The New News on ARV Resistance

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Top 3 PrEP (and Resistance) Candidates

<u>Oral PrEP</u>
Truvada
(TDF-FTC)

<u>Vaginal Ring</u>
Dapivirine
(DPV)

<u>Injectable</u>
TMC-278LA
(RPV)

PrEP Resistance Concerns

- Breakthrough infection and subsequent selection of resistance with continued use of PrEP during acute infection could compromise the effectiveness of first-line ART
- Efficacy of PrEP could be reduced if the transmitted variant is from a partner failing an ART regimen with virus that is cross-resistant to PrEP

The Latest News on…

1. TDF-FTC Resistance
2. Dapivirine Resistance
3. Rilpivirine Resistance

Should we fear resistance from TDF/FTC PrEP?

TDF/FTC PrEP Resistance Occurs Infrequently in Seroconverters

Seroconverted on TDF/FTC Arm during follow-up

Study	Seroconverters in TDF/FTC Arm	TFV Resistance		FTC Resistance	
		Standard	Sensitive	Standard	Sensitive
FEM-PrEP	33	0	0	4	1
iPrEX	36	0	0	0	2
TDF2	9	0	0	0	0
Partners PrEP	21	0	1	0	5
VOICE	61	0	0	1	2
TOTAL	**160**	**0 (0%)**	**1 (0.6%)**	**5 (3%)**	**10 (6%)**

-Parikh and Mellors, Current Opinions in HIV/AIDS, 2015 (in press)

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5 Cases of FTC Resistance

TDF/FTC Arm; Standard Genotyping

FEM-PrEP	CASE 1	intracellular TNV-DP equivalent to 4 tablets/week
	CASES 2 & 3	*acute infection at enrollment could not be ruled out*
	CASE 4	*seroconverted 48 weeks after discontinuing study product*
VOICE	CASE 5	Detectable tenofovir

-van Damme, NEJM, 2012 & Parikh CROI 2014

10 Cases of Low Frequency FTC Resistance

FEM-PrEP	Case 1	0.66%
iPrEX	Cases 2-3	0.53 & 0.75%
VOICE	Cases 4-5	0.7 & 5%
Partners PrEP	Cases 6-10	All >1%

- Detection of these low frequency mutants may be intermittent
- No proof that they were selected by TDF/FTC
- Clinical significance of these low frequency drug-resistant variants is unknown.

-Grant AIDS 2015; Leigler JID 2014; Panousis CROI 2015; Lehman JID 2015

NO Cases of TDF Resistance

- No cases of TDF resistance detected by standard genotyping.

- One participant in Partners PrEP with low frequency K65R from the TDF/FTC arm > 1%.
  - Clinical significance unknown

-Parikh CROI 2014; Lehman JID 2015

Resistance to TDF/FTC PrEP Common in Acute Infection

Acutely Infected at Enrollment

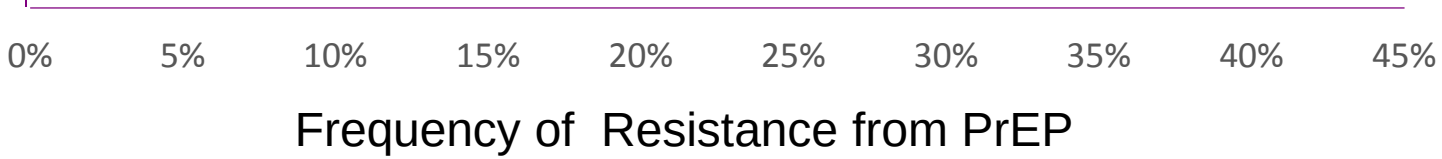
Study	Seroconverters in TDF/FTC Arm	TFV Resistance	FTC Resistance
		Standard	Standard
FEM-PrEP	1	0	0
iPrEX	2	0	**2**
TDF2	1	**1**	**1**
Partners PrEP	4	0	**2**
VOICE	9	0	**2**
TOTAL	**17**	**1 (6%)**	**7 (41%)**

-Parikh and Mellors, Current Opinions in HIV/AIDS, 2015 (in press)

TDF/FTC PrEP Resistance

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!

Should we fear resistance from DAPIVIRINE RING?

Mutations Important for DPV Resistance

- Minimal resistance data available because dapivirine is not used therapeutically

- Mutations associated with dapivirine resistance:
  - *In vitro* selection with sub C-HIV-1: E138K & **Y181C** (Schrader 2012)
  - Cross-resistance: **Y181C, K103N, L100I, Y188L** (Fletcher 2009)

- **In ASPIRE, standard resistance testing and next generation sequencing (NGS) will determine the frequency of NNRTI/DPV resistance mutations in active vs placebo arms**

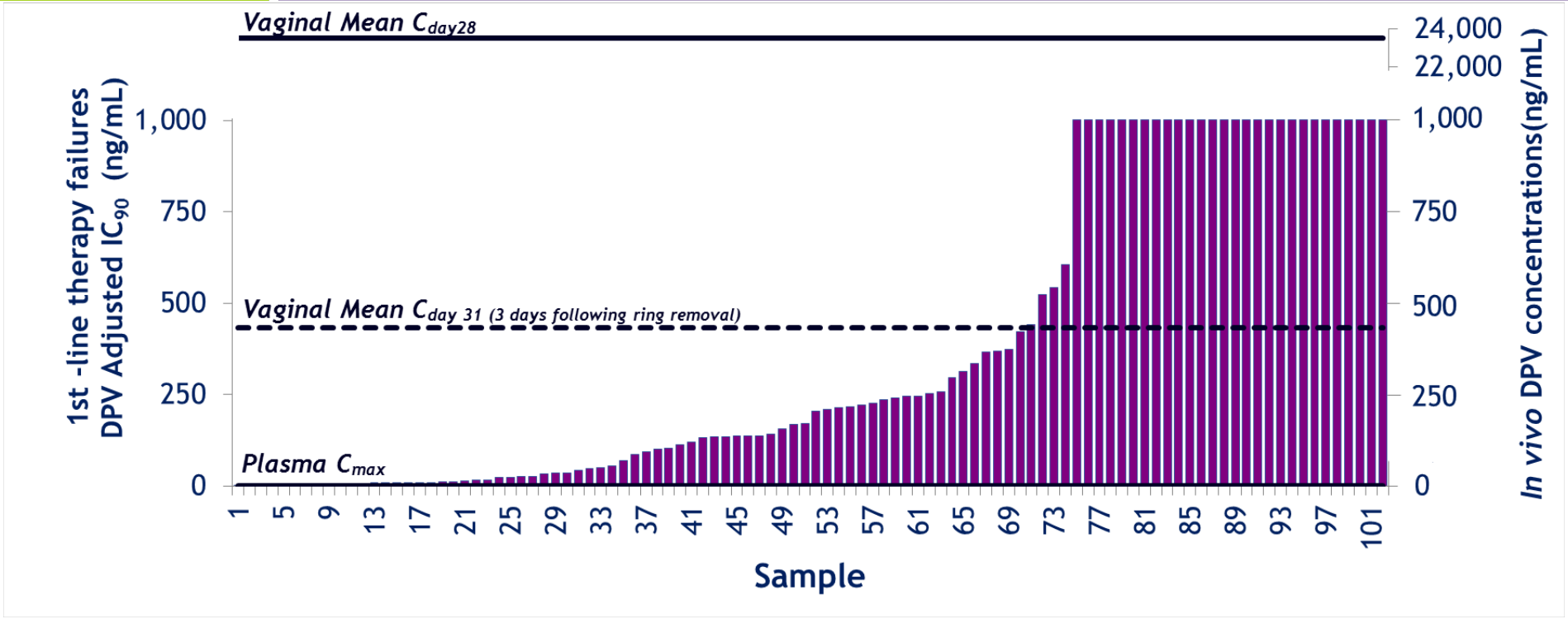
Dapivirine Cross-Resistance

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

- Patient viruses derived from 1st line ART failures with ≥ 1 ARV mutation & RNA >10,000 c/ml
- K103N and L100I significantly associated with maximum DPV resistance

Risk of DPV Breakthrough Infection?



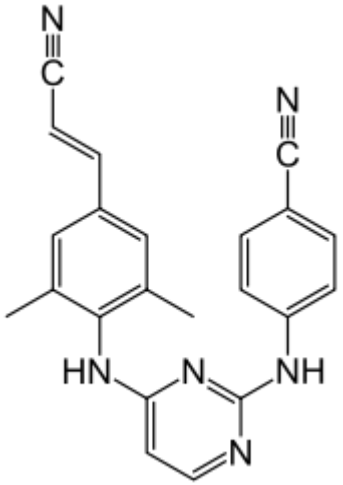
- Vaginal $C_{day\ 28}$ exceeds adjusted IC_{90} of all samples by >23-fold

- Risk of breakthrough is seen in a short window following ring removal; 32/102 (31%) viruses exceed C_3 days following ring removal

DPV Resistance Summary

- **NNRTI-resistant virus from 1st line treatment failures are usually resistant to dapivirine**
- **Local [dapivirine] >> IC_{90} of NNRTI-resistant virus**
  - May be sufficient to block both wild type and resistant virus
  - Critically important to continue to evaluate both selected and transmitted resistance with dapivirine ring use
- **Plasma [dapivirine] from monthly ring use are low**
  - But may be too low to select resistance with wild type infection
- **Critically important to continue to evaluate both selected and transmitted resistance with dapivirine ring use**

Should we fear resistance from injectable TMC-278LA?



RPV Resistance

- 47 HIV+ ARV-naïve participants on RPV monotherapy for 7 days → no resistance (Cohen JAIDS 2012)
- Prevalence of RPV-associated mutations:
  - 5% in treatment-naïve
  - 59% in NNRTI-containing 1st-line ART failures
- 17 mutations associated with RPV resistance:
  - L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C and M230I/L
- ECHO and THRIVE: E138K with M184I most commonly emerged in virologic failures

SSAT 040 Study

PK evaluation of the exposure and distribution of TMC278LA (RPV), for use as PrEP, in plasma and genital tract/rectal compartments, following a single IM injection at different doses

Study Population

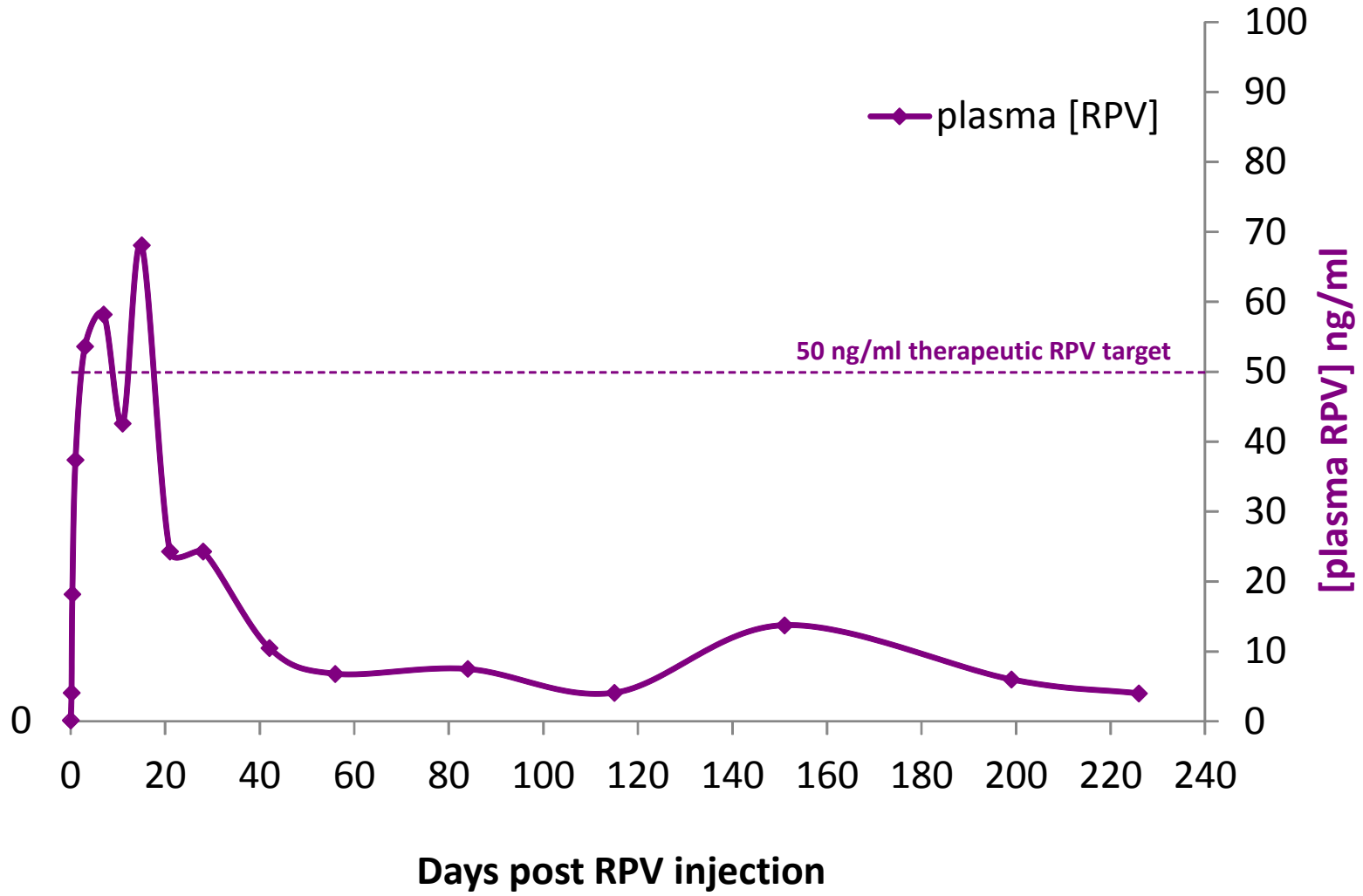
- 60 HIV-negative female volunteers
- Received single IM dose of RPV:
  - 300, 600 or 1200 mg

Unexpected seroconverter in 300 mg arm

Case History

Day	
0	• Patient received single 300 mg IM injection
41	• Exposure is believed to have occurred
57	• First detectable viral load (370 copies/ml)
84	• Seropositive (HIV-1/2 Ag/Ab EIA)
115	• ART with TFV/FTC and DRV/r started

Residual RPV Led to Resistance Selection



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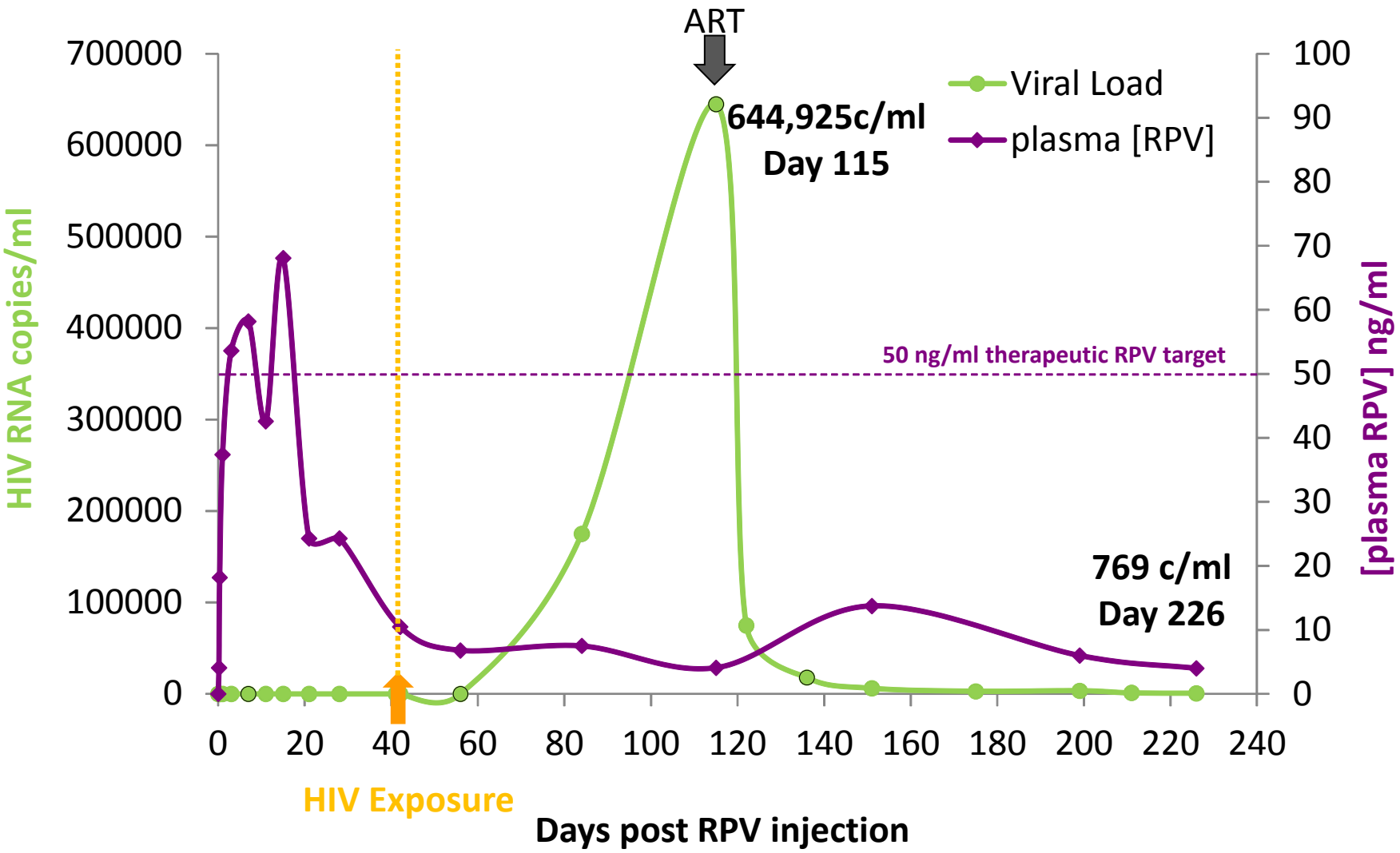

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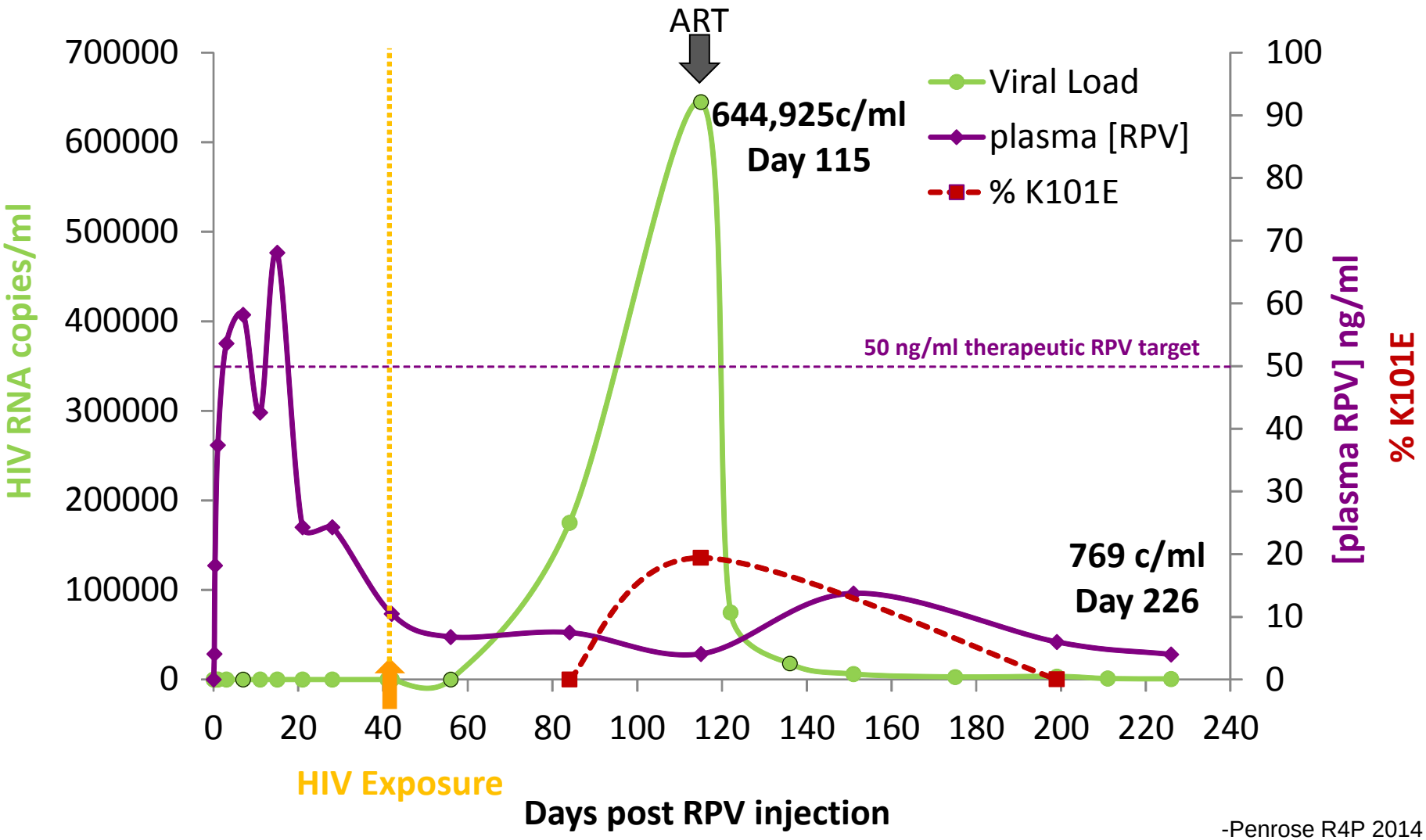


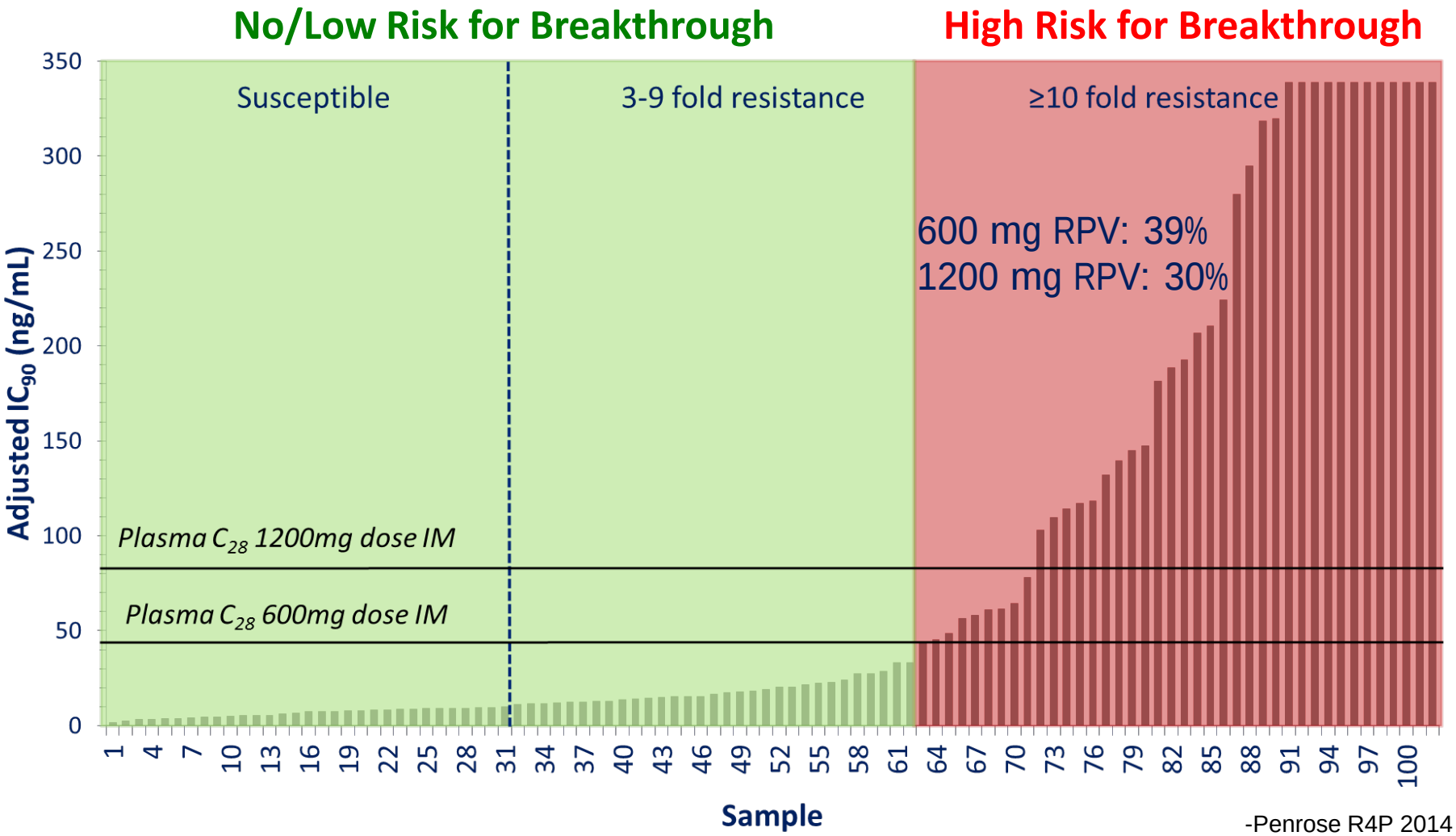
-Penrose R4P 2014

K101E Selected After Transmission

Days post injection	84	115	151	199
Standard	K101	K101E/K	K101E/K	K101
ASPCR (%K101E)	0	19.4	Sample not available	0.1
HIV RNA (c/mL)	175,060	644,925	6,204	3,558

-Penrose R4P 2014

Risk of Breakthrough Infection with 1200 or 600 mg monthly injectable RPV

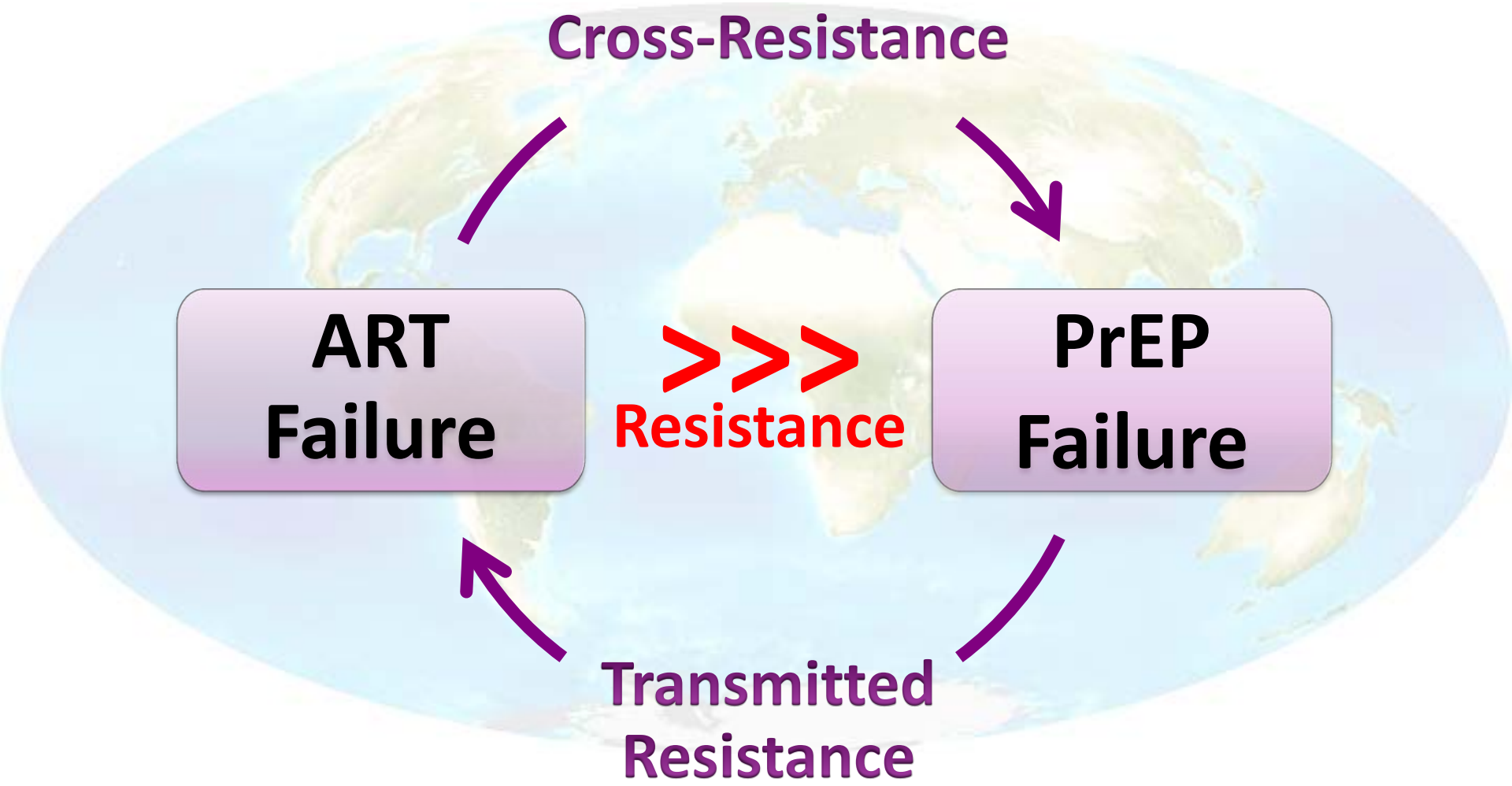


-Penrose R4P 2014

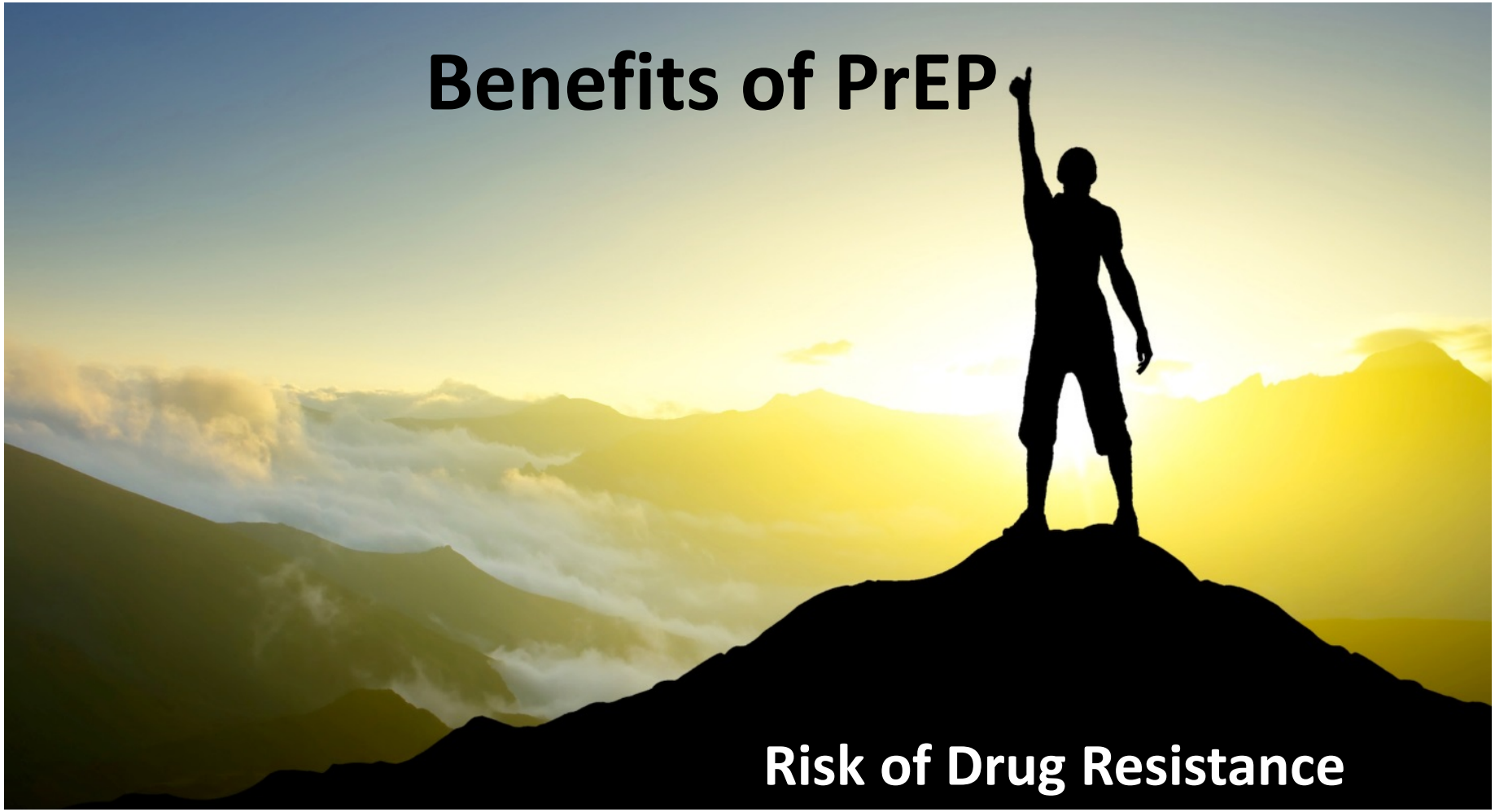
RPV Resistance Summary

- The lowest dose (300 mg) of TMC278LA did not prevent HIV-1 in one individual in the SSAT 040 trial
- Frequent cross-resistance to RPV is observed among HIV-1 subtype C viruses from individuals experiencing failure of first-line NNRTI-containing ART.
- The frequency of resistance selection from long-acting PrEP agents should be carefully investigated

Global Threat of Resistance



Overcome Fear of Resistance!



But Continue Diligence in Monitoring for Resistance from PrEP!

Critically important to monitor ART failures and PrEP failures for standard and low-frequency resistance in trials and during roll-out.

GEMS
GLOBAL EVALUATION OF MICROBICIDE SENSITIVITY

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Images in slide set from google.com

Questions?