



What is the Real World Impact of ARV Resistance?

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MTN Regional Meeting Cape Town, SA

10 Sept 2019

DRUG RESISTANCE



PrEP

ART

Will it Rain?

- Global trends in drug resistance
- Impact of Resistance on ART
- Impact of Resistance on PrEP
 - TDF/FTC PrEP: Trials to Rollout
 - DPV PrEP: Trials to Open Label
- Closing Thoughts

WHO Definitions

ADR

ACQUIRED DRUG RESISTANCE

Resistance emerges in someone taking ARV

TDR

TRANSMITTED DRUG RESISTANCE

A person is infected with drug resistant HIV

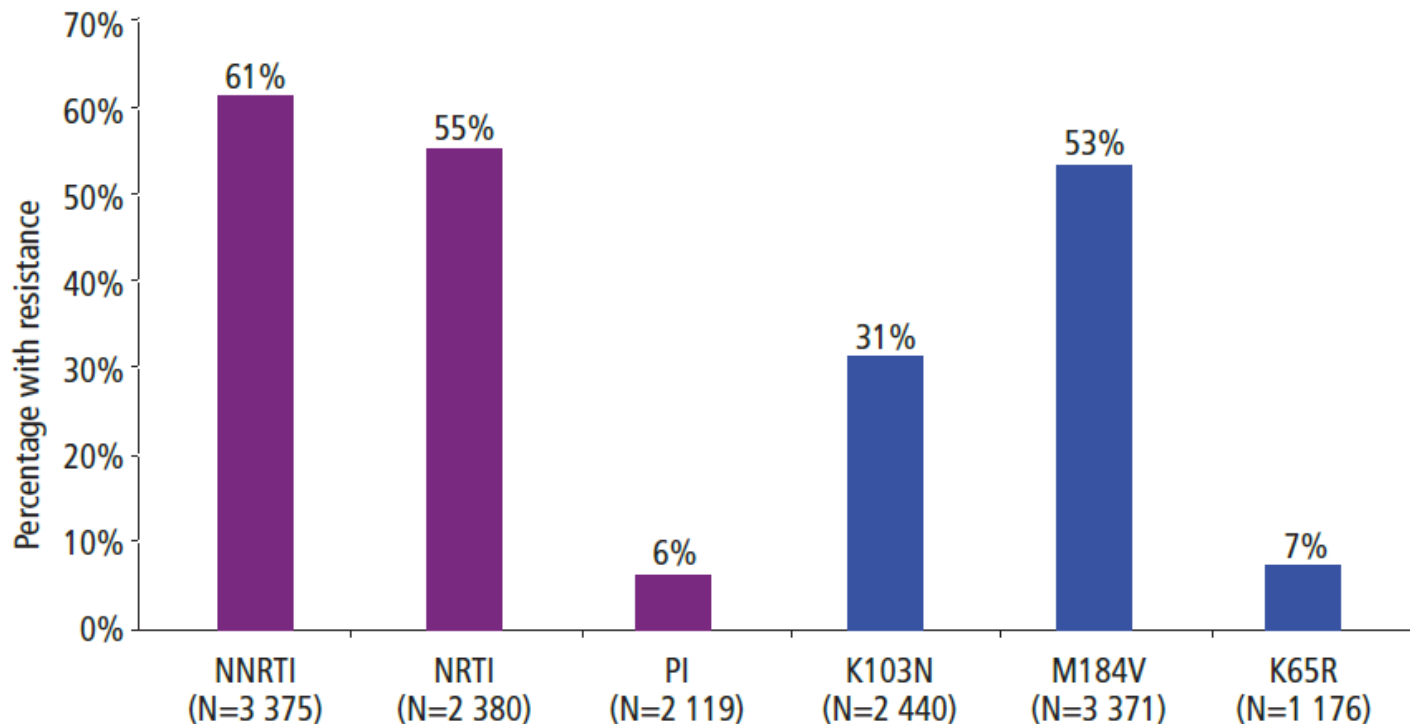
PDR

PRE-TREATMENT DRUG RESISTANCE

Drug resistance detected in someone starting ART

ADR among Individuals on ART

Based on systematic literature review, 2014 – 2017, WHO Resistance Report 2017

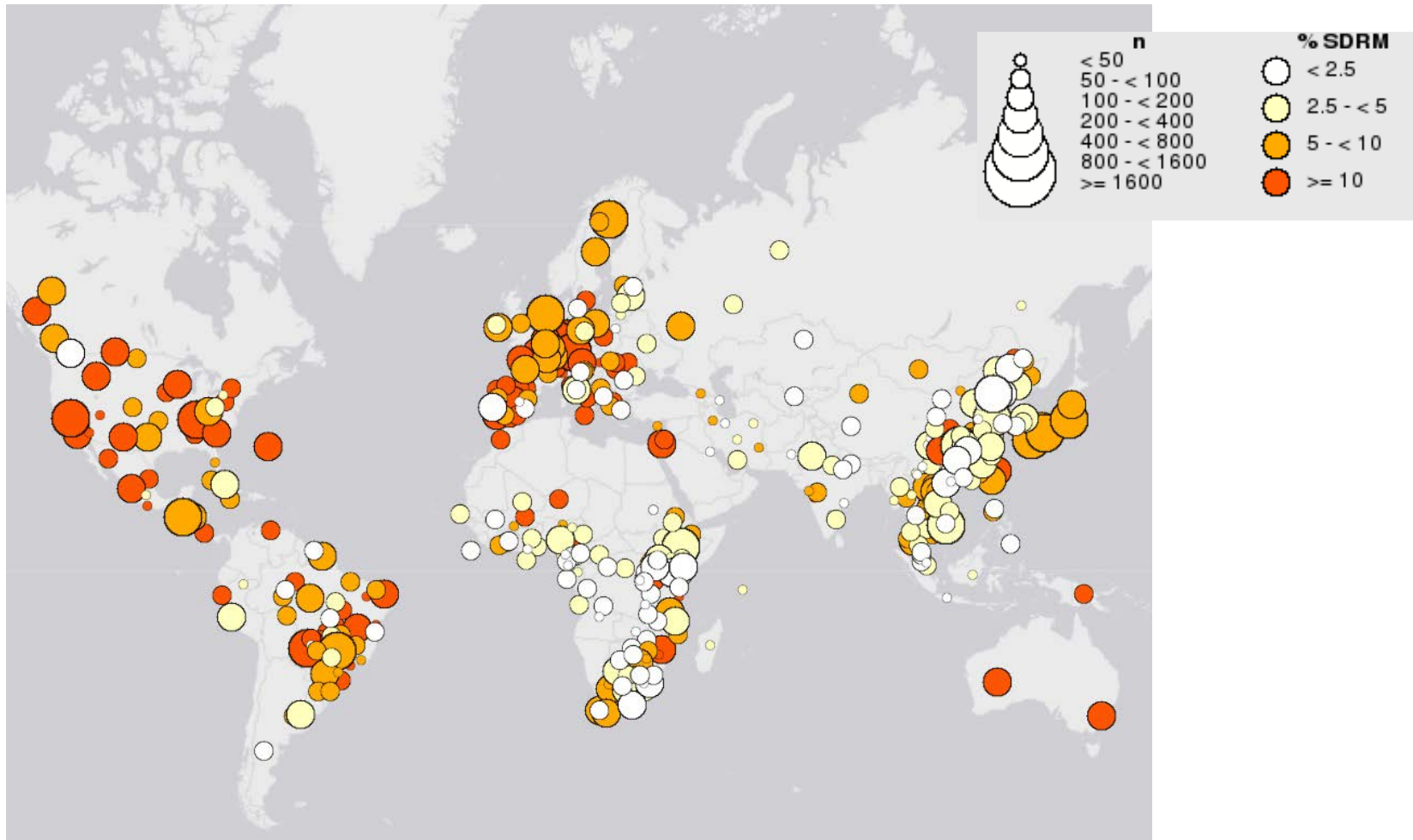


NNRTI=non-nucleoside reverse-transcriptase inhibitor
NRTI=nucleoside reverse-transcriptase inhibitor
PI=protease inhibitor

Global Rates of PDR

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

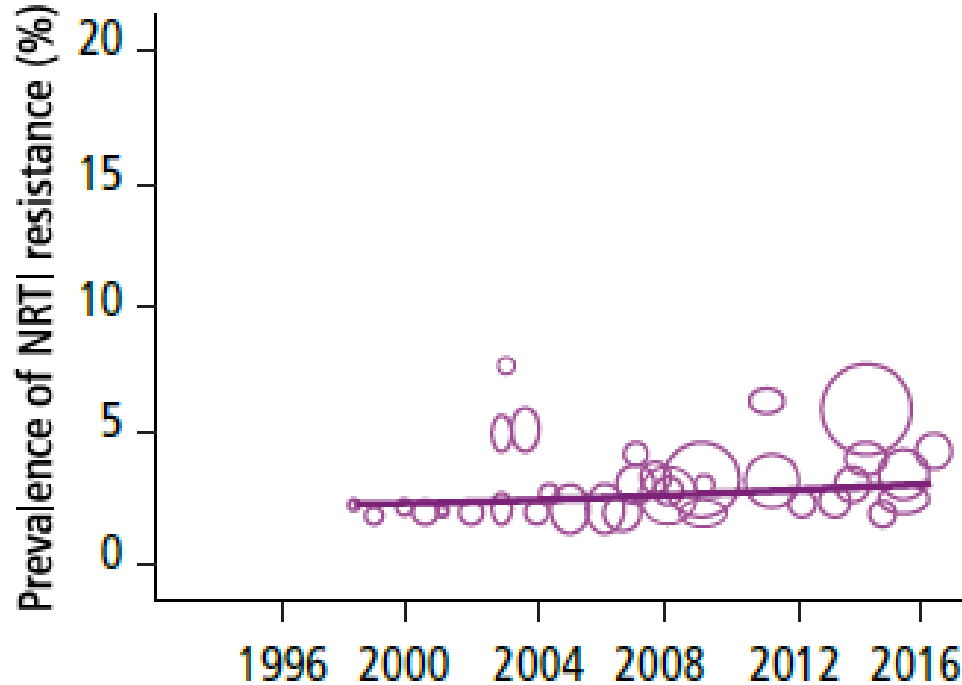
Compendium of published virus sequences from 95,024 persons, 442 studies, June 2019



NRTI PDR

PDR = Pre-treatment drug resistance (transmitted + prior ARV exposure)

Southern Africa



Significant
increase but
rates still low
($<5\%$)

Studies: 61 Patients: 11 855
P-value for association: 0.0154

NNRTI PDR

PDR = Pre-treatment drug resistance (transmitted + prior ARV exposure)

WHO National Survey Data

WHO region	Country	Survey year	All (women and men)	Women	Men
African region	Cameroon	2015	<10%	10-30%	<10%
	Eswatini	2016	10-30%	10-30%	<10%
	Namibia	2015	10-30%	10-30%	10-30%
	Uganda	2016	10-30%	10-30%	10-30%
	South Africa	2017	10-30%	10-30%	10-30%
	Zimbabwe	2015	10-30%	10-30%	<10%

Prevalence of PDR to EFV and/or NVP:



<10%



10-30%



>30%

Projected Impact of HIVDR

HIV Synthesis Model, Sub-Saharan Africa 2016 - 2030

Projections	AIDS Deaths	New Infections
With HIVDR	5,600,000	5,100,000
PDR < 10%	710,000 (13%)	380,000 (7%)
PDR ≥ 10%	890,000 (16%)	450,000 (9%)

**AIDS deaths and new HIV infections may increase
with increasing prevalence of PDR**

Consequences of ADR and PDR with ART and PrEP

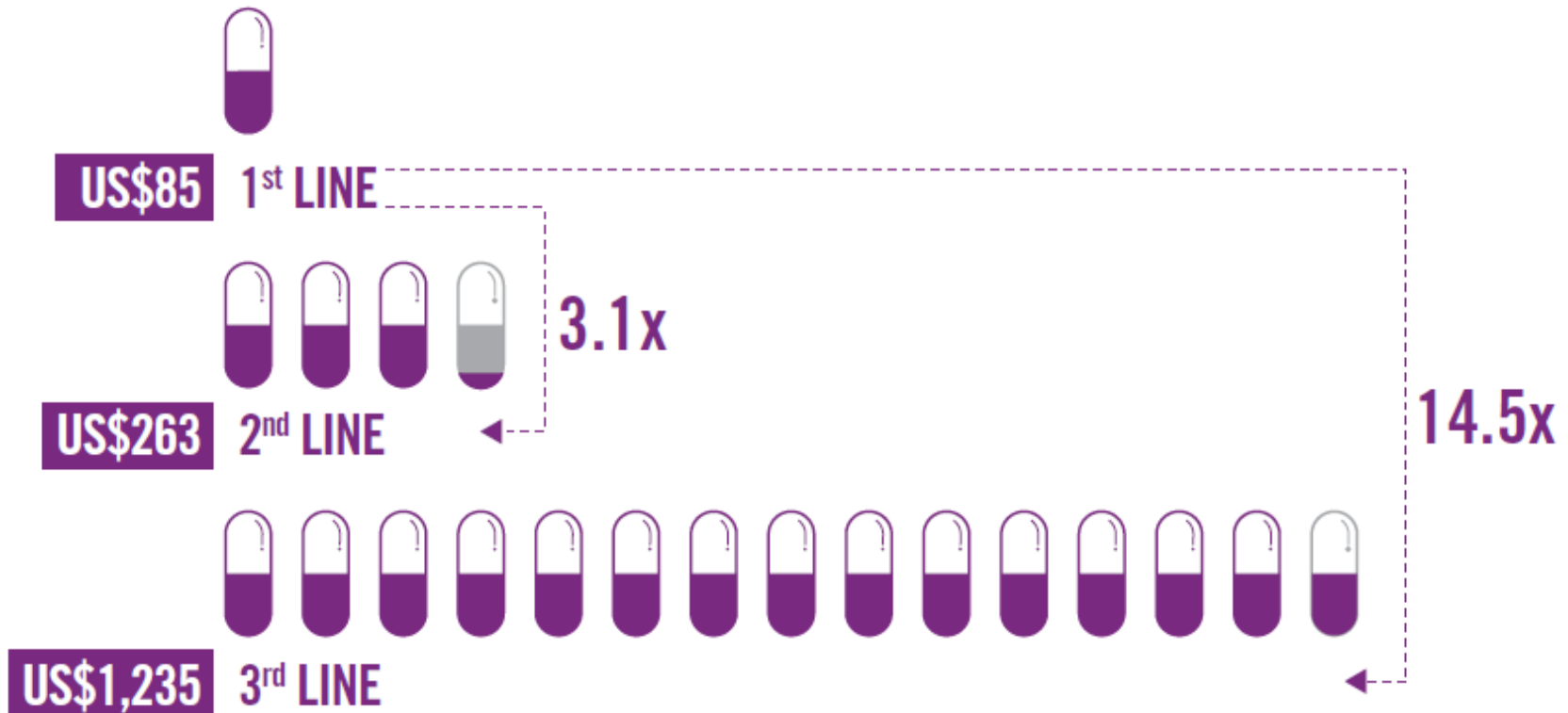
Rising rates of PDR

- PDR reduces the effectiveness of 1st line ART. DTG promising but data is limited
- Newly infected people have to start with more complex 2nd line regimens
- PrEP fails to protect against resistant virus from partner

High prevalence of ADR in treatment failures

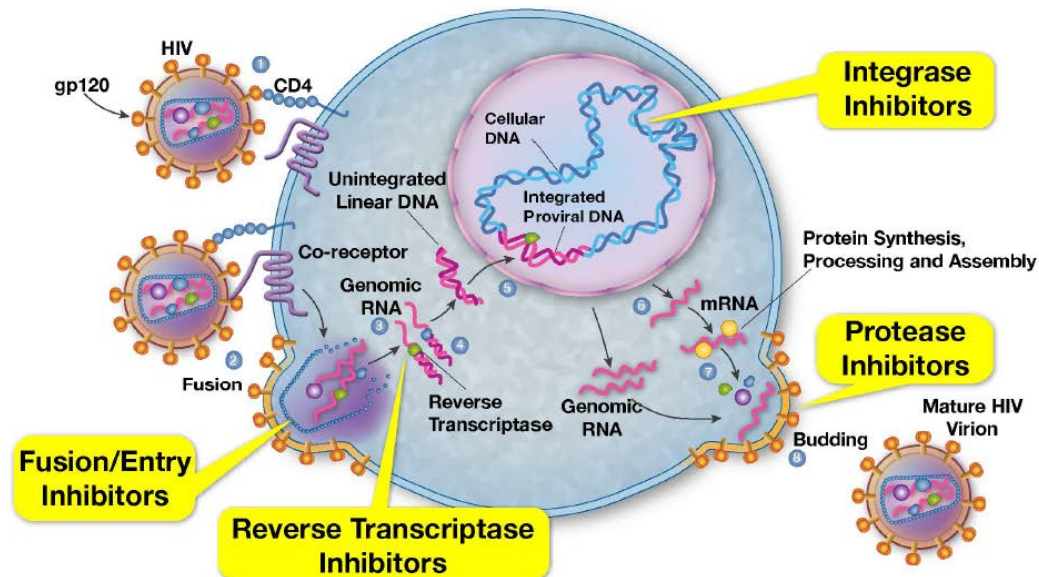
- Greater risk that someone with ADR will transmit resistant virus to their partner
- Increased risk of morbidity and mortality
- More expensive and complex treatment regimens

Increasing Cost and Complexity with Therapy Switches



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

Class	ART	PrEP
NRTI	Tenofovir, FTC, TAF	Tenofovir, FTC, TAF
NNRTI	Efavirenz, Rilpivirine	Dapivirine
Integrase Inhibitors	Dolutegravir	Cabotegravir





TDF/FTC PrEP

TDF/FTC Resistance from Trials and Open Label Studies

Randomized Clinical Trials



FEM-PrEP



iPrEX



TDF₂



Partners PrEP



VOICE

N = 5475

Open-Label and Demo Studies



HPTN-067



PROUD



IPERGAY



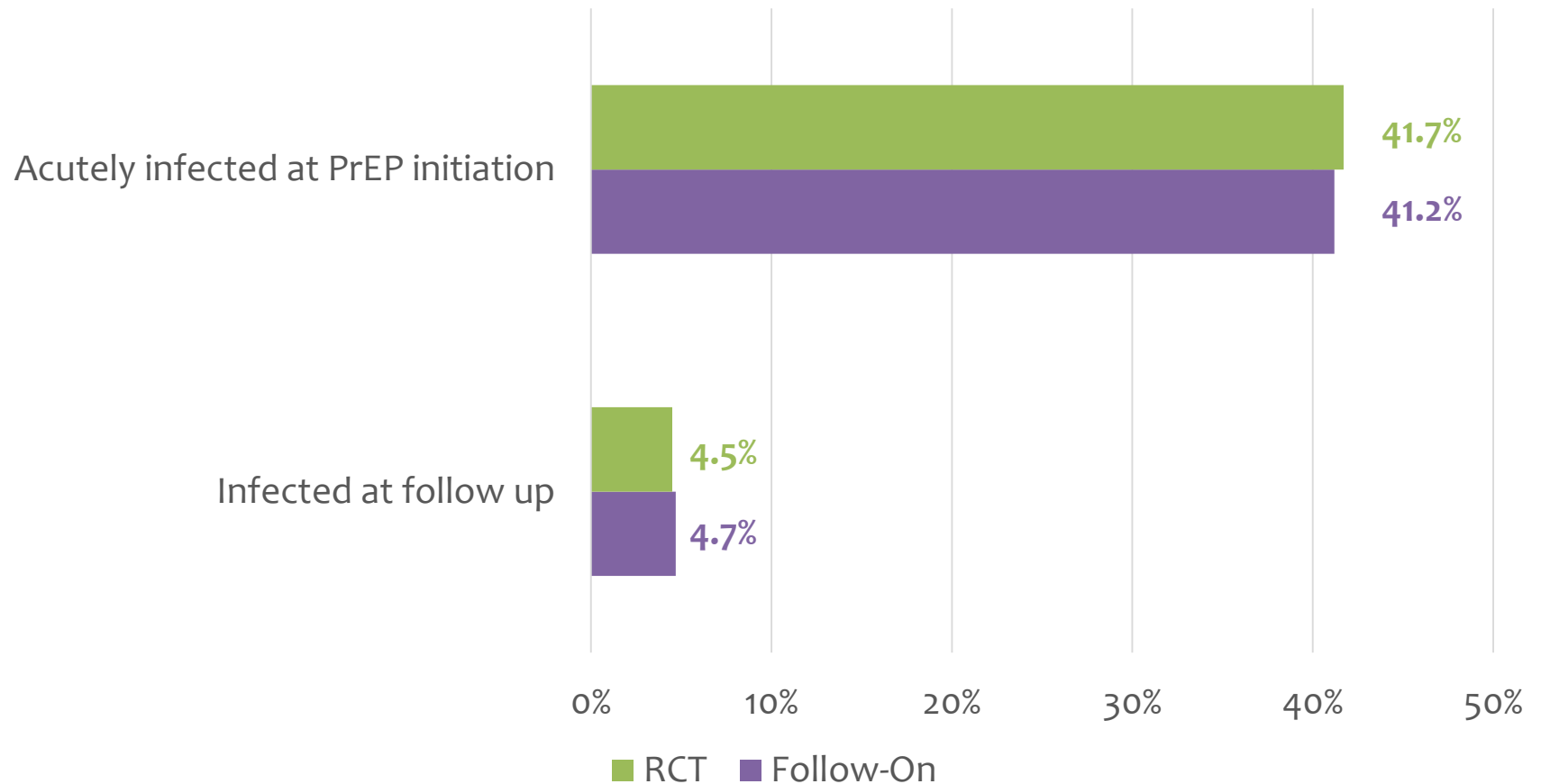
USA DEMO



iPrEX OLE

N = 2878

TDF/FTC Resistance from Trials and Open Label Studies



Trials vs Real World

Trials

Monthly HIV testing; rule out acute infection with VL

Standard and sensitive resistance test; PK testing

Stable source of product

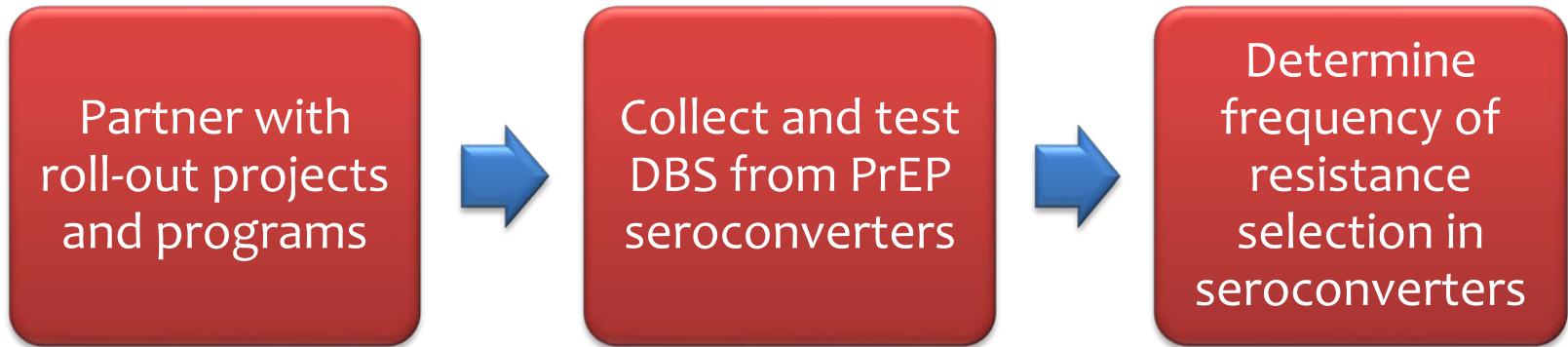
Real World

Quarterly or less frequent testing

Resistance and PK testing only through projects

Drug stock outs, changes in access, intermittent use

PrEP Resistance Monitoring: Rollout



Coordinated by:

GEMS, MOH, National Labs, USG Partners (CDC, USAID), NGO and Academic Project Partners

Sample Size:

Approximately 500 infected clients in 3-5 countries



USAID
FROM THE AMERICAN PEOPLE



Resistance Monitoring in TDF/FTC PrEP Rollout



Kenya

Protocol implemented as part of national rollout



South Africa

Implemented by project partners



Zimbabwe

Protocol implemented as part of national rollout



Uganda

Implemented by project partners



Eswathini

Planning in progress

Current Partners in Four Countries

Kenya



South Africa



Zimbabwe



Uganda



UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER

64,000 lives on PrEP through 28 partners being monitored for HIVDR

5 Reported TNV/FTC Breakthrough HIVDR Cases

Case	Patient	PrEP Duration	Adherence	Resistance	Ref
1	Toronto 43yo MSM	>21 months	High (PK)	High: 3TC, FTC, NVP, EVG Intermediate: ABC, EFV, ETR, RTG Low: TFV, DTG	Knox NEJM 2017
2	New York 26yo MSM	4 months	High (PK)	K65R+M184V, K103S, E138Q, Y188L	Markowitz JAIDS 2017
3	North Carolina 34yo MSM	~11 months	Adequate	K65R, M184V, K103N	Thaden CROI 2018
4	King Country MSM	Unknown	High (Self-Report)	reported resistance to both drugs in Truvada	Golden, unpublished
5	San Francisco 21yo MSM	13 months	High (PK)	L74V, L100I, M184V, K103N	Cohen IDWeek 2018

Amsterdam Case (CROI 2017): No resistance

What does it mean?

- PrEP works to prevent HIV infection in those who use it.
- Number of reported seroconverters on PrEP is very small, but if you do get infected on PrEP, there is a risk of resistance
 - May have already been infected when PrEP was started
 - Inconsistent adherence before and after infection occurred
- **Resistance should continue to be monitored with PrEP rollout.**

Treatment after PrEP Seroconversion

If a PrEP user becomes infected with HIV, will first line ART still work?

WHO First Line Recommendations

1. DTG-based regimen (2018)
2. TDF + 3TC or FTC + EFV_{600mg} (2013 and 2015)

Modelling Approach:

- Individual-based model of heterosexual transmission and progression of HIV and the effect of ART. This same model used to address a variety of policy questions relating to prevention, testing and treatment programmes
- Calibrated to KZN



Dolutegravir: Promising but with Concerns

- 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



- DTG monotherapy can select resistance (Wijting, et al. Lancet HIV 2017)
- TDF/FTC is still used with PrEP and first line ART
- Double dosing of DTG required with rifampin (Tb)

Limited Data on 1st line DTG

- Will DTG be effective against PDR with M184V and/or K65R?
- 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



DPV Ring

4 Dapivirine Ring Studies

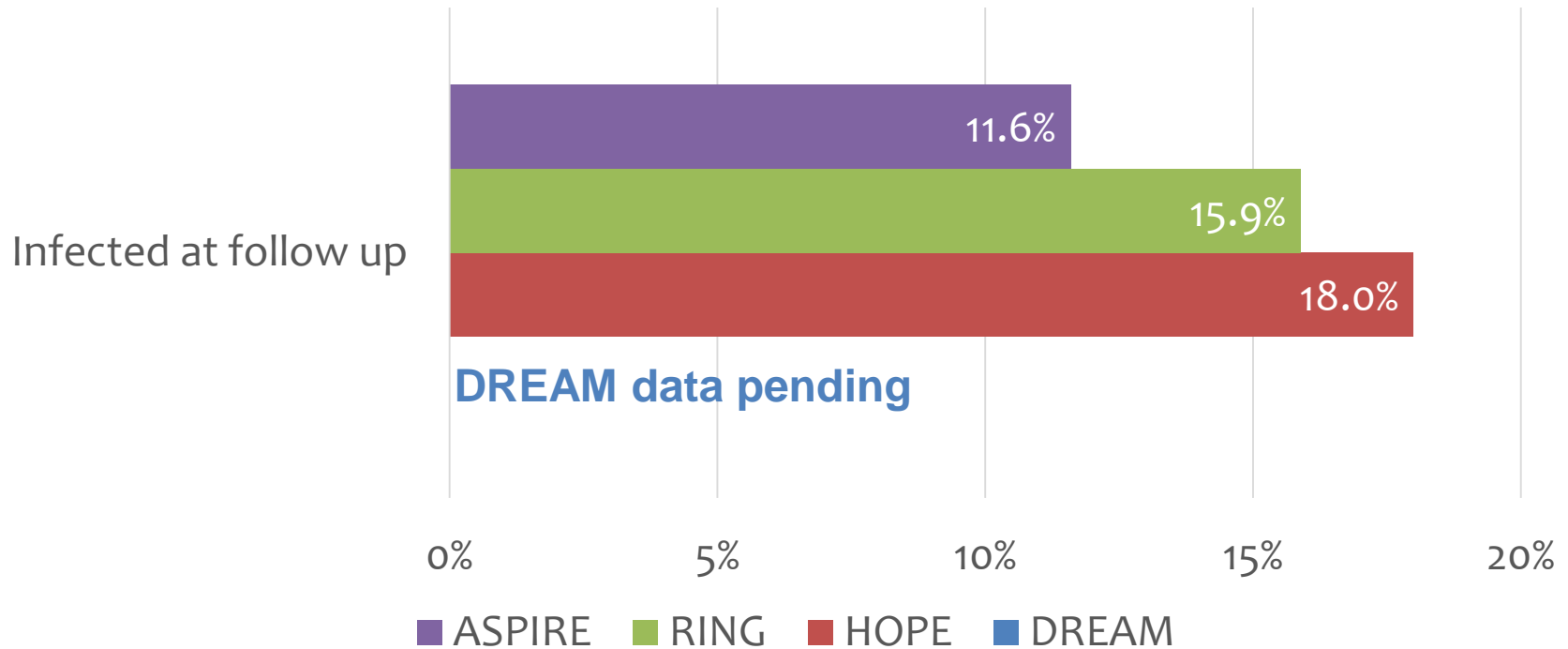
Randomized Clinical Trials



Open-Label Studies



Standard Genotyping: DPV Ring



Number and % with NNRTI Mutations

NO DPV

ASPIRE PLB
10 of 96 (10.4%)

RING PLB
8 of 57 (14.0%)

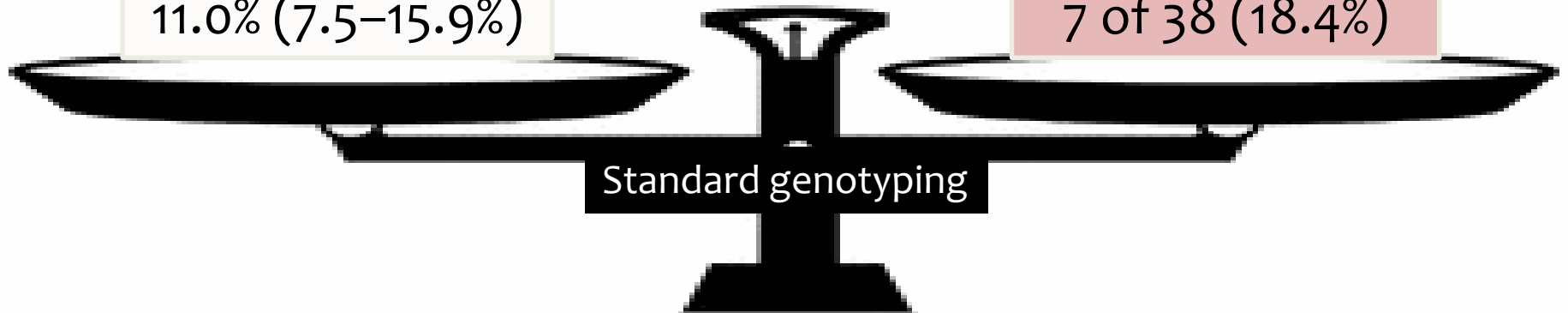
2014-16 PDR
11.0% (7.5–15.9%)

DPV RING

ASPIRE
8 of 69 (11.6%)

RING
13 of 82 (15.9%)

HOPE
7 of 38 (18.4%)



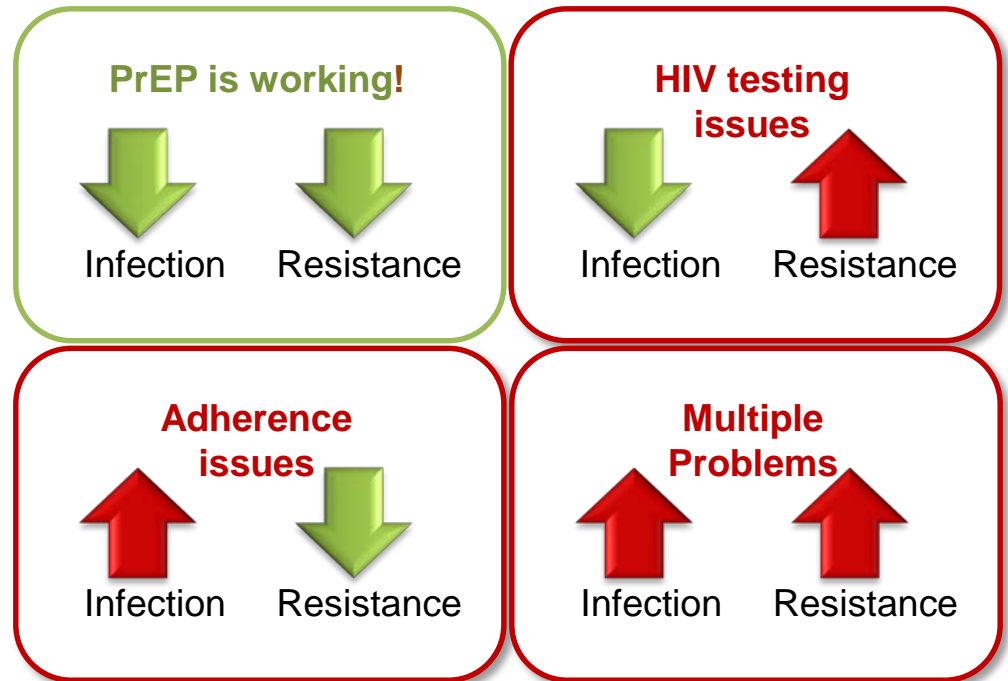
NO DIFFERENCE



Beyond the Trials

Resistance Concerns with PrEP

- Resistance is a risk with seroconversion on PrEP
- Can help identify programmatic issues
- **Critical for preserving ARVs for both treatment and prevention.**



Resistance Concerns with ART

Long-term (4-5 year)
suppression rates of 60-
85%

Spotty viral load (HIV
RNA) monitoring

Resistance testing is
limited

ARV stock-outs

WHO Global Action Plan Strategic Objectives

1. PREVENTION AND RESPONSE



Implement high impact interventions to prevent and respond to HIVDR.

2. MONITORING AND SURVEILLANCE



Obtain quality data on HIVDR and HIV service delivery from periodic surveys, while expanding routine viral load and HIVDR testing.

3. RESEARCH AND INNOVATION



Encourage relevant and innovative research which will have the greatest public health impact in minimizing HIVDR.

4. LABORATORY CAPACITY



Support and expand use of viral load testing and build capacity to monitor HIVDR.

5. GOVERNANCE AND ENABLING MECHANISMS



Ensure country ownership, coordinated action, awareness/advocacy and sustainable funding are in place to support action on HIVDR.

Knowledge Gaps

- Updated survey data on HIVDR
- Efficacy of recycled NRTIs for second line ART
- Optimal strategies for adherence and retention support for key populations

Conclusions

- As long as there is imperfect use of PrEP and suboptimal adherence of ART, resistance will happen in the real world.
- **But monitoring resistance through updated surveillance and managing resistance through more options for ART and PrEP will limit its impact on morbidity and mortality from HIV/AIDS.**

DRUG RESISTANCE



PrEP

ART

Acknowledgements

University of Pittsburgh,
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Division of Infectious Diseases

John Mellors
Kerri Penrose
Amy Heaps
Kelley Gordon
Breanna Goetz
Kevin McCormick



Bioinformatics

Uma Chandran
Rahil Sethi
Jacob Waldman
William Schwarzmann

National Cancer Institute,
Frederick, Maryland

Valerie Boltz
Mary Kearny
Wei Shao



The International Partnership for
Microbicides developed the
Dapivirine Vaginal Ring and supplied
the rings for this trial.



**INTERNATIONAL
PARTNERSHIP FOR
MICROBICIDES**

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1Alo68633, UM1Alo68615, UM1Alo6707), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.

Fred Hutchinson Cancer
Research Institute, Seattle,
Washington; Statistical Center
for HIV/AIDS Research and
Prevention (SCHARP)

Marla Husnik
Danny Szydlo
Haixiao Huang
Jason Pan
Sara Aranda



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