avoiding collisions!

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