Should We Be Worried about HIV Resistance in Prevention Trials?

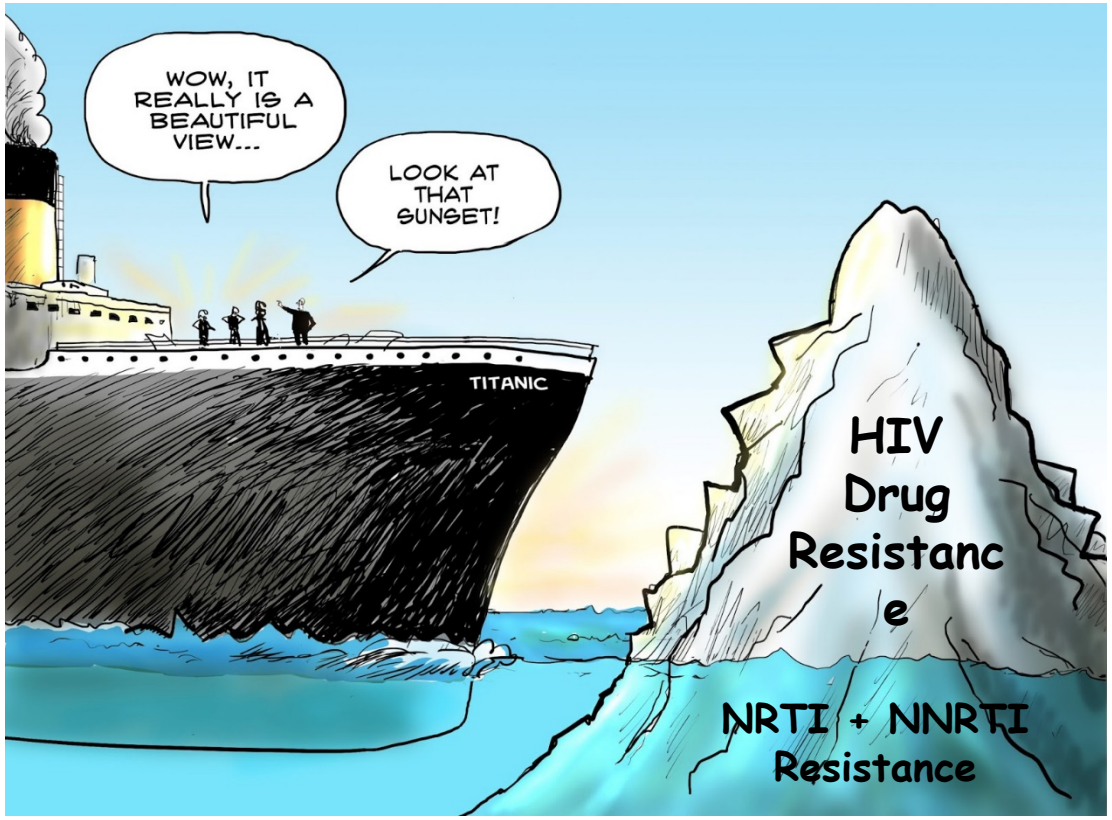
John W Mellors, MD

MTN Regional Meeting Cape Town, SA

25 Sept 2018

YES

HIV Drug Resistance?



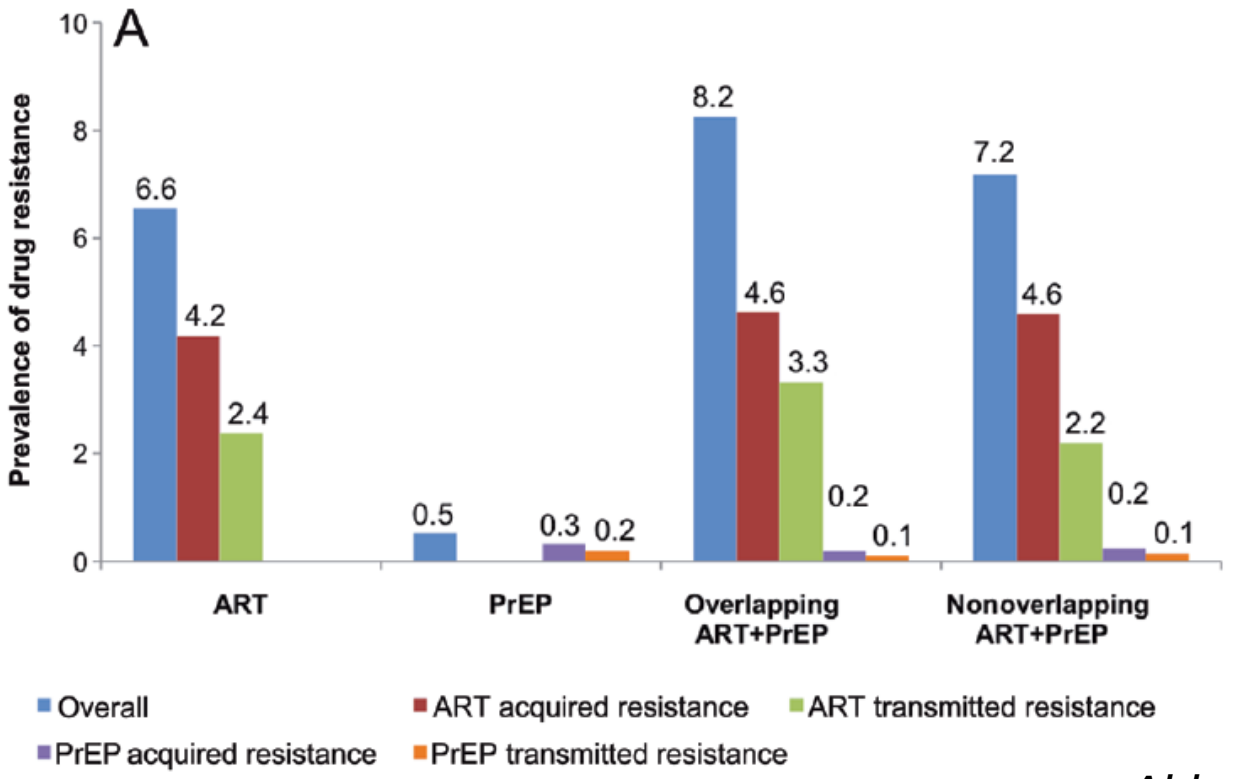
Courtesy Urvi Parikh

Topics

- **Resistance from ART**
- Resistance from PrEP

➢Solutions needed

ART NOT PrEP Drives Spread of HIV Drug Resistance



Abbas, Mellors
JID 2013

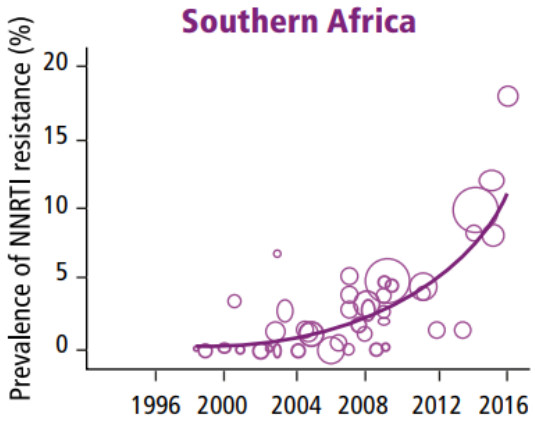
Good News About ART

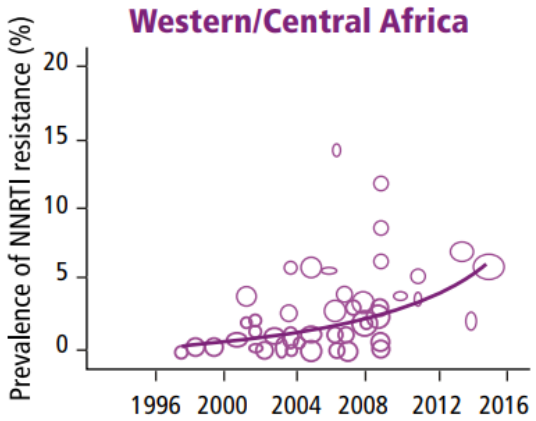
- Has saved 7-8 million lives
- ~21 million are on it (about 50% of all PLWH)
- Major reductions in MTCT
- NRTIs have residual drug activity despite signature mutations
  - Still inhibit wild-type virus
  - Resistance is relative not absolute
  - Complex resistance interactions, e.g. 184V hypersusceptibility to TNV
  - ➢ Surprisingly good efficacy of PI-based 2nd line-ART with recycled NRTI

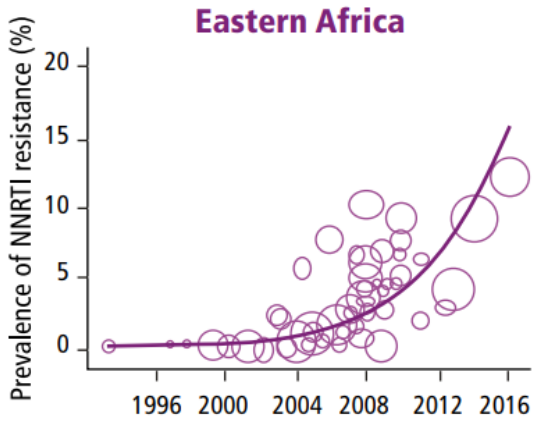
Not So Good News About ART

- Long-term (4-5 year) suppression rates of 60-85%
  - Worse in children, adolescents, MSM, and post-partum women
  - 80% not suppressed have resistance
    - 15-40% on ART could transmit resistance
- Spotty viral load (HIV RNA) monitoring
- Infrequent resistance testing
- Late switches from failing ART
- Surveillance systems are in arrears

Increase in NNRTI PDR







WHO HIV Drug Resistance Report 2017

WARNING

We're Using The Same Drugs and Drug Classes for ART and PrEP!

TDF or TAF and 3TC or FTC

EFV and **DPV**

TLD to the Rescue!

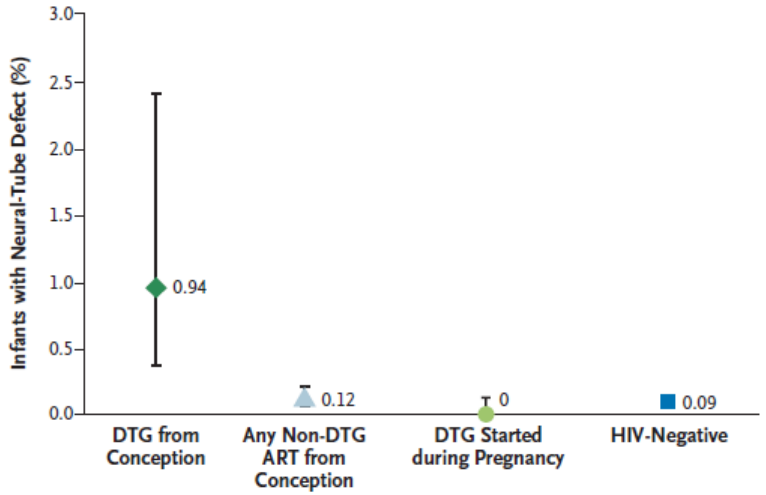
Tenofovir/Lamivudine/Dolutegravir (TLD)

- Better tolerated and higher efficacy than EFV-based regimens (TLE)
  - Little to no transmitted DTG resistance
- PEPFAR rollout/switch starting ($75 per year!)
  - 1st line, 2nd line, beyond
- Cautions
  - DTG monotherapy can select resistance (Wijting, et al. Lancet HIV 2017)
  - TL components overlap with TLE and TNV/FTC for PrEP
  - Double dosing of DTG required with rifampin (Tb)
- ACTG 5381
  - ACTG-PEPFAR Cohort study (N = 1500)
  - TLD for 1st line, 2nd line, 3rd line, and Tb co-infection
  - Adolescents (>10 years) and adults
  - Kenya, Uganda, Zimbabwe, Malawi, SA, and Haiti

Trouble for TLD!

CORRESPONDENCE

Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception



No. of infants with defect	4	14	0	61
No. of exposures	426	11,300	2812	66,057
Percent with defect (95% CI)	0.94 (0.37 to 2.4)	0.12 (0.07 to 0.21)	0.0 (0.0 to 0.13)	0.09 (0.07 to 0.12)
Difference in prevalence (95% CI) — percentage points	Reference	−0.82 (−0.24 to −2.3)	−0.94 (−0.35 to −2.4)	−0.85 (−0.27 to −2.3)

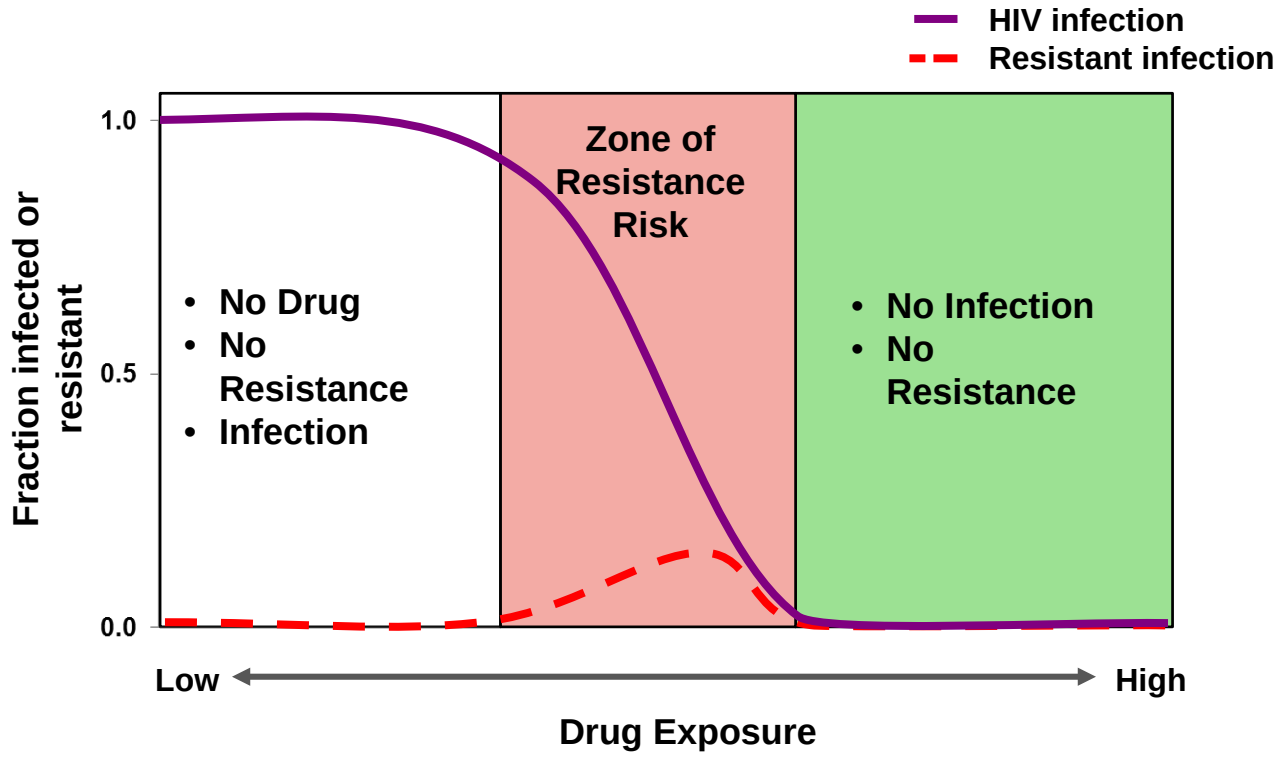
Zash, Mahema, Shapiro. N Engl J Med July 24, 2018

Stay Tuned!

PrEP Resistance Concerns

- Breakthrough infection and subsequent selection of resistance with continued use of PrEP could:
  - Compromise the effectiveness of 1st-line ART for that individual
  - Result in secondary transmission of drug-resistant HIV
- Efficacy of PrEP could be reduced if:
  - Transmitted variant is from a partner failing ART with virus that is cross-resistant to PrEP, or
  - A partner had acquired PrEP-resistant HIV

Theoretical Infection-Exposure-Resistance Relationships

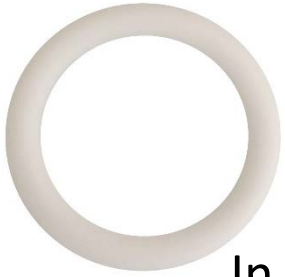


J. Mellors FDA Hearing 2012

Current Status TDF/FTC PrEP and DPV IVR

Oral PrEP
Truvada
(TDF-FTC)

Clinical Trials → Open-Label Extension → Roll-Out



Vaginal Ring
Dapivirine
(DPV IVR)
In Regulatory Review

Resistance in Seroconverters in Studies of TDF/FTC PrEP

Randomized Clinical Trials

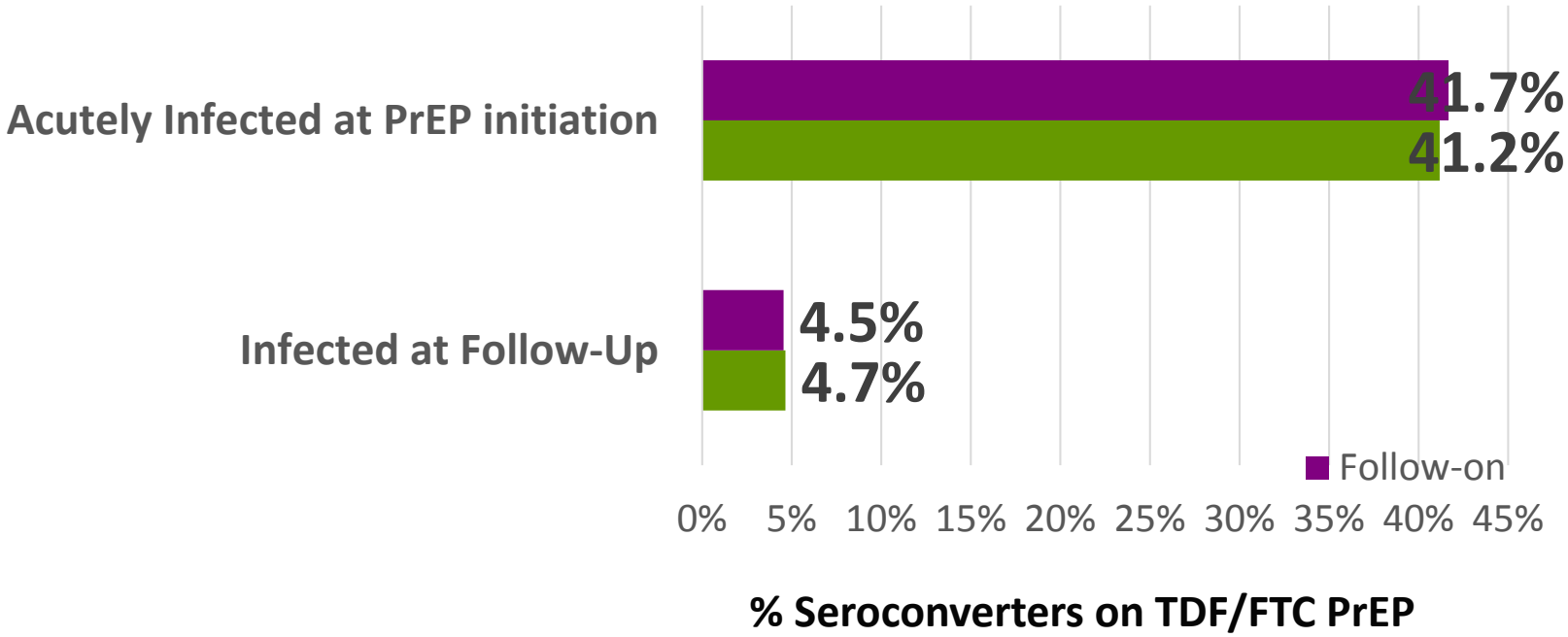
- FEM-PrEP
- iPrEX
- TDF2
- Partners PrEP
- VOICE

Open-Label and Demo Projects

- HPTN-067
- PROUD
- IPERGAY
- USA DEMO
- iPrEX OLE

Total: 216 seroconverters in 8353 PrEP users

Resistance rates higher in acute infection



3 REPORTED PrEP Breakthrough TDR Cases

Case	Patient	PrEP Duration	Adherence	Resistance	Ref
1	Toronto Case 43yo MSM	>21 months	Pharmacy Records TFV levels high	High: 3TC, FTC, NVP, EVG Intermediate: ABC, EFV, ETR, RTG Low: TFV, DTG	Knox et al. NEJM 2017
2	New York Case 26yo MSM	4 months	TFV and TFV-DP levels in hair and DBS consistent with daily use	K65R+M184V, K103S, E138Q, Y188L	Markowitz et al. JAIDS 2017
3	North Carolina Case 34yo MSM	Approx 11 months	Adequate	K65R, M184V, K103N	Thaden CROI 2018

JUST IN CASE: MONITORING RESISTANCE from PrEP Roll-Out

Partner with roll-out projects and programs

Collect and test DBS from PrEP seroconverters

Determine frequency of resistance selection in seroconverters

GEMS
GLOBAL EVALUATION OF MICROBICIDE SENSITIVITY


Kenya


South Africa

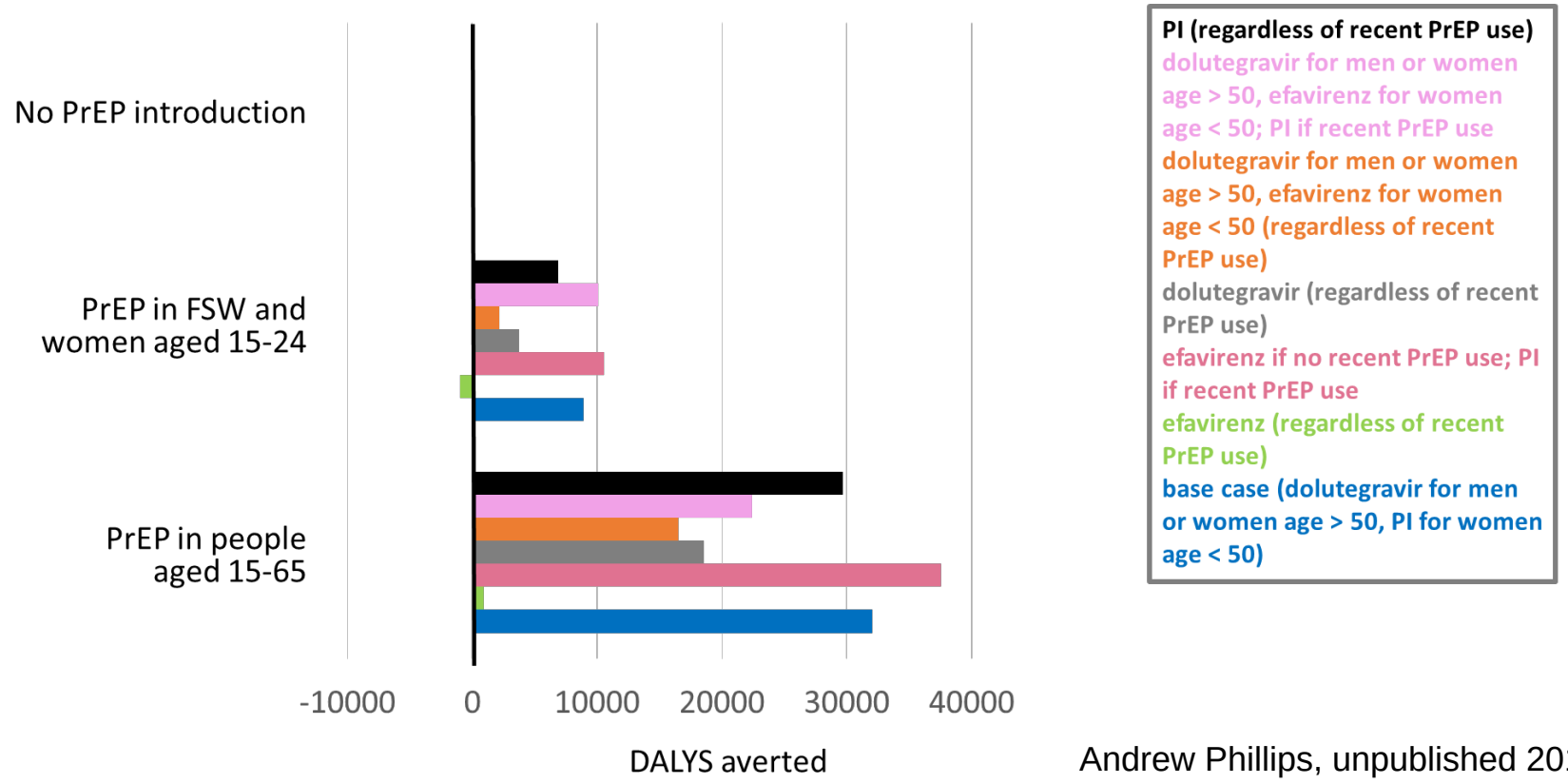

Zimbabwe

USAID
FROM THE AMERICAN PEOPLE

TDF/FTC Resistance Summary

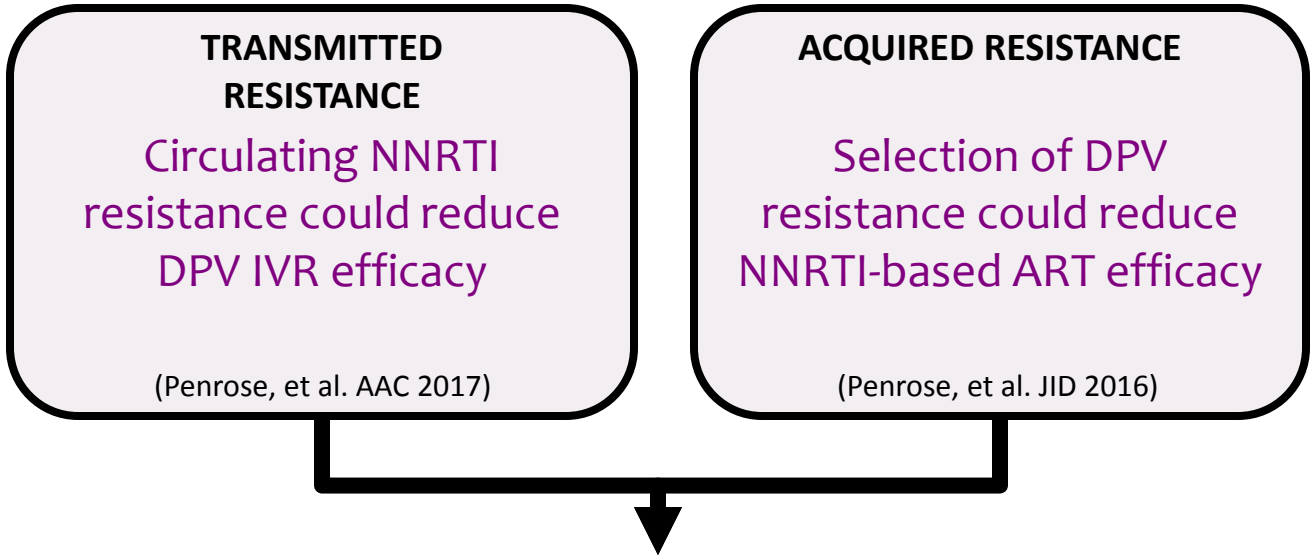
- **Resistance is infrequent (3%)** from use of oral TDF/FTC PrEP if HIV-1 infection is not present at the time PrEP is started
- **Resistance is more common (41%)** if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection
- **Acute HIV-1 infections should be excluded before starting PrEP!**
- **Important to monitor resistance** with PrEP rollout – rates of resistance outside of trial setting unknown.

Use of EFV-based ART in PrEP Seroconverters May Lead to Increase in NNRTI Resistance



Andrew Phillips, unpublished 2018

Resistance Risk with DPV IVR

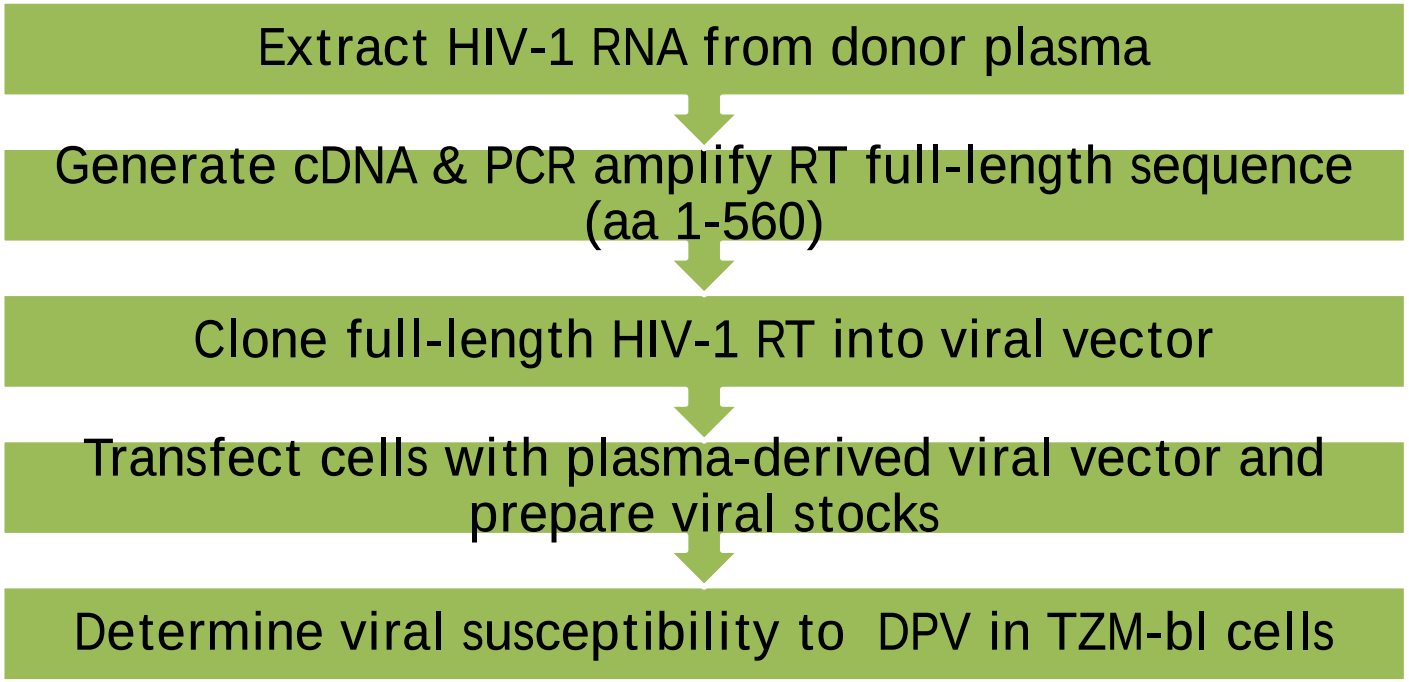


Both would produce an imbalance in resistance of seroconverters between study arms

MTN microbicide trials network

DPV Activity against NNRTI-resistant variants

In-house population phenotyping using plasma-derived recombinant viruses from donors failing 1st line ART with ≥ 1 ARV mutation & RNA >10,000 c/ml



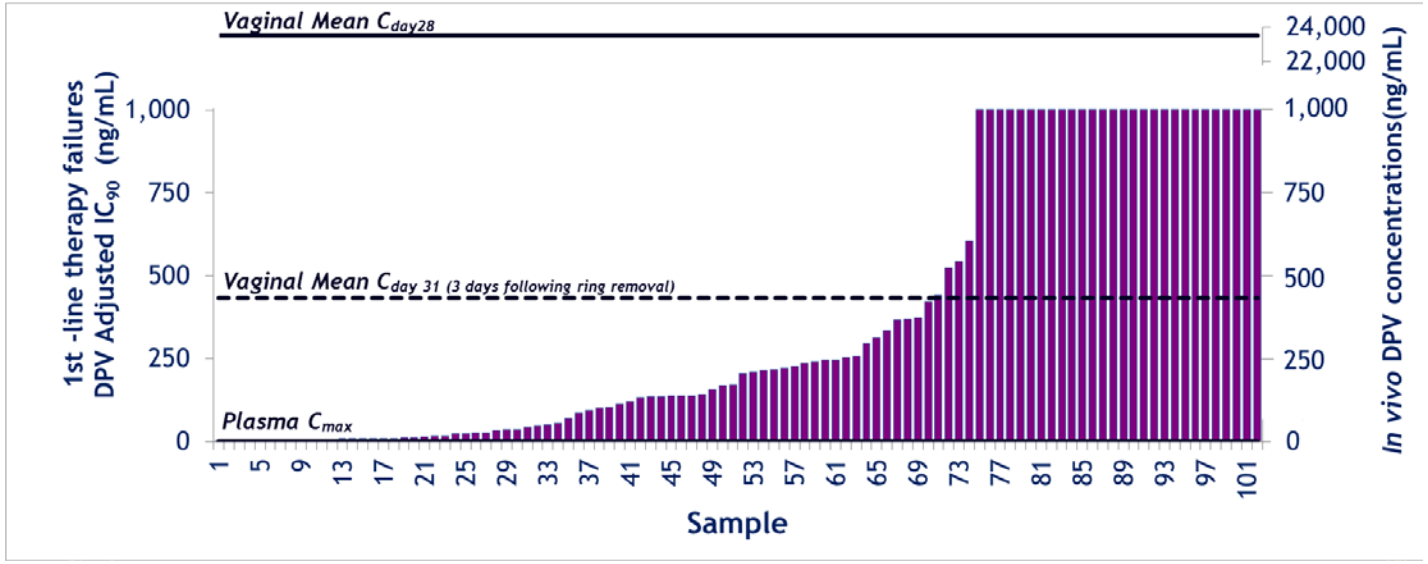
Dapivirine Cross-Resistance

Level of DPV Resistance*	# of Samples (n = 102)
High (≥ 10-fold)	79 (77%)
Intermediate (3 to 9-fold)	14 (14%)
Susceptible (≤ 2-fold)	9 (9%)

* All virus were >10-fold resistant to NVP and EFV

- **K103N and L100I significantly associated with maximum DPV resistance**

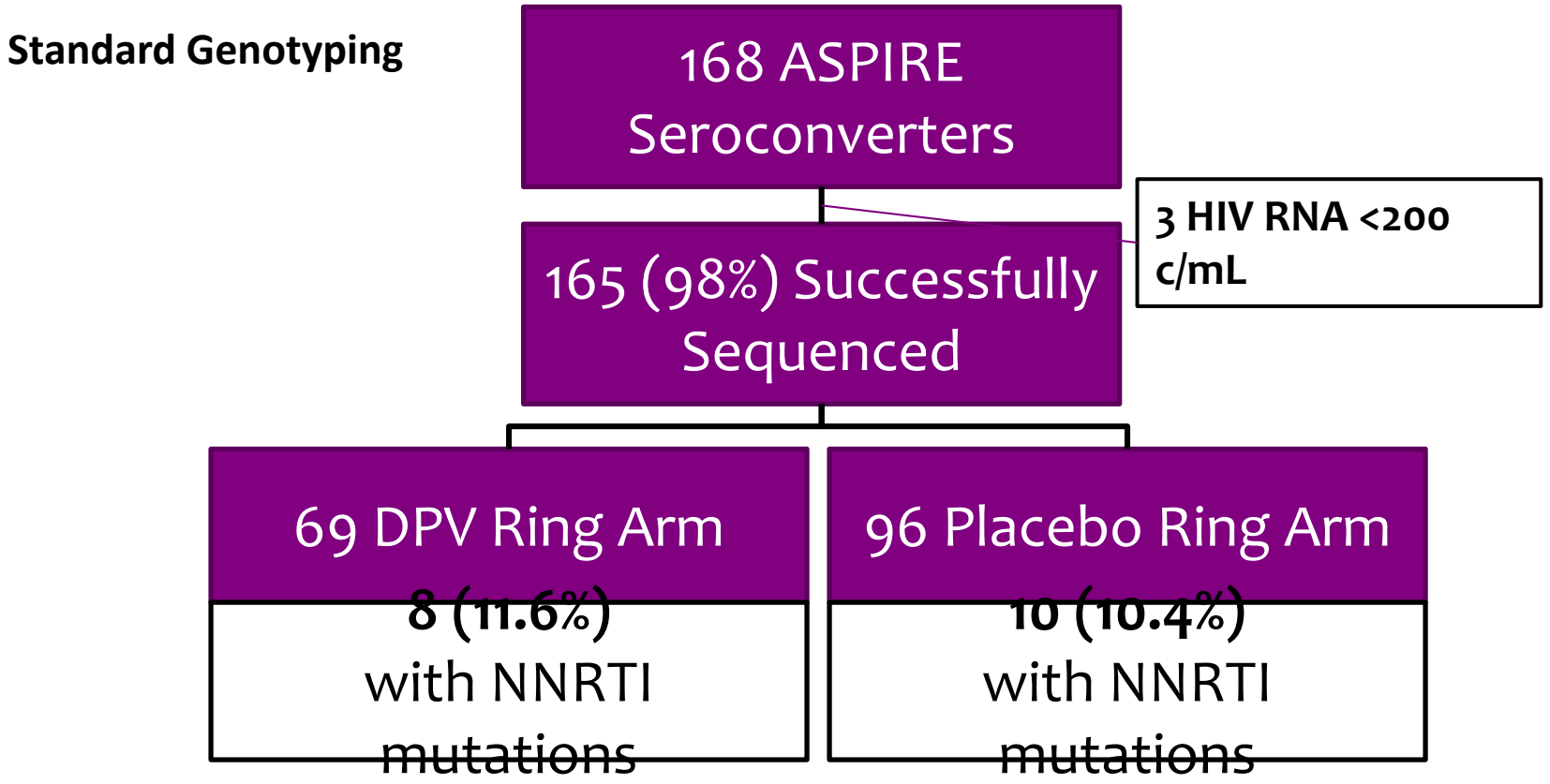
Risk of DPV Breakthrough Infection



- **Vaginal $C_{day\ 28}$ exceeds adjusted IC_{90} of all samples by >23-fold**
- **Risk of breakthrough is seen in a short window following ring removal;**
- **32/102 (31%) viruses exceed $C_{day\ 31}$ following ring removal**

(DPV pK: Nel AM, et *al.* J AIDS Clin Res 2014.)

Same rate of resistance in DPV and PLB arms



Response to 1st-Line ART in Seroconverters from ASPIRE?

MTN-015 Study population			
	All (N=158)	Placebo (N=93)	Dapivirine (N=65)
Age (years)	23 (21, 27)	25 (22, 27)	22 (20, 27)
Clade C virus**	142/155 (92%)	84/92 (91%)	58/63 (92%)
Initial HIV RNA (log_{10} copies/ml)	4.6 (3.9, 5.2)	4.6 (4.0, 5.2)	4.6 (3.6, 5.1)
Initial CD4 count (cells/mm^3)	547 (429, 707)	523 (396, 674)	601 (464, 793)
Median follow up (months)	28.3	29.0	26.7
Initiated ART	87 (55%)	54 (58%)	33 (51%)
At least 6 months FU on ART	67/87 (77%)	43/54 (80%)	24/33 (73%)
Virologic failure	**14/67 (21%)**	**10/43 (23%)**	**4/24 (17%)**

Riddler, et al., In Review

Resistance from 1st-line ART failure in seroconverters from ASPIRE

Resistance mutations at estimated seroconversion and virologic failure (VF)				
Participant	**ASPIRE Arm**	**Initial ART regimen**	**NNRTI mutations at seroconversion**	**Mutations at VF**
1	DPV	EFV/FTC/TDF	None	K103N
2	DPV	EFV/FTC/TDF	V108I/V, E138A	E138A
3	DPV	EFV/FTC/TDF	None	None
4	DPV	EFV/FTC/TDF	H221Y	**V106M, Y181Y/C, H221Y**
5	Placebo	EFV/FTC/TDF	None	None
6	Placebo	EFV/3TC/TDF	None	K103N
7	Placebo	NVP/3TC/d4T	None	G190G/A
8	Placebo	EFV/3TC/TDF	None	K103K/N
9	Placebo	NVP/3TC/d4T	None	K103N

Riddler, et al., In Review

DPV Resistance Summary

- Overall NNRTI mutation frequency did not differ by ASPIRE arm ($p > 0.05$)
- DPV-associated mutations E138K, L100I or Y181C were not detected
- The polymorphism E138A was the most common mutation amongst seroconverters but its frequency did not differ by arm.

- **No obvious difference in response to NNRTI-based 1st-line ART or resistance in DPV vs. Placebo arms of ASPIRE in MTN-015**
- **NGS Data ongoing – will be presented at tomorrow's plenary**

Yes, we should worry about PrEP resistance…

But more so about resistance to PrEP from ART

What to do?

- Aggressive surveillance
  - ART starts
  - PrEP and ART failures
    - NGS
- Define the HIV RNA (Viral load) cascade
  - Proportion on ART tested
  - Proportion tested suppressed/not suppressed
  - Proportion switched within 3 months
  - Proportion switched that are suppressed/not – 1, 3, 5 years

What to do?

- Assess and improve the VL cascade
  - Quantify drug-resistant viremia AUC
- Plan for the long-term!
  - If TLD plan fails, what next?
  - TAF/FTC/DRV/c?
  - DRV/c/ETV/InSTI?

Conclusions

- HIV drug resistance threatens the ART rollout
  - and PrEP rollout secondarily
- Let's hope that no additional NTDs appear from TLD
  - Default is starting TLE despite spreading NNRTI resistance
    - May not be good for DPV IVR
  - Need better 2nd line ART options
    - Including those for PrEP failures
- **Maintain diligence in monitoring ART failures and PrEP failures for standard and low-frequency resistance in trials**

Acknowledgements

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MTN Laboratory Core
VOICE Protocol Team
MTN Sites
All Study Participants

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Images in slide set from google.com

Questions?

HIV Drug Resistance… Not an Iceberg

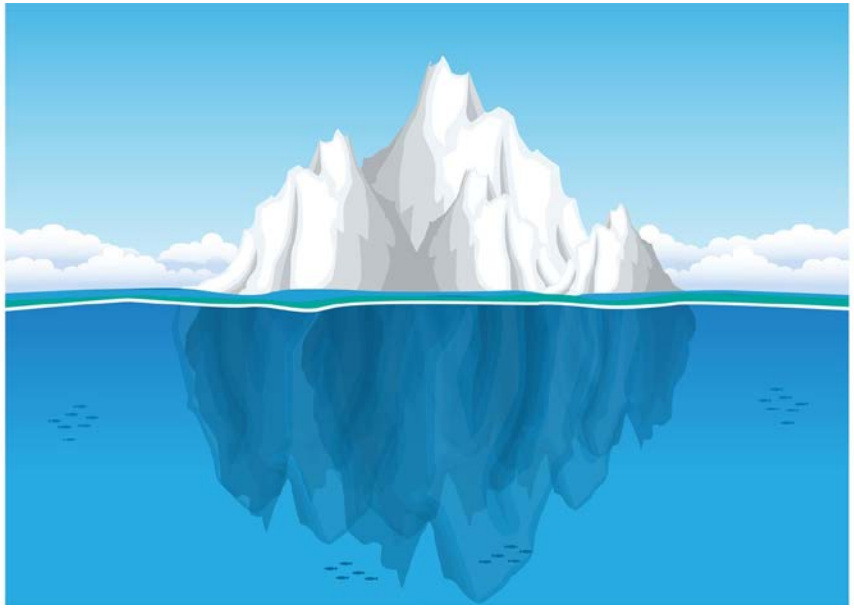
But caution advised

Resistance from PrEP

- What is known about TDF/FTC Resistance
  - TDF/FTC Resistance from trials
  - Breakthrough cases
  - Monitoring PrEP resistance in rollout
- What is known about DPV Resistance
  - Standard genotyping/NGS/phenotyping
- Concerns
  - Rising NNRTI resistance from treatment and transmission
  - ART driving resistance
  - Hold on dolutegravir means loss of 1st line ART without a good substitute

Things to Worry About

1. Rising NNRTI resistance from treatment and transmission
2. Hold on dolutegravir means loss of 1st line ART without a good substitute



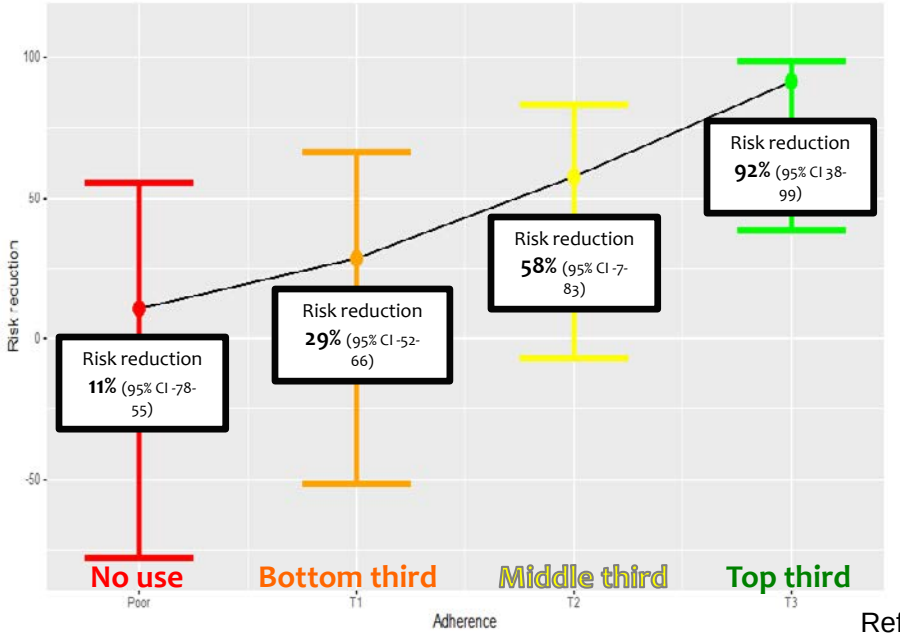
Concerns

- Increasing access to ART
- Very little individualized monitoring – mostly in private sector
- Same drugs used for treatment and prevention

DPV IVR Adherence vs. HIV protection:

Ring data three months prior to detection

Proportion of f/u	20%	27%	27%	27%	*Placebo 100%*
Incidence /100 p-y (# infections)	4.9 (10)	3.1 (8)	1.9 (5)	0.4 (1)	*4.7 (47)*

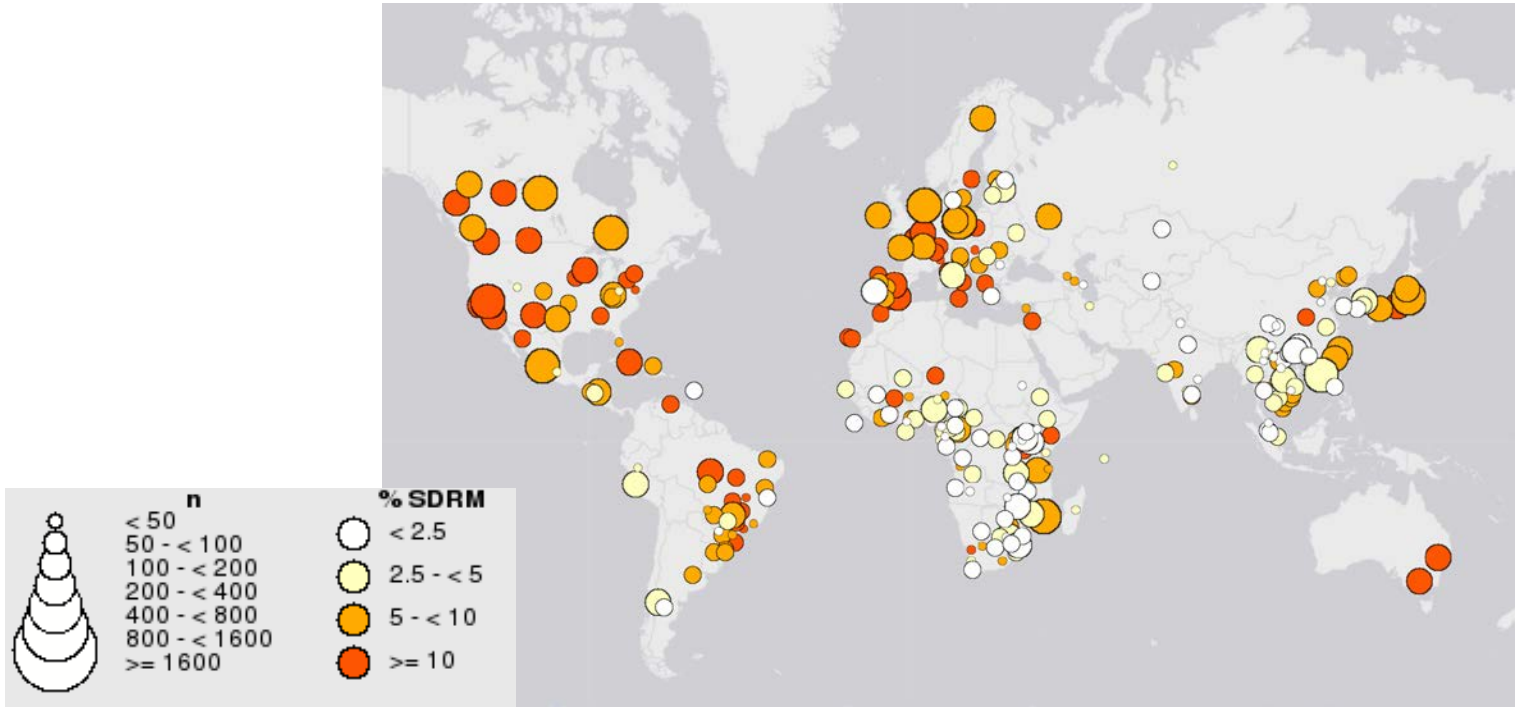


ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Ref: Brown AIDS 2016 Abst. TUAC0105LB

Transmitted Drug Resistance

Stanford Resistance Database HIV-1 Drug Resistance in ARV-naive Populations
Compendium of published virus sequences from 50,869 persons, 287 studies



Stanford Database 2018