Frequency & Mechanisms of DTG Resistance: Lessons from P1093 and IMPAACT 2010/VESTED

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Study Objectives (NWCS #623)

Among women and children living with HIV-1 non-subtype B on dolutegravir (**DTG**)-based ART, we aimed to:

- Assess the impact of pretreatment drug resistance (**PDR**) on the efficacy of DTG-ART
- Describe the emergence of DTG resistance mutations among individuals with failure
- Evaluate concordance between genotypic and phenotypic DTG resistance

Study Populations

IMPAACT P1093

Parent Study: Phase 2/3 – dose-finding, safety, and PK study of dolutegravir (**DTG**) in children

Regimen: DTG + optimized background therapy (**OBT**)

Cohort Characteristics
- INSTI-naïve (n=181; 100%)
- 4wks-2yo = ART <4w or failed ART (n=54; 100%)
- 2yo-17yo = failed ART (n=127; 100%)

Locations: Botswana, Kenya, South Africa, Tanzania, Thailand, Uganda, USA, Zimbabwe

HIV subtypes: A, B, C, D, AE, F, AG

2º Study Design: Cohort study evaluating correlates of virologic failure & DTG-resistance

IMPAACT 2010/VESTED

Parent Study: Phase 3 – randomized-controlled safety & efficacy trial of DTG (vs. efavirenz)-based ART in pregnant and breastfeeding women

Regimens: DTG + emtricitabine + tenofovir (**TDF/TAF**)

Cohort Characteristics
- Pregnant, 14-28 weeks gestation
- ART- & INSTI-naïve at study screening
- N=432 (1/432 took DTG prior to study entry)

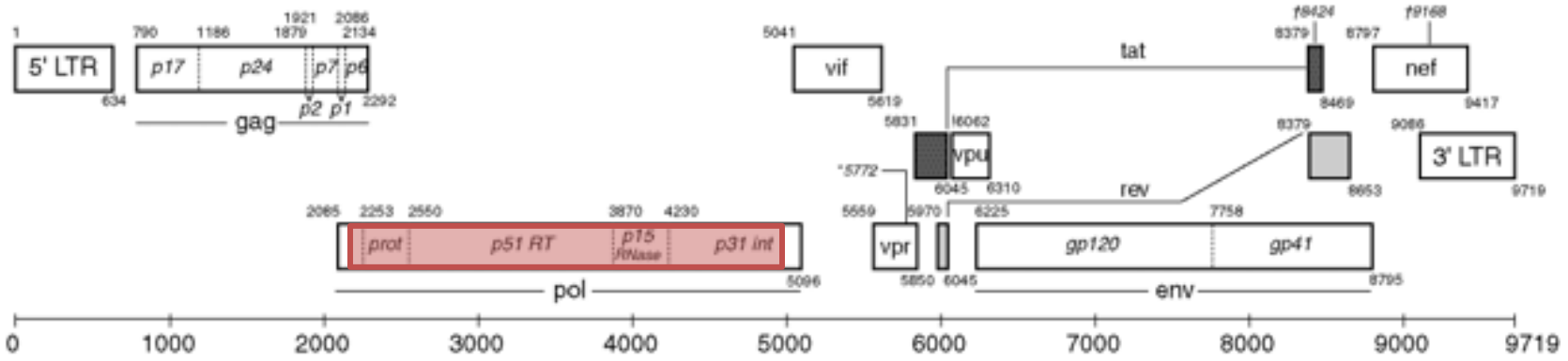
Locations: Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, USA, Zimbabwe

HIV subtypes: A, B, C, D, AE

2º Study Design: Case-control study to determine correlates of virologic failure & DTG-resistance

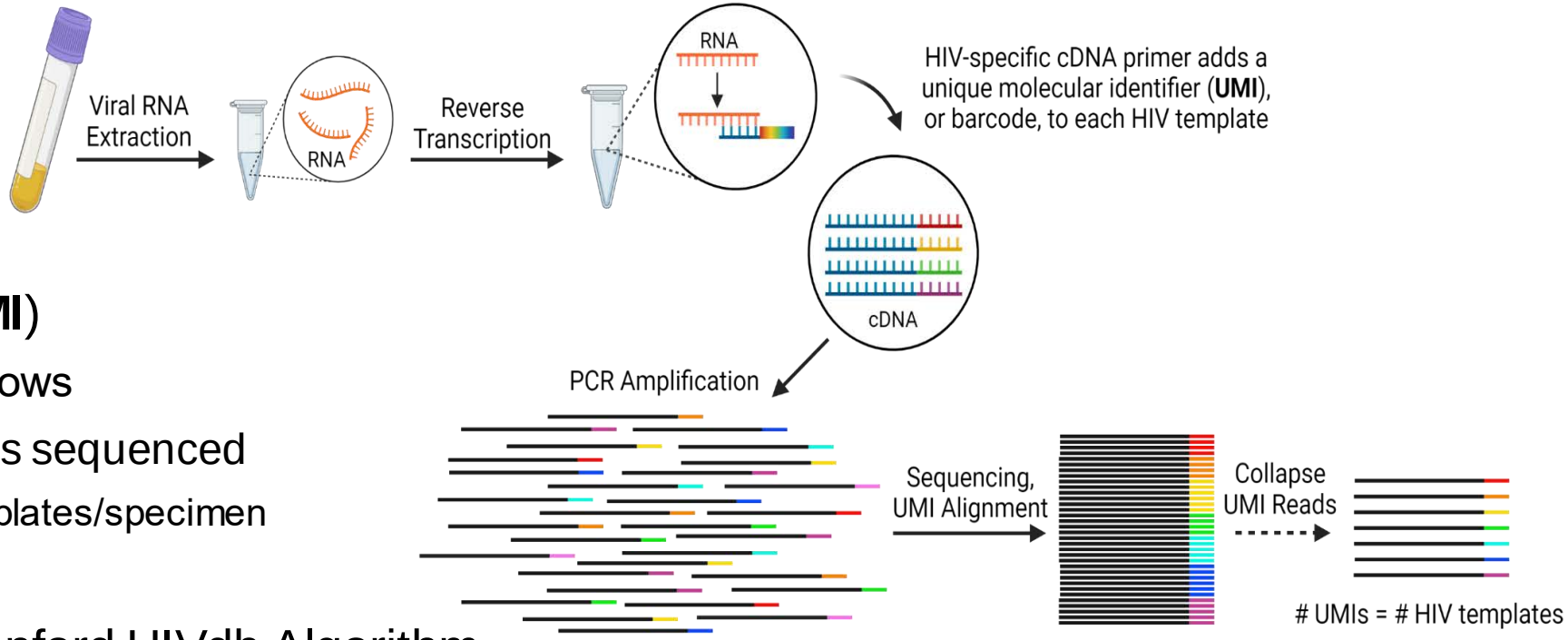
Approach: Genotypic resistance by PacBio sequencing

- Specimens tested
  - Study screen or enrollment
  - Longitudinal plasma with
    - P1093 = HIV RNA ≥400c/mL
    - 2010 = HIV RNA ≥200c/mL



- HIV *pol* PacBio
  - Region: PR 19aa - IN 270aa

- cDNA primer incorporates a unique molecular identifier (**UMI**)
  - UMI "erases" PCR errors & allows quantification of viral templates sequenced
    - Aimed to sequence ≥100 templates/specimen

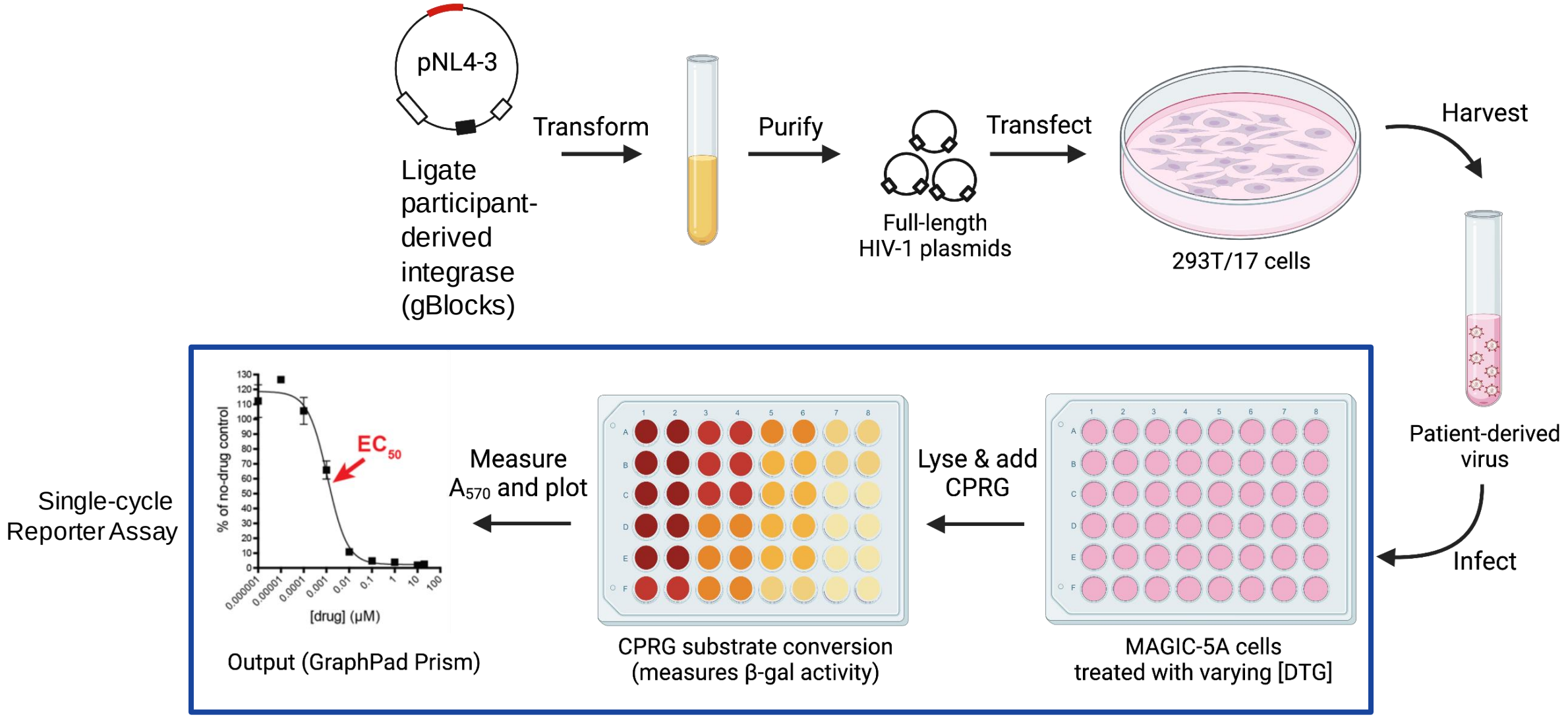


- Bioinformatic pipeline uses Stanford HIVdb Algorithm

https://hiv.lanl.org
Schema created with Biorender

Approach: Phenotypic resistance by single-cycle reporter assay

- DTG 50%-effective concentration (**EC_{50}**) using gBlocks with participants' HIV DR sequences
- EC_{50} fold-change between screen/entry and viremic timepoints

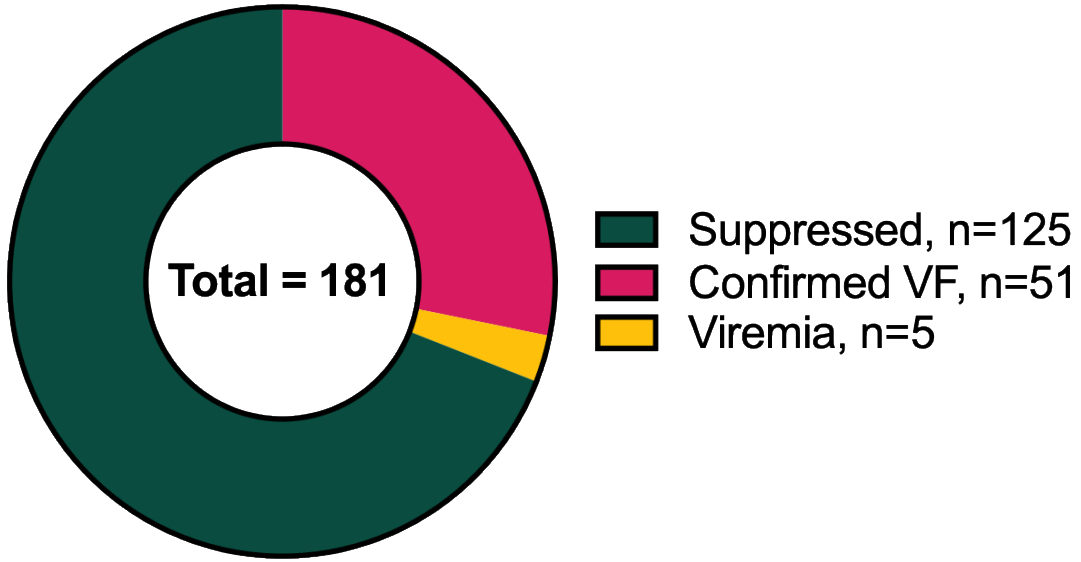


Frequency of viremia / virologic failure (VF) on DTG-based ART

IMPAACT P1093

Regimen:
DTG + optimized background therapy (**OBT**)

Outcomes:

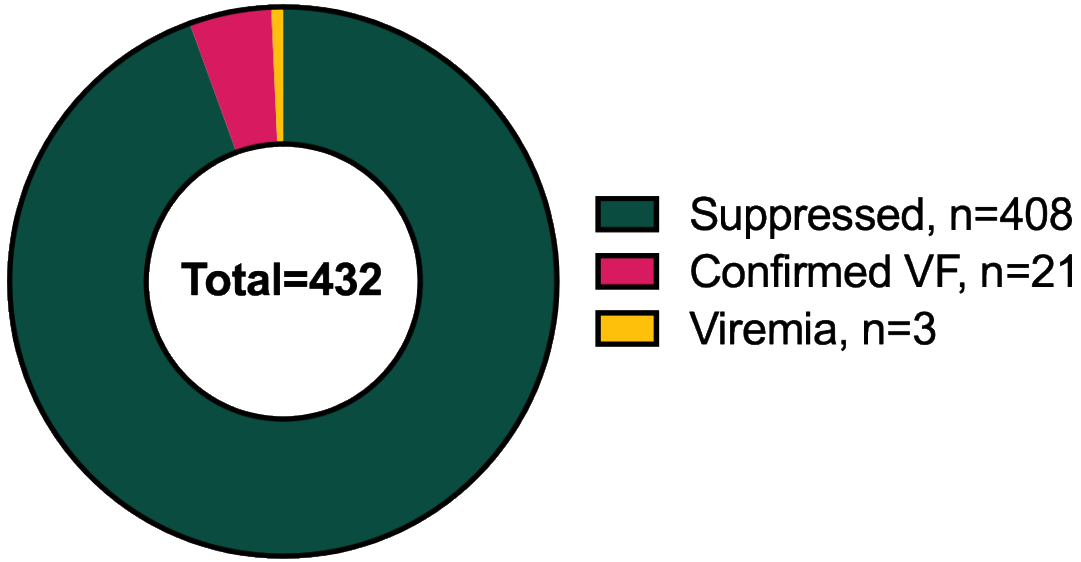


- 56/181 (**30.9%**)
  - 51 confirmed VF = ≥400c/mL x 2 sequentially
  - 5 viremias = ≥400c/mL (subsequent <400c/mL) x ≥2
  - Median viremia 5,536c/mL (IQR: 1,645-36,316c/mL)

IMPAACT 2010

Regimen:
DTG + TDF/TAF + emtricitabine

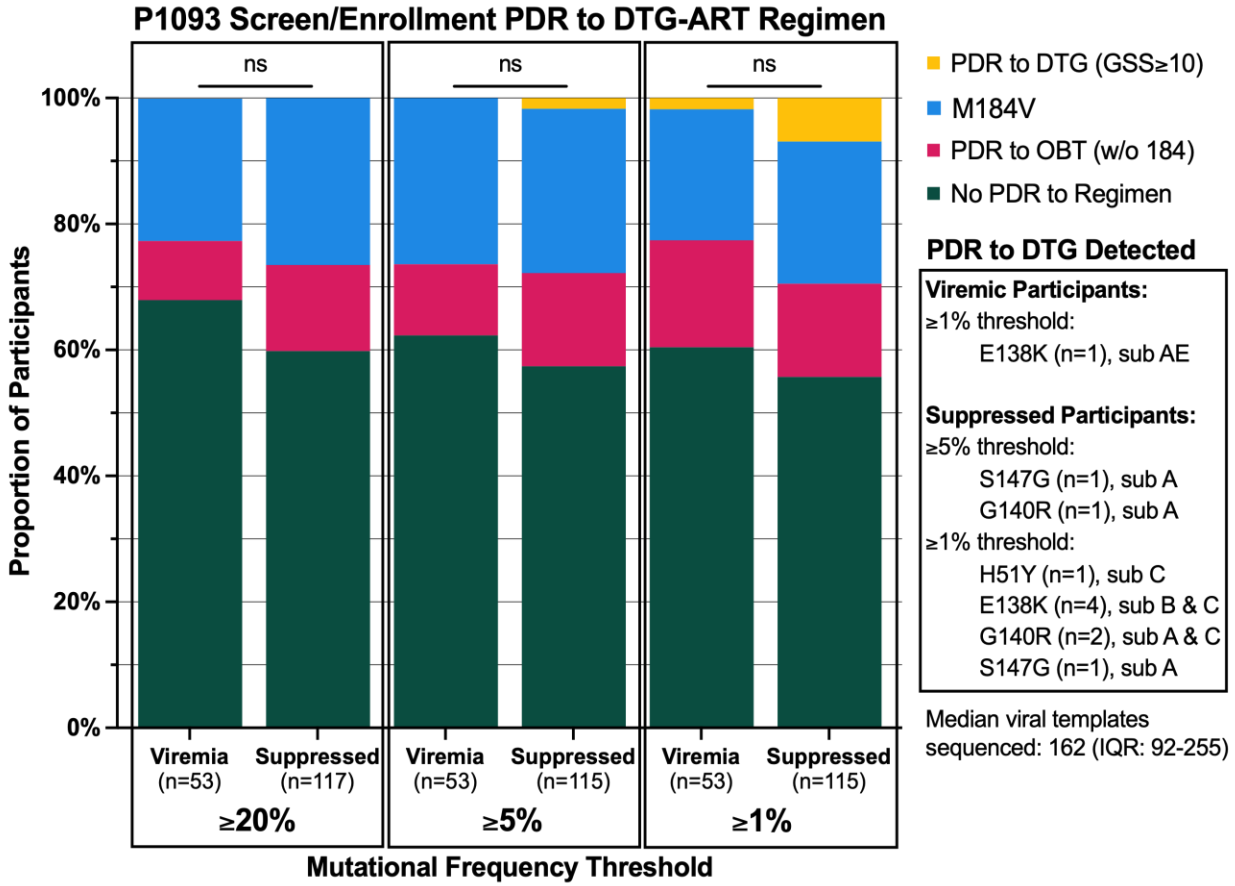
Outcomes:

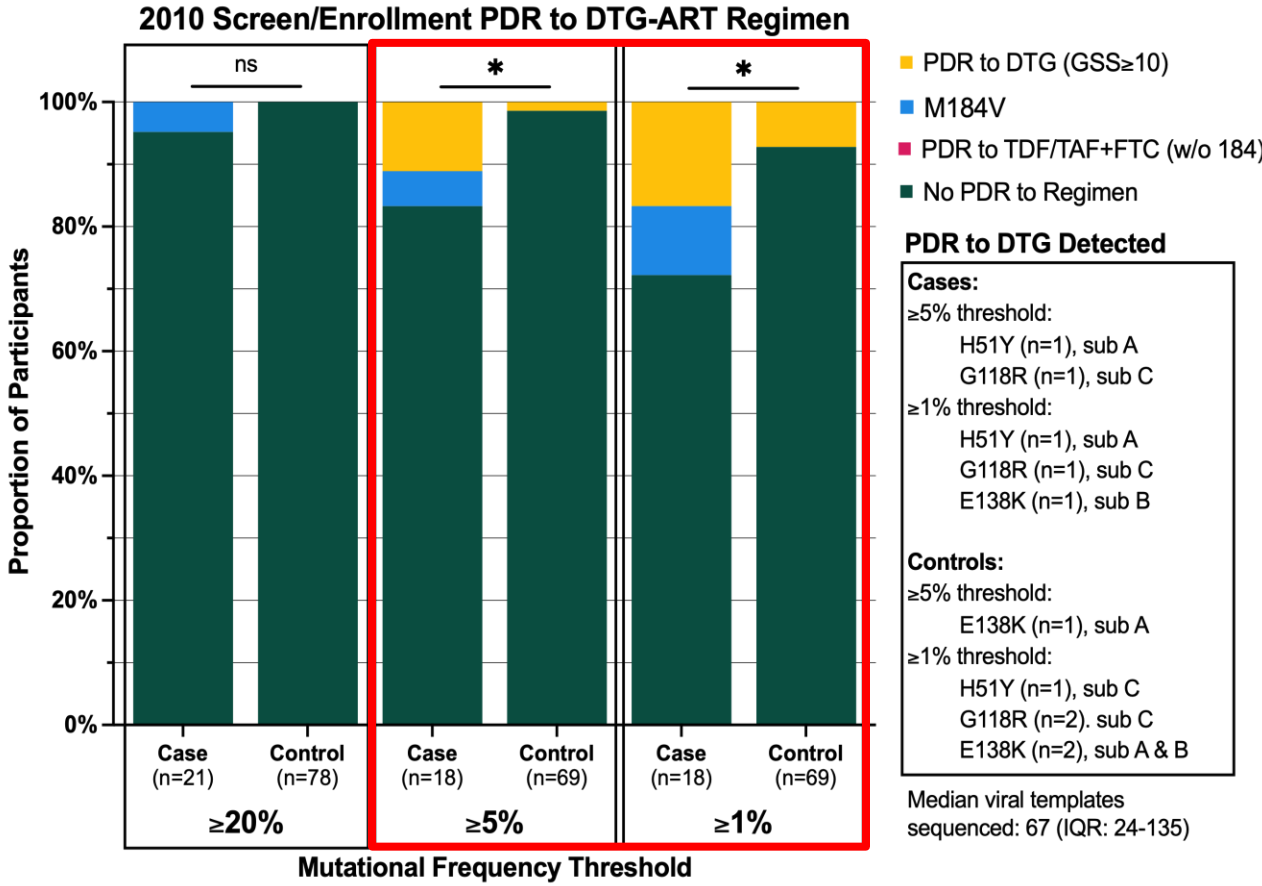


- 24/432 (**5.6%**)
  - 21 confirmed VF = ≥200c/mL x 2 sequentially
  - 3 viremias = ≥200c/mL at final study visit
  - Median viremia 9,884c/mL (IQR: 1,152-48,592c/mL)

PDR was not associated with VF / viremia in either cohort

- Screen/enrollment genotypes were successfully derived from 269/292 (92%) participants
  - 170/181 in P1093 (168 PacBio, 2 Sanger)
  - 99/111 in 2010 (87 PacBio, 12 Sanger)
- PDR at screen/enrollment was
  - not associated with VF/viremia in P1093
  - but low frequency PDR was associated with VF/viremia in 2010



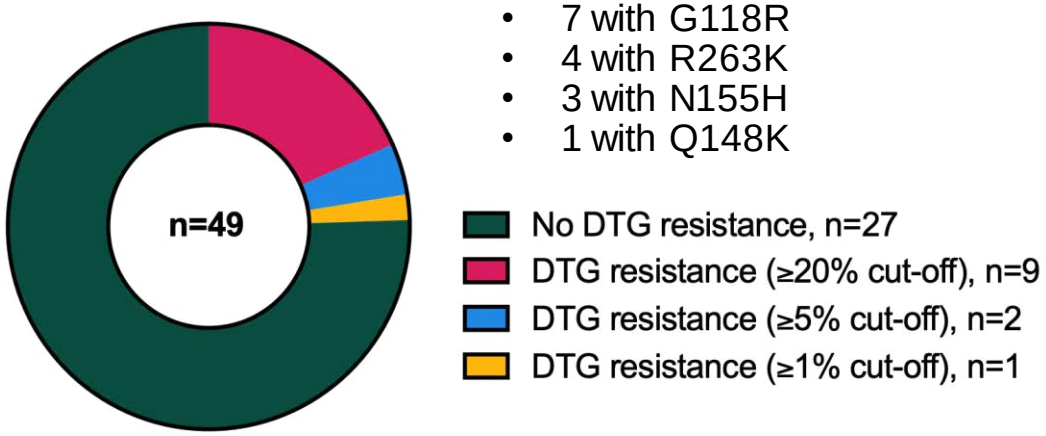


Major DTG-resistance mutations detected in 13 participants at VF/viremia

IMPAACT P1093

Regimen:
DTG + optimized background therapy (**OBT**)

DTG-resistance:
- Longitudinal genotyping = 49/56 with VF/ viremia
  - PacBio n= 117 specimens
  - Sanger n= 18 specimens
- DTG-resistance = 12/49 (**24.5%**) with major mutations



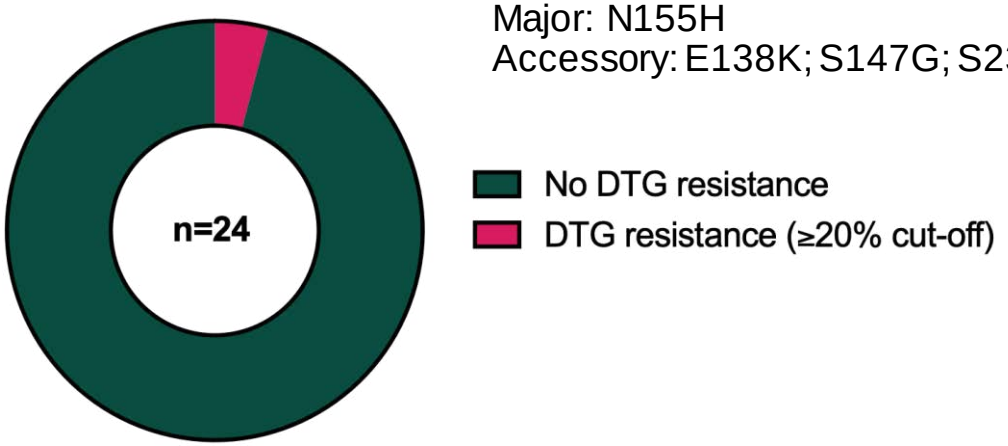
- 7 with G118R
- 4 with R263K
- 3 with N155H
- 1 with Q148K

No significant difference in % DTG-resistance among those with TDF vs. ABC/ZDV in OBT: 2/11 (**18.2%**) vs 10/38 (**26.3%**); p=0.7

IMPAACT 2010

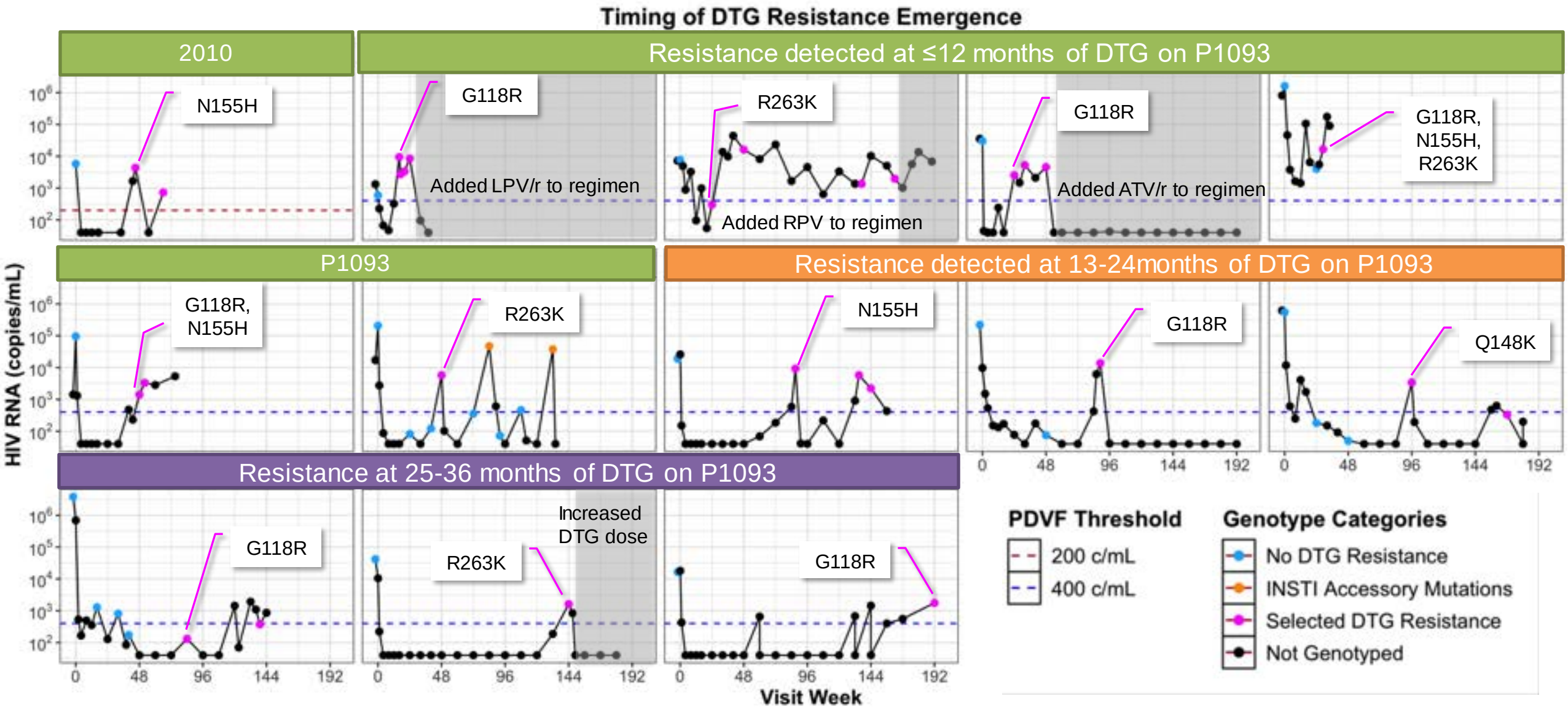
Regimen:
DTG + TDF/TAF + emtricitabine

DTG-resistance:
- Longitudinal genotyping = all 24 “cases”
  - PacBio n= 57 specimens
  - Sanger n= 2 specimens
- DTG-resistance =1/24 (**4.2%**) with major mutations

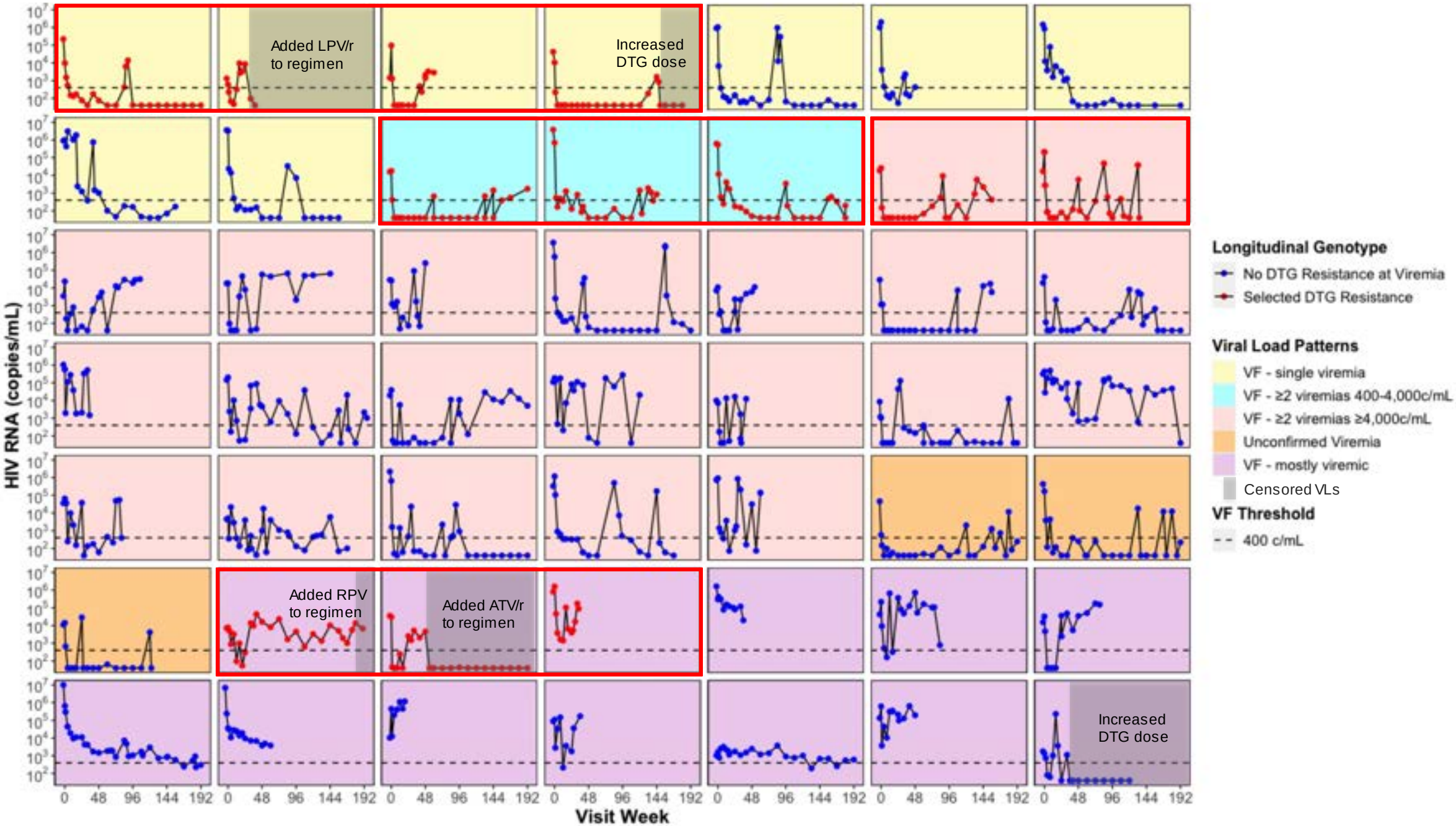


Major: N155H
Accessory: E138K; S147G; S230R

DTG-resistance selected in year 1 (7/13=53%), 2 (3/6=50%) & 3 (3/3=100%)

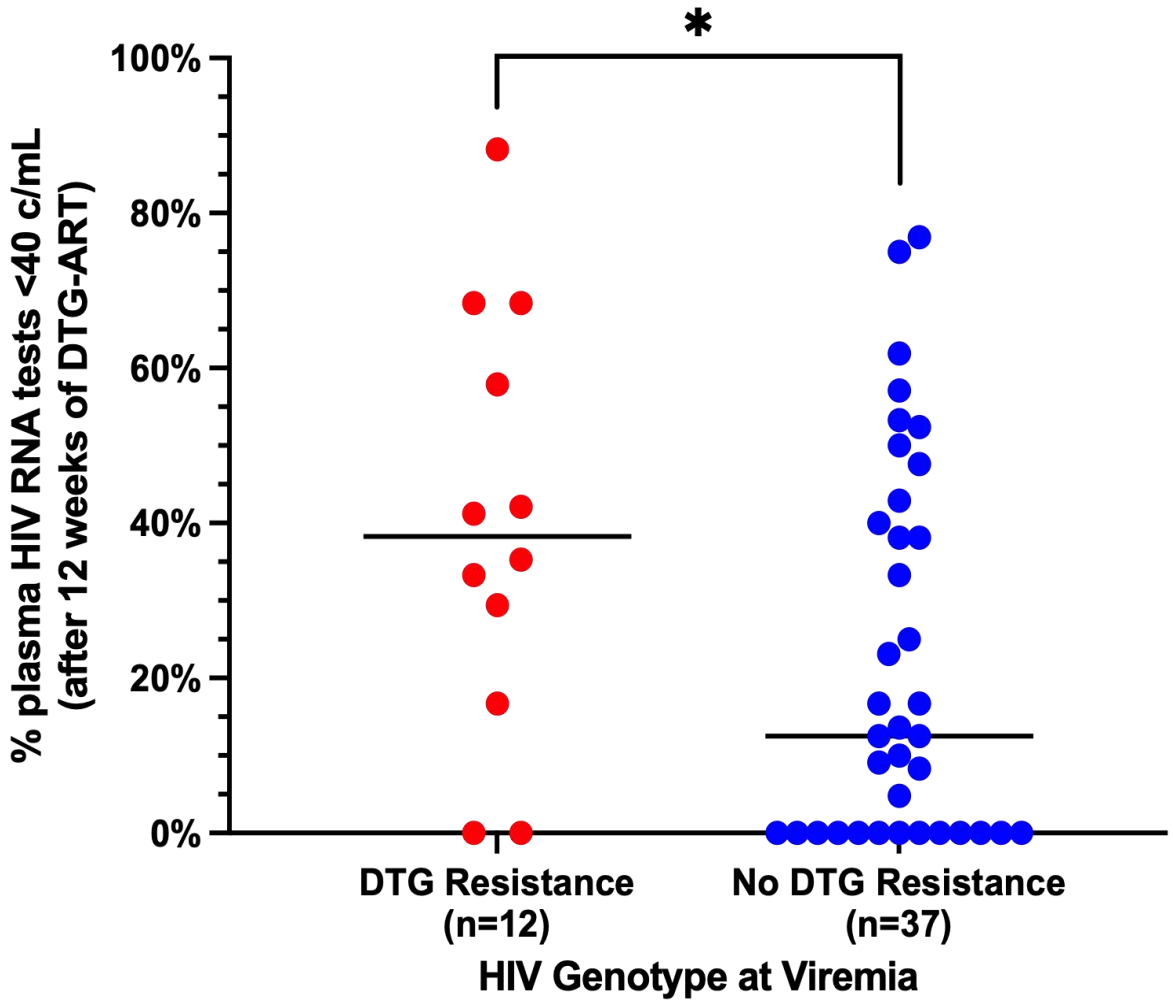


Patterns of plasma HIV RNA ≥ 400c/mL in P1093 participants who did / did not select DTG-resistance



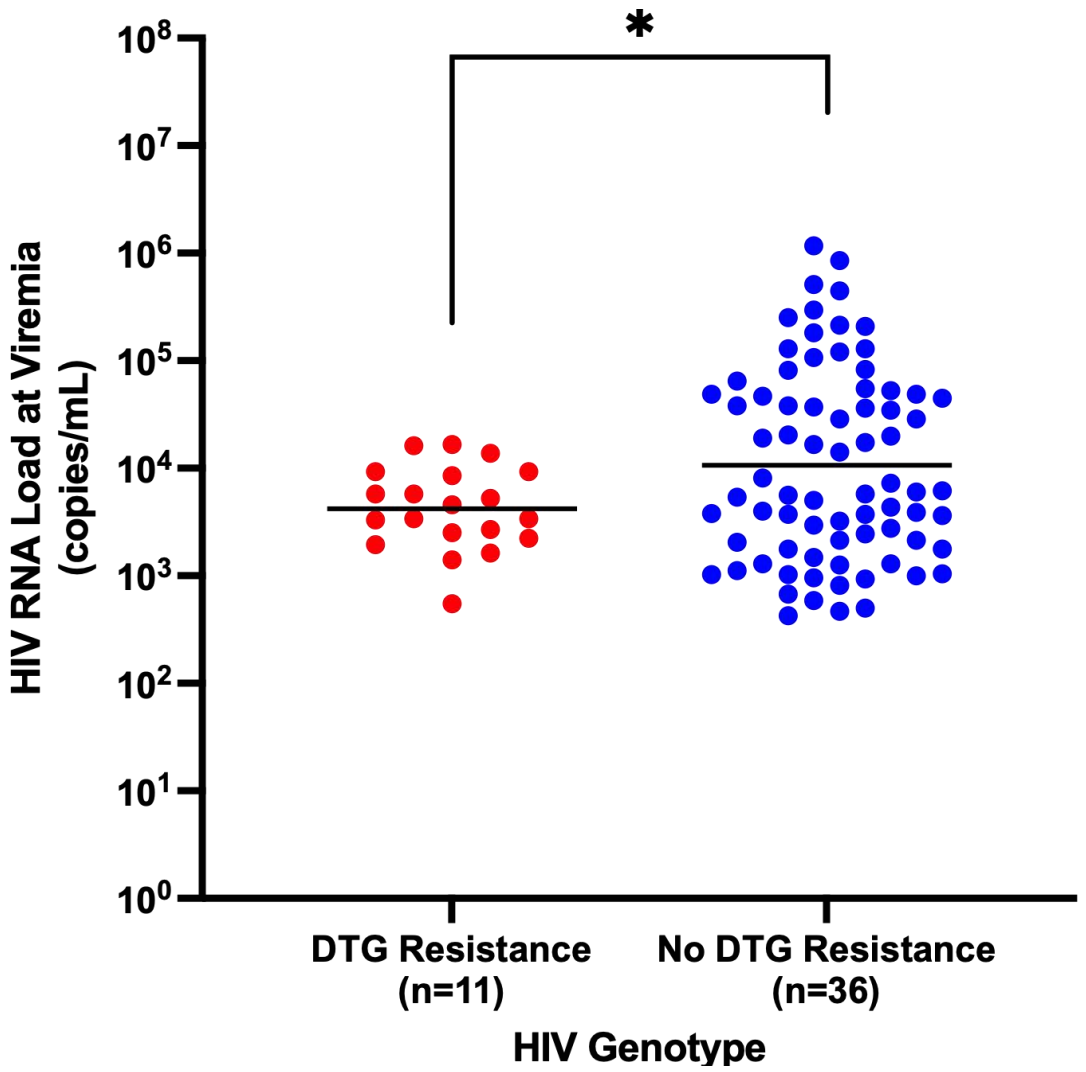
Pattern of plasma HIV RNA appears associated with DTG-resistance in P1093

- Compared
  - Proportion plasma HIV RNA tests “undetectable” (<40c/mL) over study period
  - Participants with vs without DTG-resistance (n=49)
  - Generalized estimating equations (**GEE**) was used to account for repeated measures
- Found
  - DTG-resistance associated with increased suppression (p=0.043)
  - OR 2.15, 95% CI 1.02-4.52
- **Suggests that intermittent adherence with low-level viremia allows selection of DTG-associated mutations**



DTG-resistance associated with lower HIV RNA at viremia in P1093

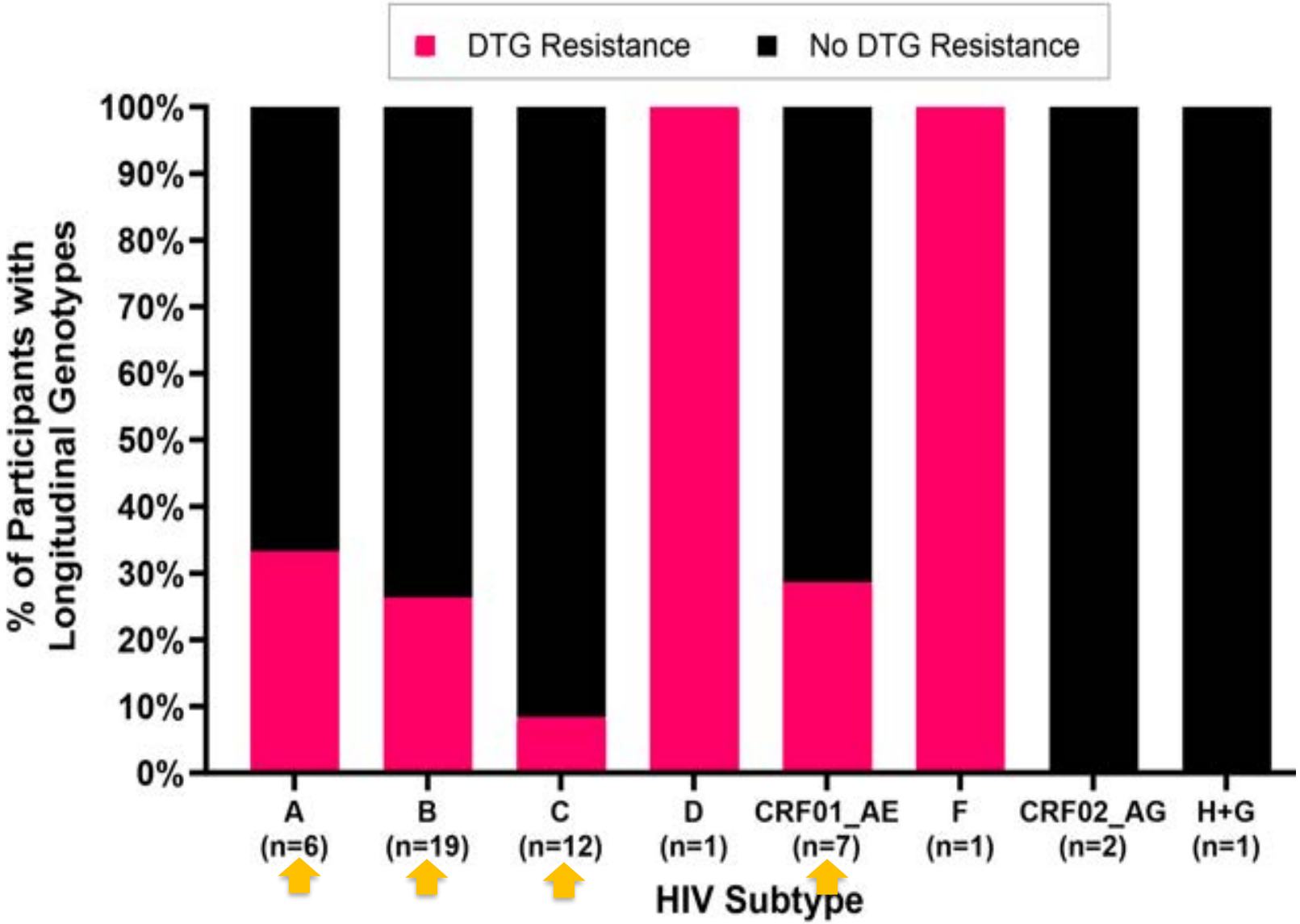
- Compared
  - Plasma HIV RNA at viremic timepoints we genotyped
  - Participants with vs without DTG-resistance (n=47*)
  - GEE was used to account for repeated measures
- Found
  - Those with DTG-resistance had lower viral loads when viremic than those who did not have DTG-resistance (p=0.0139)
    - HIV RNA 0.38 log10 lower (95% CI 0.08, 0.69)
    - Mean viremia 4,169c/mL vs 10,233c/mL
- **Supports hypothesis that low-level viremia allows selection of DTG-associated mutations**
- **Suggests DTG-associated mutations may reduce viral replication capacity**



*Two participants had plasmas with "detectable" HIV RNA genotyped, but loads were all <400 c/mL so they were excluded from this analysis

HIV Subtype & DTG Resistance in P1093

- Participants with VF / viremia
  - Compared % with DTG-resistance by HIV-1 subtype
- Found
  - Similar rates in subtypes A, B, C, CRF01_AE
  - Too few D, F, CRF02_AG
- **Suggests HIV-1 subtype may not have significant association with selection of DTG-resistance**
  - However, need to evaluate additional participants to draw any conclusions



Concordance observed between genotype & phenotype

- Phenotypic analysis
  - n=13 P1093 participants
    - 9 shown; Major DTG mutations
    - 2 with accessory DTG mutations & 2 wild-type not shown
- Comparison of phenotypes for two most prevalent mutant codons:
    - G118R
    - R263K
  - Median FC (range)
    - G118R= 16.5 (9, 62)
    - R263K= 3.7 (2.5, 5)
- Phenotypic DTG-resistance consistently greater with G118R vs R263K

Country	Subtype	Weeks of DTG	INSTI resistance mutations	RC[a]	DTG EC_{50} (nM)[b]	FC[c]
Thailand	AE	0	L74I	95	1.7 ± 0.18	
		20	T66I, L74I, **G118R**	29	**32 ± 10[d]**	**19**
USA	B	0	none	67	2.4 ± 0.52	
		162	E138T, S147G, **R263K**	55	**12 ± 2.9**	**5.0**
South Africa	C	0	none	80	1.7 ± 0.22	
		32	L74I, **G118R**	35	**18 ± 6.0**	**11**
		48	**G118R**	21	**46 ± 18**	**27**
		48	T97A, **G118R**	17	**105 ± 78**	**62**
Brazil	B	0	none	101	2.6 ± 0.21	
		29	**G118R**	21	**24 ± 11**	**9.2**
		29	**R263K**	48	5.9 ± 2.2	2.3
		29	**G118R**, **R263K**	4.0	UTD[e]	UTD
		29	E92Q, **N155H**	27	**10 ± 1.5**	**3.8**
		29	E92Q	47	4.9 ± 0.48	1.9
Brazil	B	0	none		2.0 ± 0.45	
		51	**G118R**, E138K, V151I	71	**19 ± 1.9**	**9.5**
		51	**G118R**, E138K	42	**23 ± 5.2**	**9.6**
		51	T97A, **N155H**	35	3.3 ± 0.74	1.4
Kenya	A	0	none	25	2.4 ± 0.73	
		96	E138K, **Q148K**	47	**58 ± 11**	**24**
Brazil	F	0	none	33	3.2 ± 1.2	
		139	T66I, **G118R**, E138A	13	**55 ± 19**	**17**
Kenya	A	0	none	88	1.5 ± 0.28	
		144	**R263K**	58	**5.5 ± 0.92**	**3.7**
USA	B	0	none	53	2.5 ± 0.49	
		192	L74M, **G118R**	11	**67 ± 5.9**	**27**

[a] Replication capacity as % HIV-1_{NL4-3} ; [b] Mean ± SD; [c] Fold change; [d] Bold significant change ($p<0.05$) compared to EC_{50} for week-0 clone; [e] UTD, unable to determine due to insufficient replication capacity

Summary

- Viremia/virologic failure (**VF**) during DTG-ART was increased in participants w/ previous viremia/VF
- PDR was not associated with viremia/VF during DTG-ART
- Major DTG-resistance mutations detected at
  - High rate (24.5%) in a pediatric participants
  - Low rate (4.2%) in pregnant/breastfeeding participants
- DTG-resistance frequently selected within 12 months of DTG-ART
- Pattern of viremia (low plasma HIV RNA + ART-suppression) associated w/ DTG-resistance in children
- Phenotypic resistance concordant within two most frequent Major DTG-resistance mutations
  - G118R and R263K

Conclusions

- Frequencies of VF (31%; 95% CI 25, 38) and DTG-resistance (24.5%; 95% CI 14, 38) in P1093 are greater than most other adult/pediatric cohorts in clinical trials
  - Likely due to patterns of non-adherence / viremia
  - Potentially due to length of study/follow-up
- Despite DTG's higher barrier to drug resistance vs. NNRTI-based ART
  - DTG-resistance can be selected ≤12 months; which has implications for continuing DTG despite viremia
  - DTG- based ART may need to be combined with tenofovir or other ARV with long $t_{1/2}$ to maximize barrier to resistance; which has implications for children

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