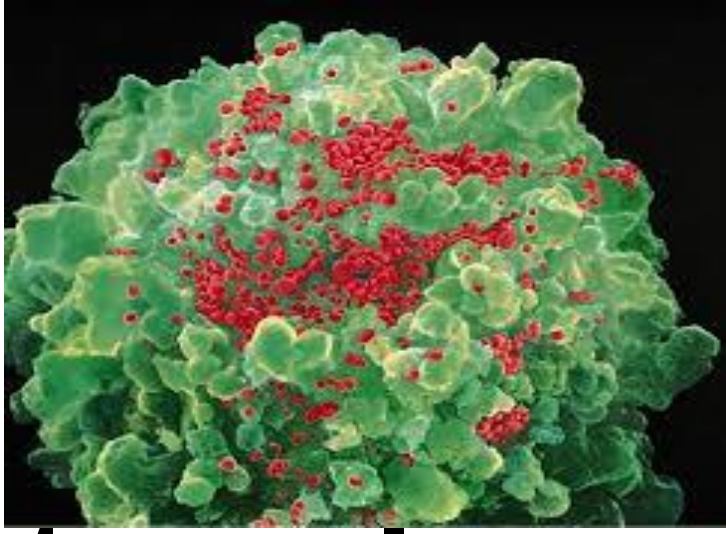
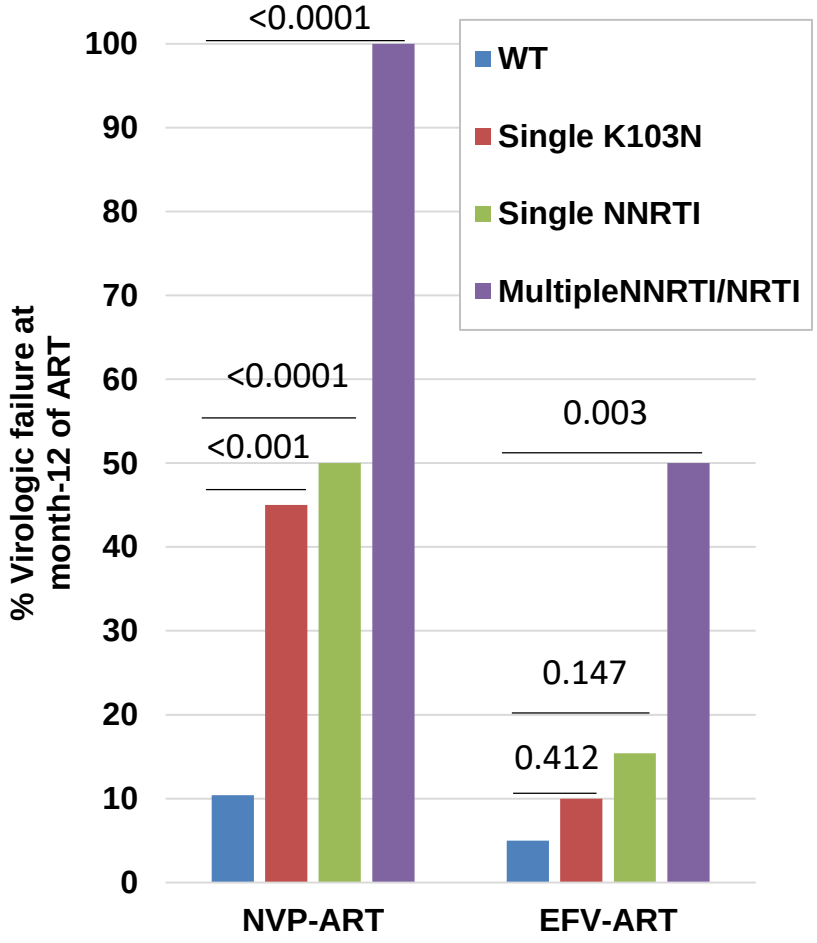


PROMISE Maternal Study of HIV Drug Resistance

IMPAACT Meeting - 2018

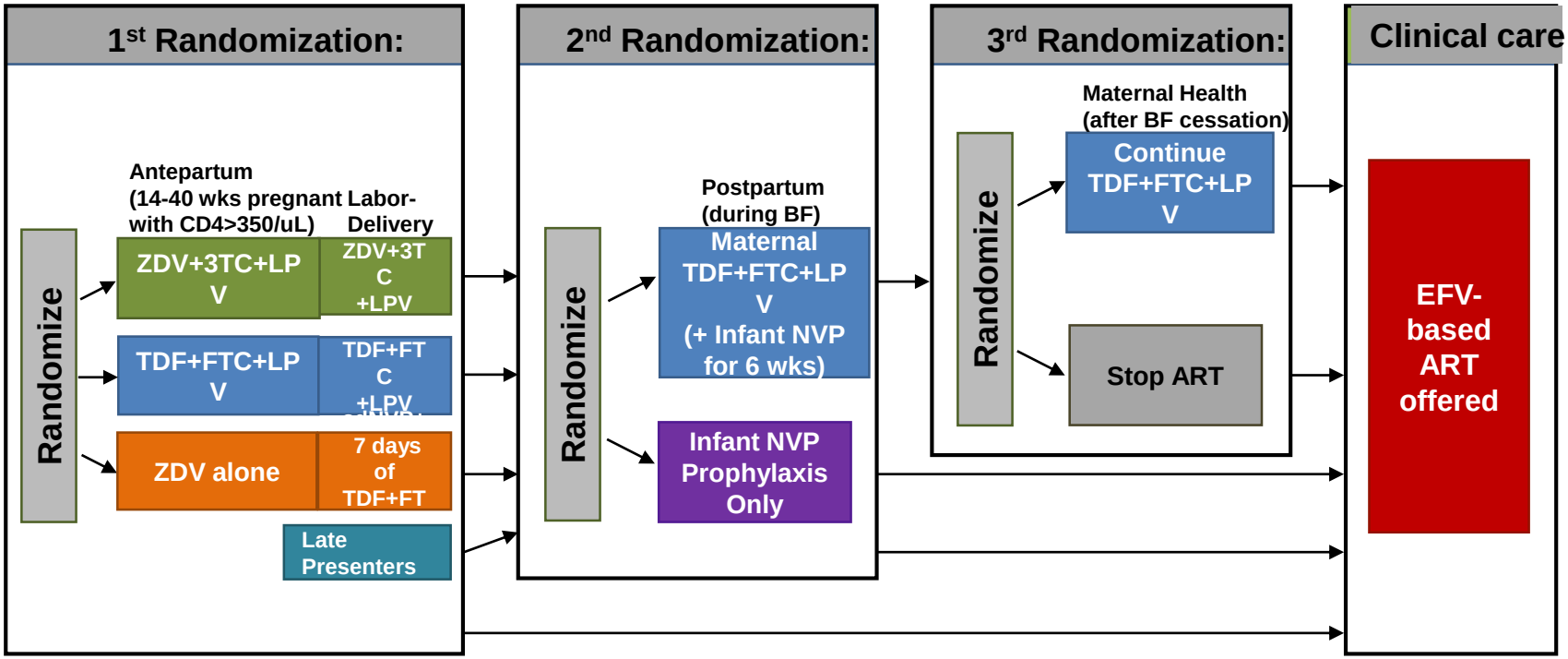
Findings in Kenyan Studies

- In studies of 1,228 Kenyans initiating NNRTI-ART between 2006-14:
  - PDR increased to 11% to >20% in women 18-24y
  - The NNRTI switched from NVP to EFV
- Virologic outcomes were affected:
  - Single DRMs (K103N, Y181C, G190A, M184V) increased VF to NVP+ZDV+3TC, but not EFV+TDF+3TC
  - Multiple DRM increased VF to both NVP- and EFV-ART
- PROMISE provided an opportunity to validate or refute the associations of



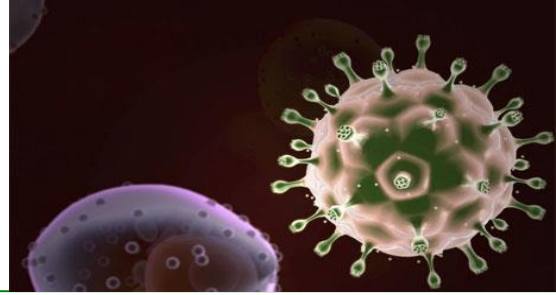
PROMISE Randomization Schema

- **In PROMISE, women underwent 3 randomizations**



- **EFV-based ART could be initiated at any point during the study, with most EFV-ART initiated after results of START trial**

Significance, Goal & Aims



PROMISE specimens collected just prior to initiation of EFV-ART were genotyped to examine associations of single or combinations of DRMs with VF during EFV-ART in a novel population

- **Aim 1: Describe the prevalence of PDR and virologic failure rates in women by site**
- **Aim 2: Assess the association of maternal DRM prior to EFV-ART with risk of VF at 6 or 12 months of ART**
- **Aim 3: Assess if maternal minority variant (MV) DRM are associated with VF**

Study Population & Methods

Study Population:

- **PROMISE women who initiated EFV-ART**
  - **Enrollment plasma HIV RNA was >400c/mL and available**
  - **Plasma available just prior to EFV-ART initiation**
  - **Plasma HIV RNA known at month-6 and -12 of EFV-ART**

Methods:

- **RNA extraction using QIAmp Viral RNA kit**
- **RT-PCR amplification of Protease & RT regions using Takara 1-step RT-PCR kit v2**
- **Consensus sequencing of PCR products**
- **Phylogenetic and bioinformatic quality assurance analyses**

Drug Resistance Mutations for Analyses

- NRTI- & NNRTI-associated mutations that were counted as DRMs or excluded from our analyses are shown below:

Included

NRTIs	NNRTIs
M41L	A98G
K65R	L100I
D67N	K101_
K70_	K103_
L74I	V106_
V75I	V108I
M184_	Y181C
T215_	Y188_
K219_	G190_
	H221Y
	P225H
	M230L
	K238T

Excluded

NRTIs	NNRTIs
E44D	V179_
A62V	F227_
T69_	E138_
F77L	

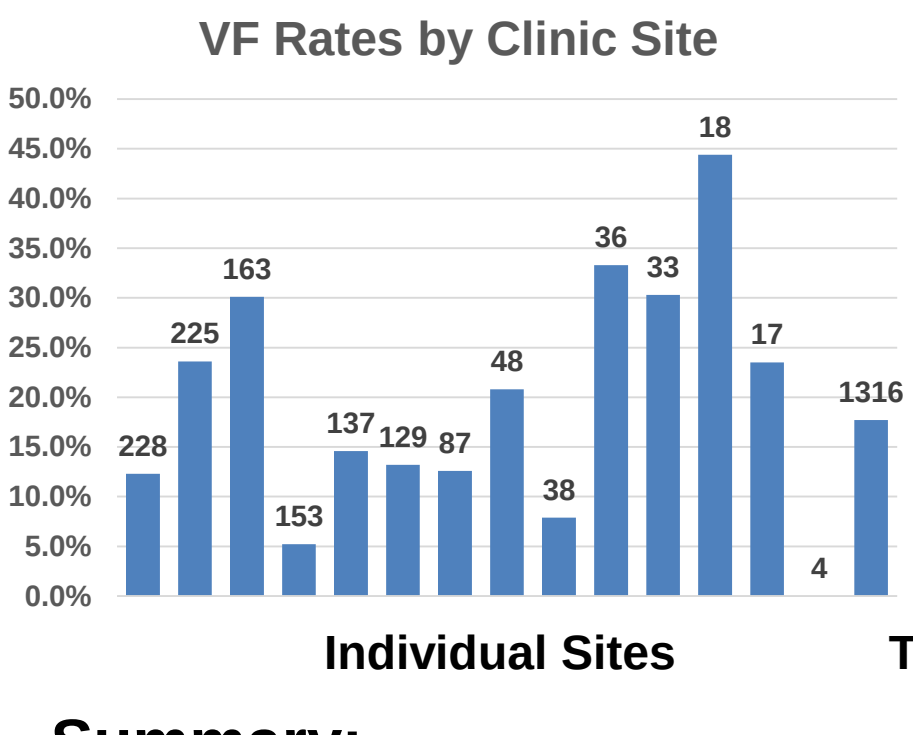
- PI-associated mutations were identified but not analyzed (as very rare)

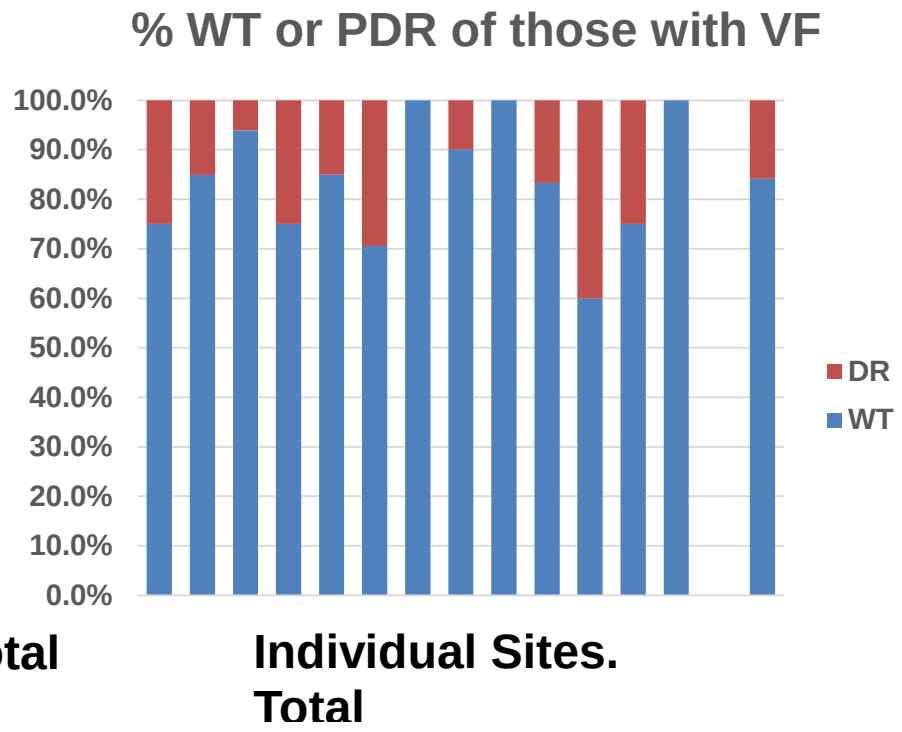
Results.
Aim 1: Prevalence of Pre-ART Drug Resistance (PDR)

Site	Total # Participants	# (%) PDR		95% Confidence Interval
	228	**47**	**(20.6)**	**15.6-26.5**
	225	**33**	**(14.7)**	**10.3-20.0**
	163	**23**	**(14.1)**	**9.2-20.4**
	153	**20**	**(13.1)**	**8.2-19.5**
	137	**23**	**(16.8)**	**10.9-24.1**
	129	**21**	**(16.3)**	**10.4-23.8**
	87	9	(10.3)	4.8-18.7
	48	11	(22.9)	12.0-37.3
	38	4	(10.5)	2.9-24.8
	36	7	(19.4)	8.2-36.0
	33	7	(21.2)	9.0-38.9
	18	3	(16.7)	3.6-41.4
	17	1	(5.9)	0.1-28.7
	4	0	(0.0)	0.0-60.2
Total	**1316**	**209**	**(15.9)**	**13.9-18.0**

Overall prevalence of PDR is 15.9%

Results.
Aim 1: Rates of Virologic Failure (VF) & PDR Genotype





Summary:

- Overall VF rate was 17.7%; however, VF rates varied by site
- Of those who failed, most were WT prior to EFV-ART

Results.
Aim 1: Virologic failure rates by pre-EFV genotype across sites

Site	Total # Subjects	% VF of Total	Total # WT Subjects	% WT with VF	Total # DR Subjects	% DR with VF
	228	12.3%	**181**	**11.6%**	**47**	**14.9%**
	225	23.6%	**192**	**23.4%**	**33**	**24.2%**
	163	30.1%	**140**	**32.9%**	**23**	**13.0%**
6	153	5.2%	**133**	**4.5%**	**20**	**10.0%**
	137	14.6%	**114**	**14.9%**	**23**	**13.0%**
	129	13.2%	**108**	**11.1%**	**21**	**23.8%**
	87	12.6%	78	14.1%	9	0.0%
	48	20.8%	37	24.3%	11	9.1%
	38	7.9%	34	8.8%	4	0.0%
	36	33.3%	29	34.5%	7	28.6%
	33	30.3%	26	23.1%	7	57.1%
	18	44.4%	15	40.0%	3	66.7%
	17	23.5%	16	25.0%	1	0.0%
	4	0.0%	4	0.0%	0	0.0%
Total	**1316**	**17.7%**	**1107**	**17.7%**	**209**	**17.7%**

There was no difference between overall rate of VF by genotype

Results.
Aim 2: Risk assessment of DRMs associated with VF

- VF in women with vs without any or specific DRM by CS
- ≥2 DRMs (NRTI- or NNRTI-associated) did not increase risk of VF

	Pre-EFV Genotype	# women	# (%) with VF		P-Value
NRTI	WT	1,107	196	(17.7)	reference
	K65R only	0	0	(N/A)	N/A
	M184V only	1	0	(0)	1.0000
	1 NRTI only	13	0	(0)	0.2362
	≥ 2 NRTI only	0	0	(N/A)	N/A
NNRTI	WT	1,107	196	(17.7)	reference
	K103N only	97	18	(18.6)	0.8918
	Y181C only	8	1	(12.5)	1.0000
	G190A only	5	0	(0)	1.0000
	1 NNRTI only	169	26	(15.3)	0.5897
	≥ 2 NNRTI only	19	4	(21.1)	0.7674
NRTI & NNRTI (≥ 2 total)		8	7	(87.5)	<0.0001

N/A = not analyzed

Results.
Aim 2: Risk assessment of DRMs associated with VF by AP treatment arm

Hypothesis: Failure rate for ZDV monotherapy antepartum treatment arm will be greater than the failure rate for the two ART antepartum treatment arms combined

AP Treatment Arm	Total # Participants	# (%) with VF		P-Value
ZDV+sdNVP+TRV tail	553	87	(15.7)	Reference
ART (FTC-TDF or 3TC-ZDV + LPV-RTV)	763	146	(19.1)	0.1941

Fisher's Exact Test of ZDV-monotherapy arm versus ART = no significant difference in overall rate of VF

Results.
Aim 2: Risk assessment of DRMs associated with VF by AP treatment arm

Any DRM is variably and combined NRTI+NNRTI are associated with VF in the ZDV-sdNVP-TRV tail AP treatment arm

AP Treatment Arm	Pre-EFV Genotype	Total # Participants	# (%) with VF		P-Value
ART (3TC-ZDV/LPV-RTV)	Total	581	119	(20.5)	N/A
	WT	496	104	(21.0)	Reference
	Any DRM	85	15	(13.8)	0.5618
	NRTI & NNRTI (≥2 total)	5	4	(80.0)	0.0086**
ART (FTC-TDF/LPV-RTV)	Total	182	27	(14.8)	N/A
	WT	149	16	(10.7)	Reference
	Any DRM	33	11	(31.3)	0.0024**
	NRTI & NNRTI (2 total)	1	1	(100)	0.1133
ZDV sdNVP+TRV tail	Total	553	87	(15.7)	N/A
	WT	461	76	(16.5)	Reference
	Any DRM	92	11	(10.0)	0.3468
	NRTI & NNRTI (≥2	2	2	(100)	0.0281*

*p < 0.05; **p < 0.01, N/A = not analyzed

Summary and Conclusions

- **Prevalence of PDR across sites ~16%**
- **In WT women, rate of VF varied 5%-30% by sites**
- **Rate of VF was ~18% for WT and for DR (why not different?)**
- **1 NRTI or ≥1 NNRTI DRM were not associated with VF**
- **DRM to both NNRTI+NRTI associated with VF**
- **Rate of VF similar following antepartum ZDV- vs ART-arm, except in women who took TDF+FTD+LPV/rt in antepartum**

Conclusions

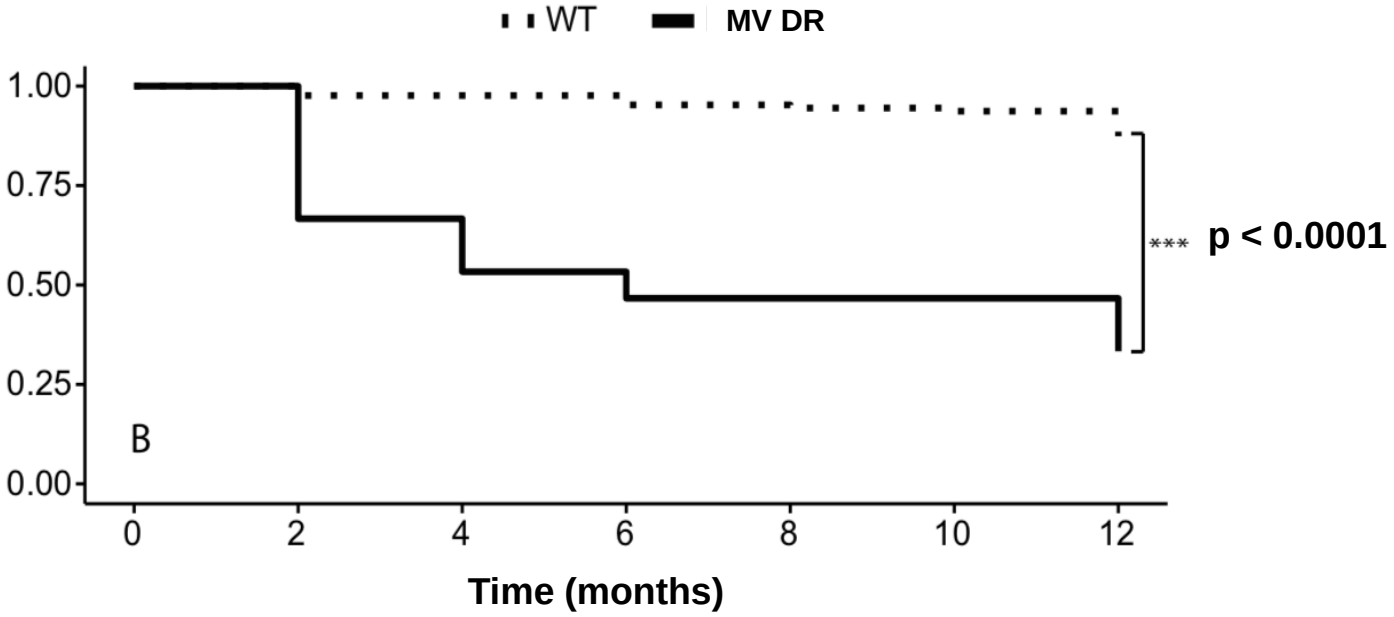
- **DRMs across drug classes increase risk of VF to EFV; as in Kenya studies**
- **The high proportion of women with VF and WT virus pre-ART:**
  - **May have had poor adherence to ART, which is supported by variable rates of VF across sites that was found**
  - **Or alternatively, these women may have PDR with minority variants that regressed due to poor ”fitness”, and therefore are not detected by CS (previously observed for ZDV, TDF and 3TC/FTC mutations)**

Aim 3: Assess association of minority variants (MV) & VF

Hypothesis: Among women WT by CS, MV DRMs will be detected by NGS and associated with increased rates of VF

Rationale:

- **Kenya Study Findings: among those WT by CS, increased rates of VF were associated with MV (detected by NGS) as shown**



Status.
Aim 3: Assess association of minority variants and VF

Study Design:

- **Examine pre-EFV specimens for the mothers who experienced VF (n = 196) for MV DRMs**
- **Case-control study with 2 controls for each case mother – matched by site and treatment arms**

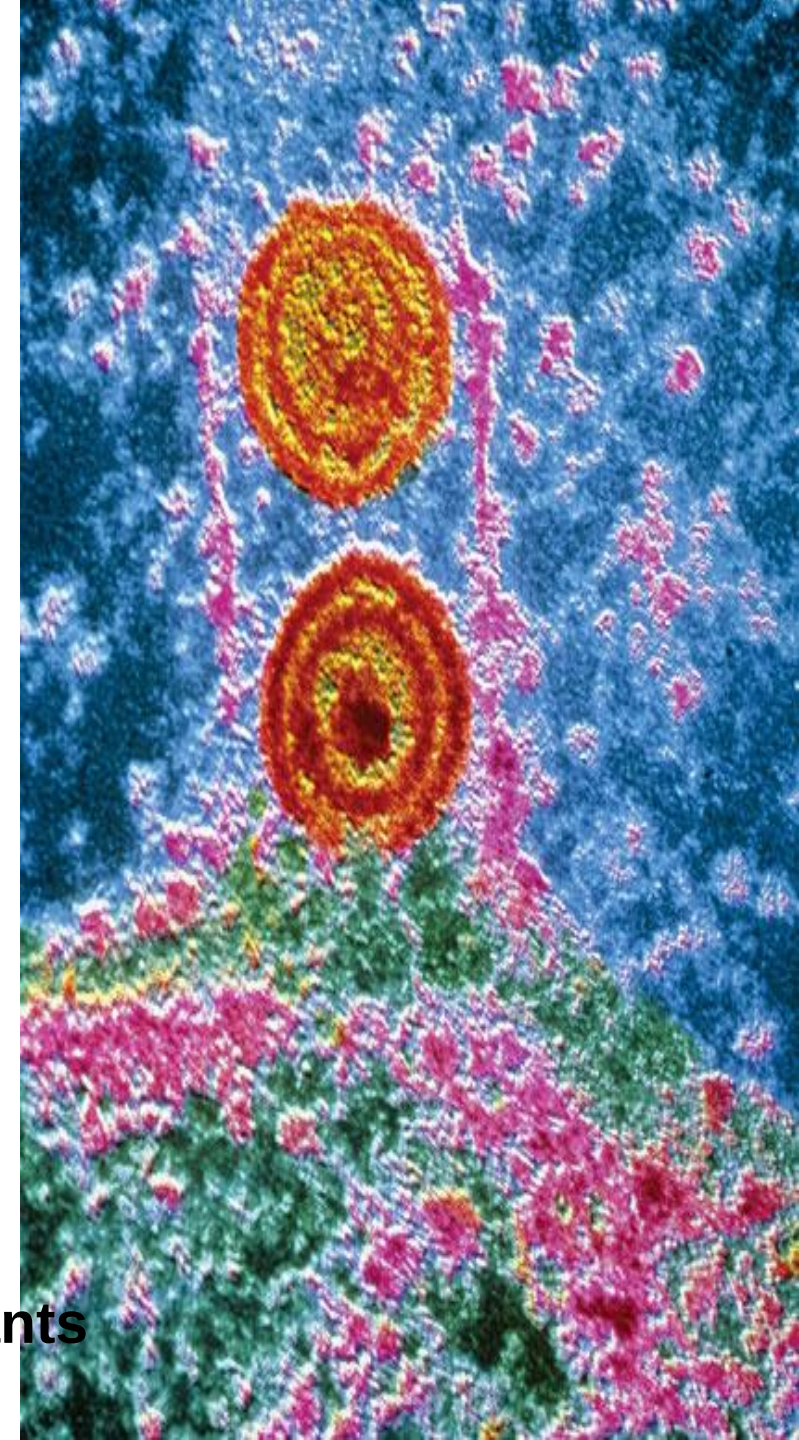
Methods:

- **Perform Illumina sequencing with "Primer ID" technology to be able to quantify the number of copies sequenced**
- **PCR and sequencing error rates at each base will be assessed by an in-house Perl script to estimate genuine PDR populations**
- **To exclude MV due to Illumina "index hopping", all MV will be confirmed by phylogenetic clustering to participants' CS**

THANKS!

- **Ceejay Boyce**
- **Ingrid Beck**
- **Daisy Ko**
- **Ross Milne**
- **Tatiana Sils**
- **Sheila Styrchak**
- **Annie Wong**

- **Camlin Tierney**
- **Nadia Konstantia**
- **Patricia De Marra**
- **Rebecca Le Blanc**
- **Alex Benns**
- **Mary Glenn Fowler**
- **All the PROMISE sites and participants**



Questions?