HIV Drug Resistance Scene Today

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Perspective

HIV Drug Resistance — An Emerging Threat to Epidemic Control

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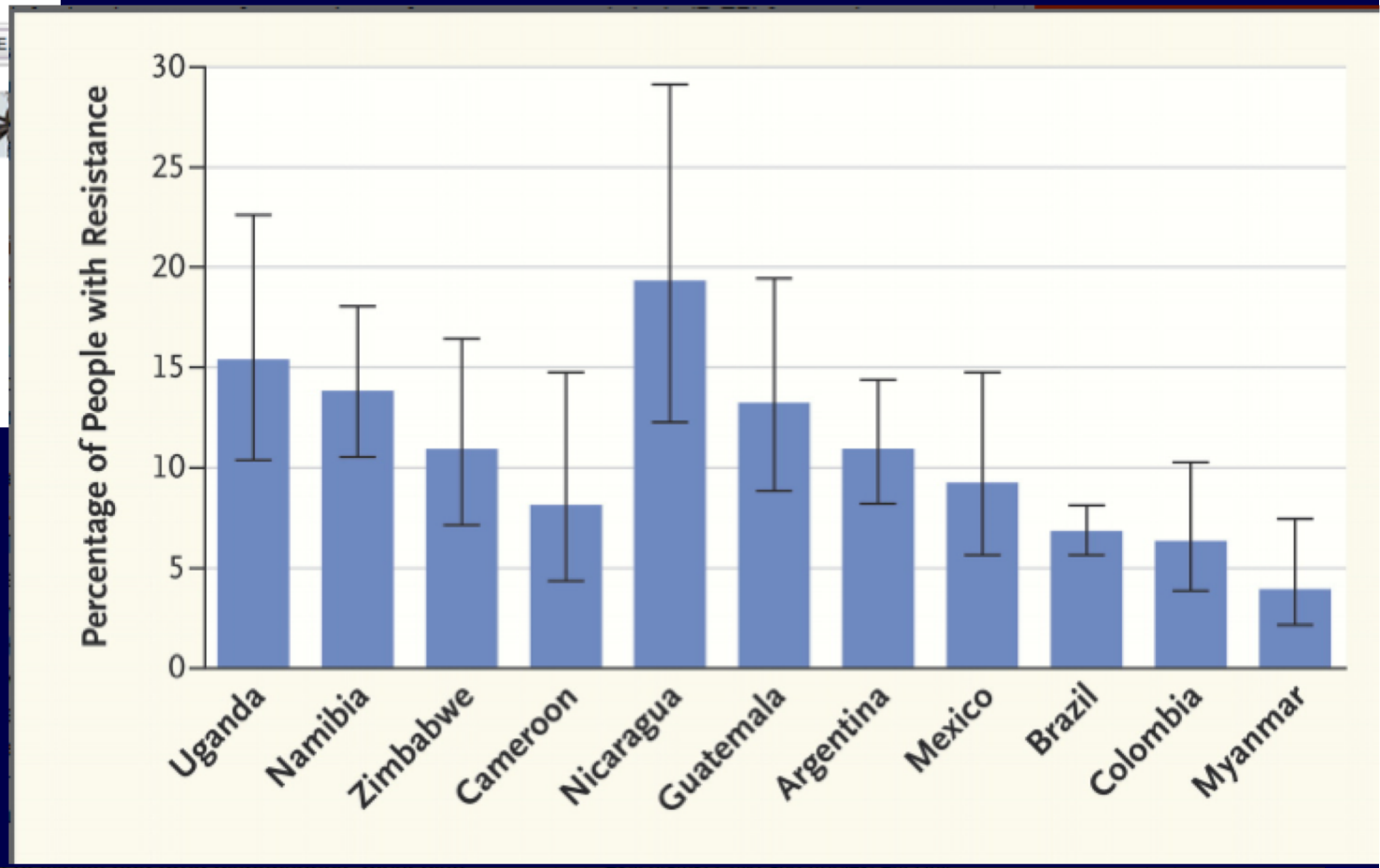
- Pre-Rx NNRTI resistance >10%
- Post-exposure to ART – 21.6%
- Children under 18 months – 63.7%



Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

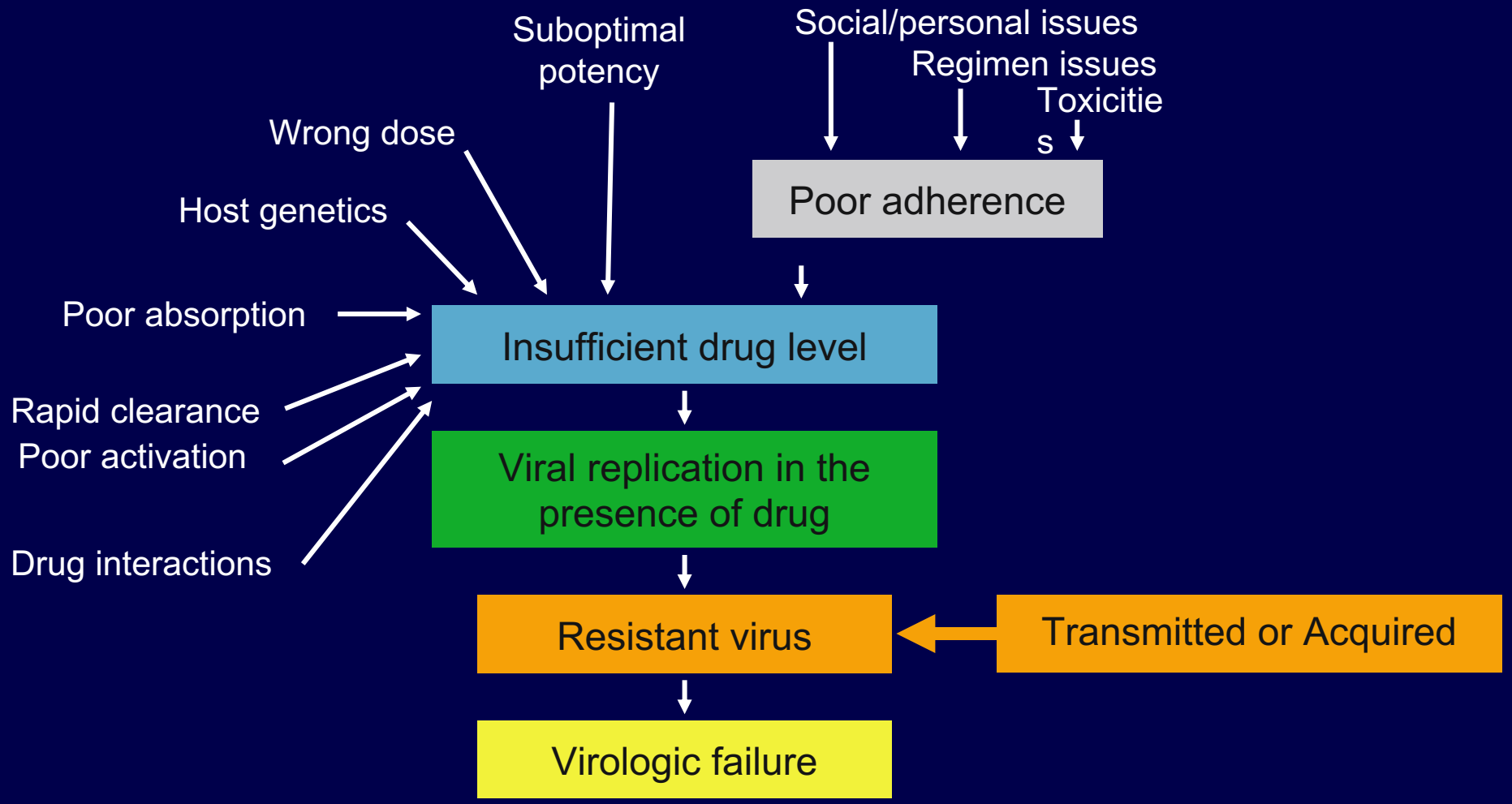
Shown are the percentages of people tested who had resistance to efavirenz or nevirapine. I bars denote 95% confidence intervals. Data are from the World Health Organization.[1]

Maintaining an undetectable viral load

- Prevents disease progression
- Improves survival
- Prevents the emergence of drug resistant virus
  - Due to cross-resistance within a drug class, fully active ARV options diminish with each successive viral failure
- Reduce the risk of transmitting HIV
  - **Communities will be at risk from viremic patients**

IT TAKES A VILLAGE

Causes of Treatment Failure

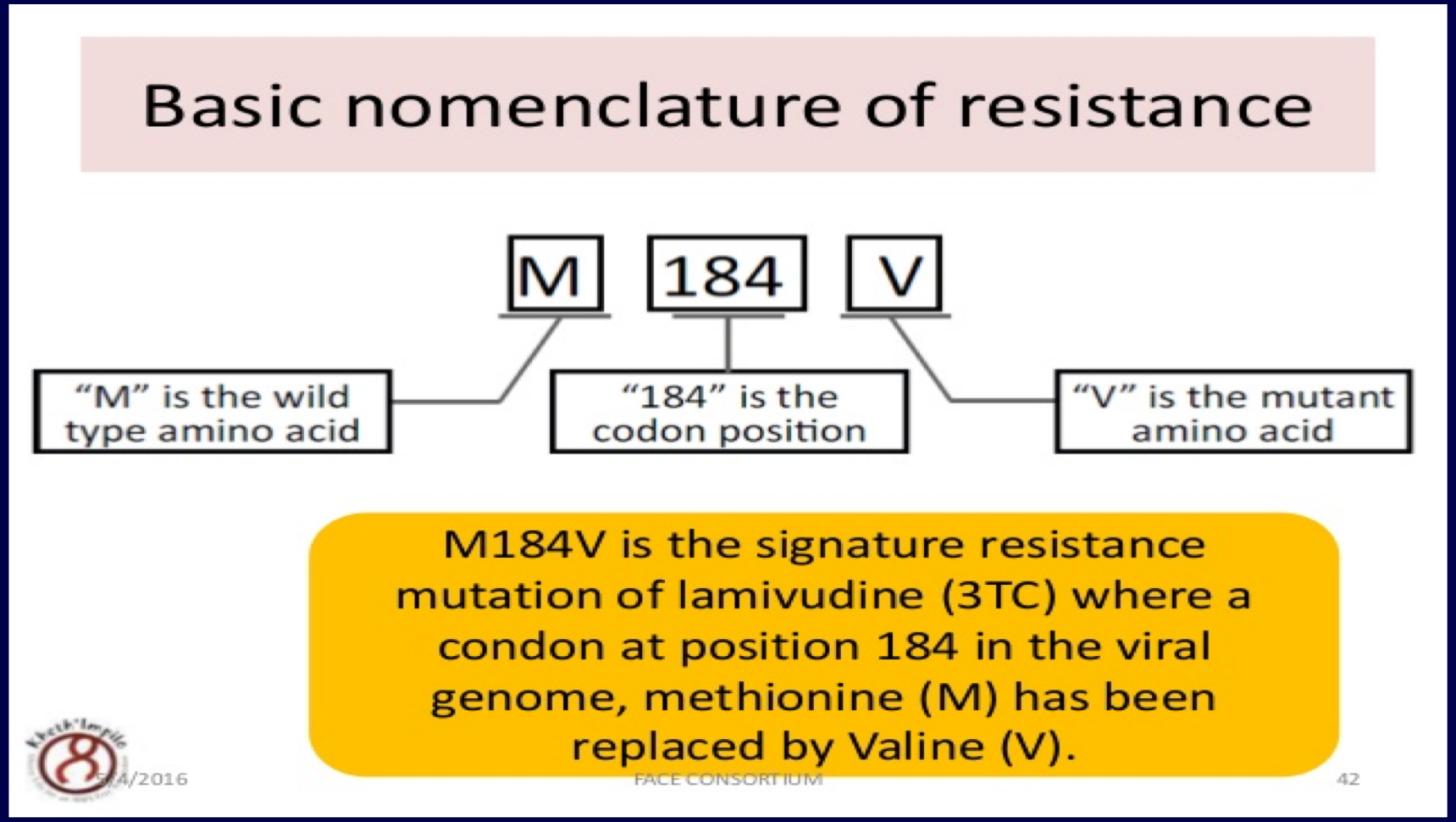


DHHS Guidelines.

Slide credit: clinicaloptions.com

Resistance

- The ability of HIV to replicate in the presence of ART
- Caused by changes in relevant parts of the virus genome (mutations)



Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate;
E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine;
K, lysine; L, leucine; M, methionine; N, asparagine; P, proline;
Q, glutamine; R, arginine; S, serine; T, threonine; V, valine;
W, tryptophan; Y, tyrosine.

MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

	M	A	▼	K	L	T	K
	41	62	69	70	210	215	219
Multi-nRTI Resistance	L	V	Insert	R	W	Y	Q
						F	E

151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A	V	F	F	Q
	62	75	77	116	151
Multi-nRTI Resistance	V	I	L	Y	M

Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M	D	K	L	T	K
	41	67	70	210	215	219
Multi-nRTI Resistance	L	N	R	W	Y	Q
					F	E

	K	L	Y	M
	65	74	115	184
Abacavir[f,g]	R	V	F	V
	E			
	N			

	K	L
	65	74
Didanosine[g,h]	R	V
	E	
	N	

	K	M
	65	184
Emtricitabine	R	V
	E	I
	N	

	K	M
	65	184
Lamivudine	R	V
	E	I
	N	

	M	K	D	K	L	T	K
	41	65	67	70	210	215	219
Stavudine[d,e,g,i,j,k]	L	R	N	R	W	Y	Q
		E				F	E
		N					

	K	K
	65	70
Tenofovir[l]	R	E
	E	
	N	

	M	D	K	L	T	K
	41	67	70	210	215	219
Zidovudine[d,e,j,k]	L	N	R	W	Y	Q
					F	E

IAS-USA Topic in Antiviral Medicine Volume 24 Issue 4 – Dec 2016/January 2017

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,m]

	90	98	100	101	103	106	108	138	179	181	188	190	225	227	230	221
Efavirenz			**I**	**P**	**N S**	**M**	**I**			**C I**	**L**	**S A**	**H**		**L**	
Etravirine[n]	I	G	**I**	E H **P**		I		A G K Q	D F T	**C I V**		S A			L	
Nevirapine			**I**	**P**	**N S**	**A M**	**I**			**C I**	**C L H**	**A**			**L**	
Rilpivirine[o]			**I**	**E P**				**A G K Q R**	**L**	**C I V**	**L**			**C**	**I L**	**Y**

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[p,q,r]

	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Atazanavir +/- ritonavir[s]	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M
Darunavir/ ritonavir[t]	V				V	L			I		I		I					T		I		L		
	11 I				32 I	33 F			**47** V		**50** V		**54** M L					74 P	**76** V	**84** V		89 V		
Fosamprenavir/ ritonavir	L				V				M	I	I		I					G	L	V	I		L	
	10 F I R V				32 I				46 I L	47 V	**50** V		54 L V M					73 S	76 V	82 A F S T	**84** V		90 M	
Indinavir/ ritonavir[u]	L		K	L	V			M	M				I				A	G	L	V	V	I		L
	10 I R V		20 M R	24 I	32 I			36 I	**46** I L				54 V				71 V T	73 S A	76 V	77 I	82 A F T	**84** V		90 M
Lopinavir/ ritonavir[v]	L		K	L	V	L			M	I	I	F	I		L		A	G	L		V	I		L
	10 F I R V		20 M R	24 I	**32** I	33 F			46 I L	**47** V A	50 V	53 L	54 V L A M T S		63 P		71 V T	73 S	**76** V		82 A F T S	84 V		90 M
Nelfinavir[u,w]	L				D			M	M								A			V	V	I	N	L
	10 F I				**30** N			36 I	46 I L								71 V T			77 I	82 A F T S	84 V	88 D S	**90** M
Saquinavir/ ritonavir[u]	L			L						G	I				I		A	G		V	V	I		L
	10 I R V			24 I						**48** V	54 V L				62 V		71 V T	73 S		77 I	82 A F T S	84 V		**90** M
Tipranavir/ ritonavir	L					L	M		K	M	I		I	Q		H		T		V	N	I		L
	10 V					33 F	36 I L V		43 T	46 L	**47** V		54 A M V	**58** E		69 K R		**74** P		**82** L T	83 D	**84** V		89 I M V

Treatment-Experienced Adult Patients – Dosing of Darunavir/r

- With NO darunavir resistance associated substitutions*
  - Darunavir (PREZISTA) 800 mg (one 800 mg tablet once daily) once daily with ritonavir 100 mg (one 100 mg) once daily and with food
- With AT LEAST ONE darunavir resistance associated substitution*
  - Darunavir (PREZISTA) 600 mg (e.g. one 600 mg tablet) twice daily with ritonavir 100 mg (one 100 mg tablet) twice daily and with food
- *V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

	G	I	V	Q	Q	N	N
Enfuvirtide[x]	**36**	**37**	**38**	**39**	**40**	**42**	**43**
	D	**V**	**A**	**R**	**H**	**T**	**D**
	S		**M**				
			E				
Maraviroc[y]	See User Note						

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS[z]

Dolutegravir[aa]								F	E	G				Q		N			R
								121	138	140				**148**		155			263
								Y	A	A				**H**		H			K
									K	S				**K**					
														R					
Elvitegravir[bb]		T				E		T	F				S	Q		N			R
		66				**92**		97	**121**				**147**	**148**		**155**			263
		I				**Q**		A	**Y**				**G**	**H**		**H**			K
		A				G								**K**					
		K												**R**					
Raltegravir[cc]			L		E		T	F	E	G	Y			Q		N			R
			74		92		97	**121**	138	140	**143**			**148**		**155**			263
			M		Q		A	**Y**	A	A	**R**			**H**		**H**			K
									K	S	**H**			**K**					
											C			**R**					

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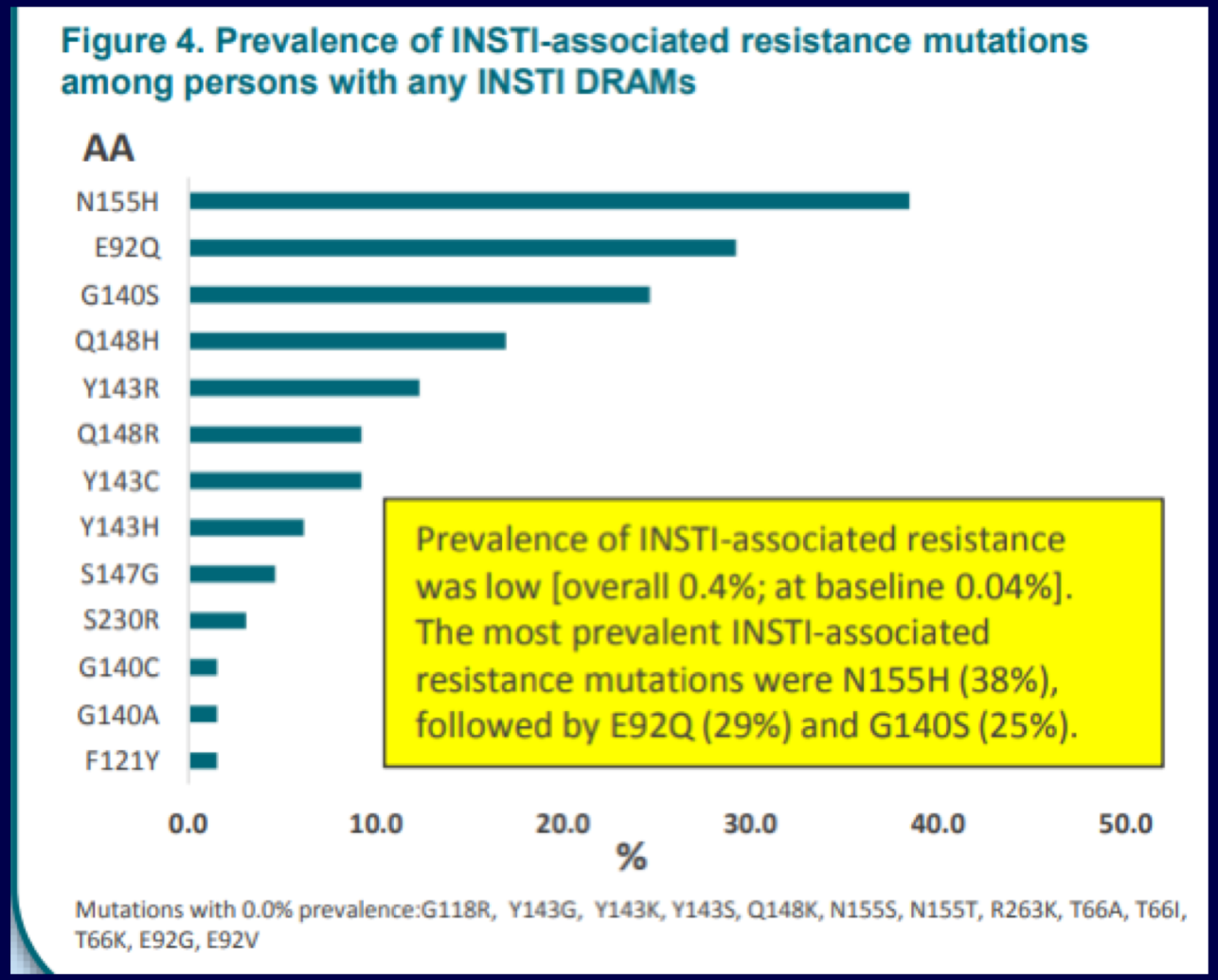
INSTI Resistance in the United States

- Analyzed 14,468 sequences from National HIV Surveillance System in 9 US jurisdictions
- INSTI genotypic testing increased over time (2010-2014)
- **Prevalence of INSTI resistance: 65/14,468 (0.4%)**
- **Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)**



Hernandez AL, et al. CROI 2017. Abstract 478.

Mutations in HIV Integrase

- Raltegravir – N**155H** mutants predominate early in Raltegravir failure but are replaced by viruses with higher resistance bearing mutations G**140S** + Q**148H/R/K** with continuing Raltegravir Treatment.
- Elvitegravir – E**92Q**, F**121Y**, T**166I**, N**155H**, Q**148H/R/K**
- Raltegravir and Elvitegravir have lower barrier to resistance and can cause cross resistance to each other
- Dolutegravir – Highest Genetic barrier to resistance
  - Single reported case of resistance in first line treatment*
  - Integrase mutations are rarely reported in experienced patients receiving Dolutegravir
- Dolutegravir can be used to treat certain patients with virus resistant to Raltegravir and Elvitegravir and the dose should be 50mg twice daily
- DO NOT use Dolutegravir in the setting of Integrase mutations at codon Q148 along with 2 or more Secondary mutations

CROI 2017 Fulcher, JA

DHHS: Recommendations for Resistance Testing

- Results used to inform design of new ART regimens for pts experiencing VF

Question	Recommendation
Who should receive resistance testing?	▪ Pts with VF and HIV-1 RNA levels > 1000 copies/mL ▪ May be considered for pts with 500-1000 copies/mL
When should testing be conducted?	▪ While on failing ART regimen or < 4 wks from treatment end ▪ May still be considered after 4 wks
What types of testing should be conducted?	▪ First-/second-line failure: genotypic testing ▪ **Suspected MDR: genotypic plus phenotypic testing** ▪ **When considering CCR5 antagonist: tropism assay** ▪ If prior failure on INSTI-containing regimen, test for INSTI resistance
Other considerations	▪ Prior treatment history should be obtained

DHHS Guidelines.

Slide credit: clinicaloptions.com

Genotypic Resistance Assay

- Detects the presence of specific drug resistant mutations in the regions of HIV genome encoding protease, reverse transcriptase, integrase
- Results are reported as the individual mutations i.e. M184V
- Followed by comments such as “susceptible”, “possibly resistant” or “resistant”
- Cheaper, quicker turn around time.
- Recommended for first or second line failures

Phenotypic Resistance Assay

- Measures the extent to which ART inhibits virus replication in vitro
- Susceptibility that is measured is the aggregate of the acquired drug mutation in the patients viral strain
- It is typically performed by demonstrating an increase in the inhibitory concentration (IC) that is required to inhibit in vitro growth by 50% (IC 50) compared with the virus replication in the absence of drug
- Results are reported as a fold change in drug susceptibly in the patients sample compared with a lab reference strain without resistance
- More expensive, longer turn around time, but better for treatment experienced patients with multiple resistance mutations

HIV RNA ≥200 and <1,000 copies/mL

- In contrast levels persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL
- Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered virologic failure, and resistance testing should be attempted, particularly with HIV RNA >500 copies/mL.
- Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL
- When resistance testing cannot be performed because of low RNA levels, the decision of whether to empirically change ARVs should be made on a case-by-case basis, taking into account whether a new regimen expected to fully suppress viremia can be constructed.

DHHS Guidelines.

HIV RNA ≥1,000 copies/mL and no current or previous drug resistance identified

- Almost always associated with suboptimal adherence.
  - –Identify and address the underlying cause(s) for incomplete adherence
  - –If possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency
- A boosted PI regimen – since boosted PI's are less likely to select for drug resistant virus in the face of continued poor adherence (preferred)
- Dolutegravir with two NRTI's (may have similar properties)

HIV RNA >1,000 copies/mL and drug resistance identified

- If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible in order to avoid progressive accumulation of resistance mutations.

- Virologic responses to new and active regimens are greater with lower HIV RNA levels and/or higher CD4 cell counts at the time of regimen changes, thus the change is best done before worsening of viremia or decline in CD4 count.

- The availability of newer ARVs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most of these patients.

DHHS: Management of First-line Failure

Failing Regimen (+ NRTIs)	
▪ Boosted PI:	Enforce adherence Modify for convenience or toxicity
▪ NNRTI:	Boosted PI + NRTIs Boosted PI + INSTI
▪ INSTI:	Boosted PI + NRTIs Boosted PI + active INSTI*

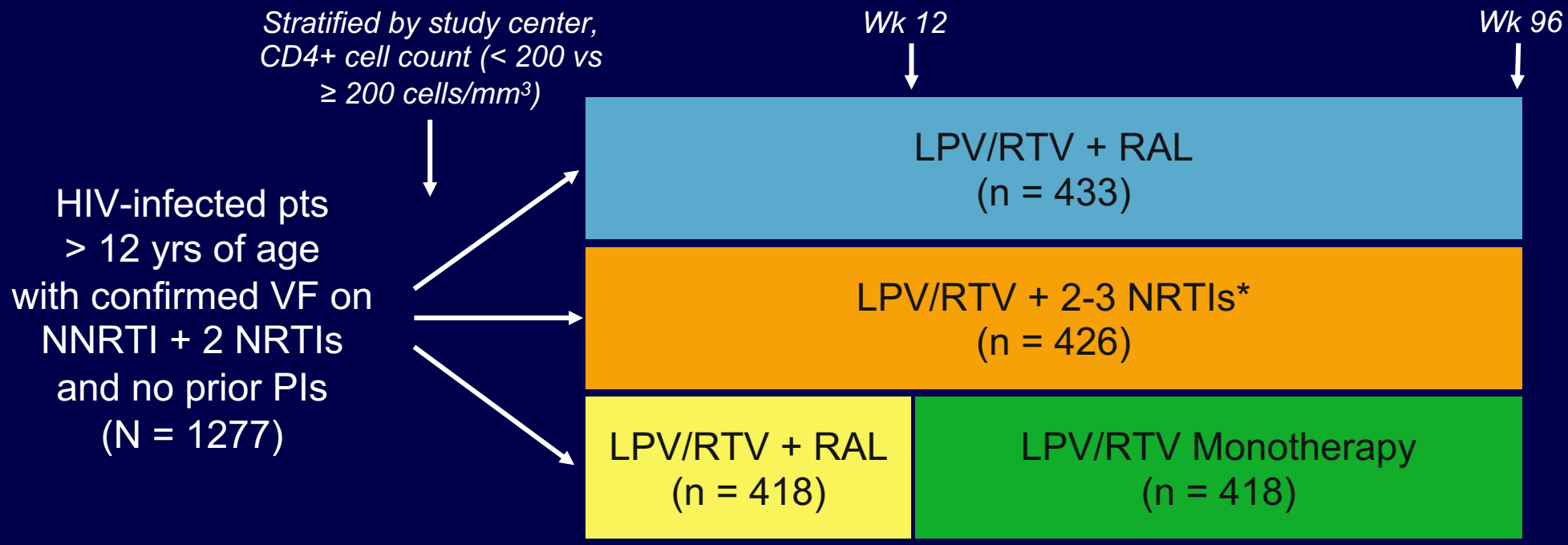
*If RAL or EVG resistance detected, DTG + boosted PI can be used if DTG susceptible.

DHHS Guidelines.

Slide credit: clinicaloptions.com

EARNEST: Second-line LPV/RTV ± RAL or 2-3 NRTIs in PI-Naive Pts

- Randomized, open-label, multicenter phase III trial in sub-Saharan Africa



LPV/RTV 400/100 mg and RAL 400 mg dosed BID.
*New or recycled NRTIs chosen WITHOUT genotype by clinician.

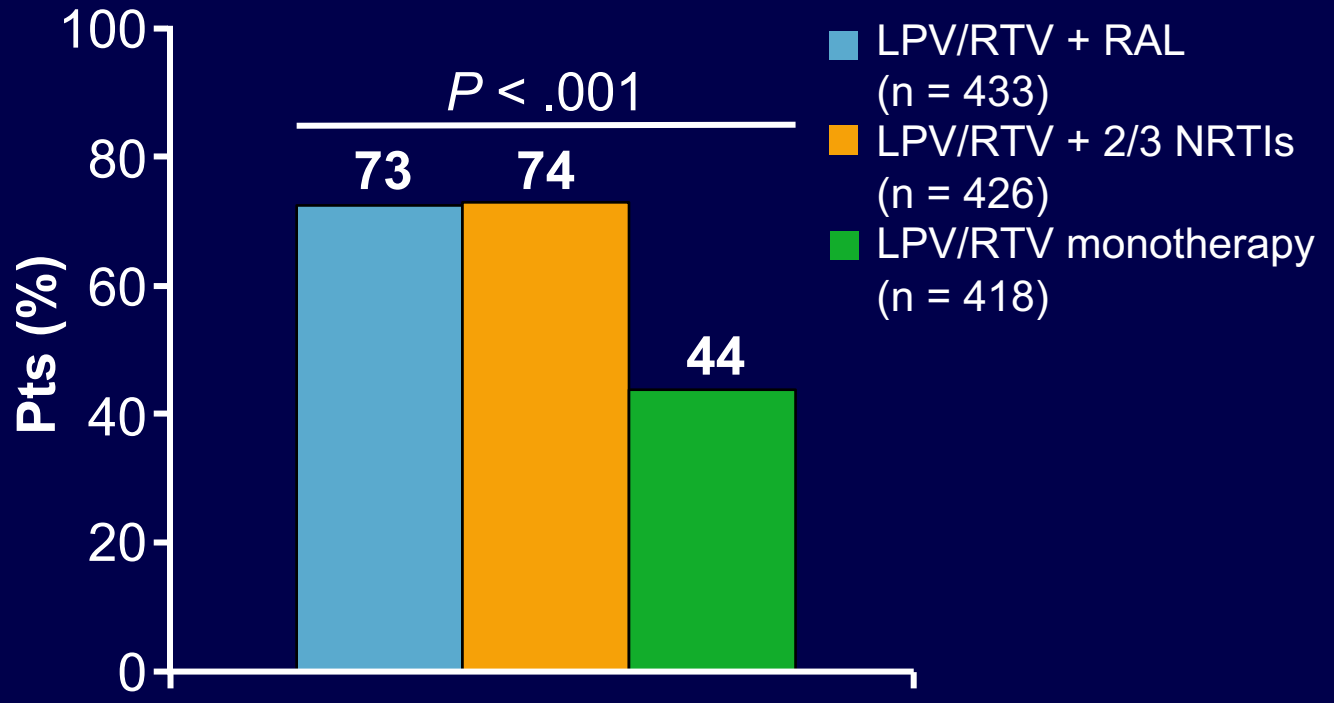
Paton NI, et al. N Engl J Med. 2014;371:234-247.

Slide credit: clinicaloptions.com

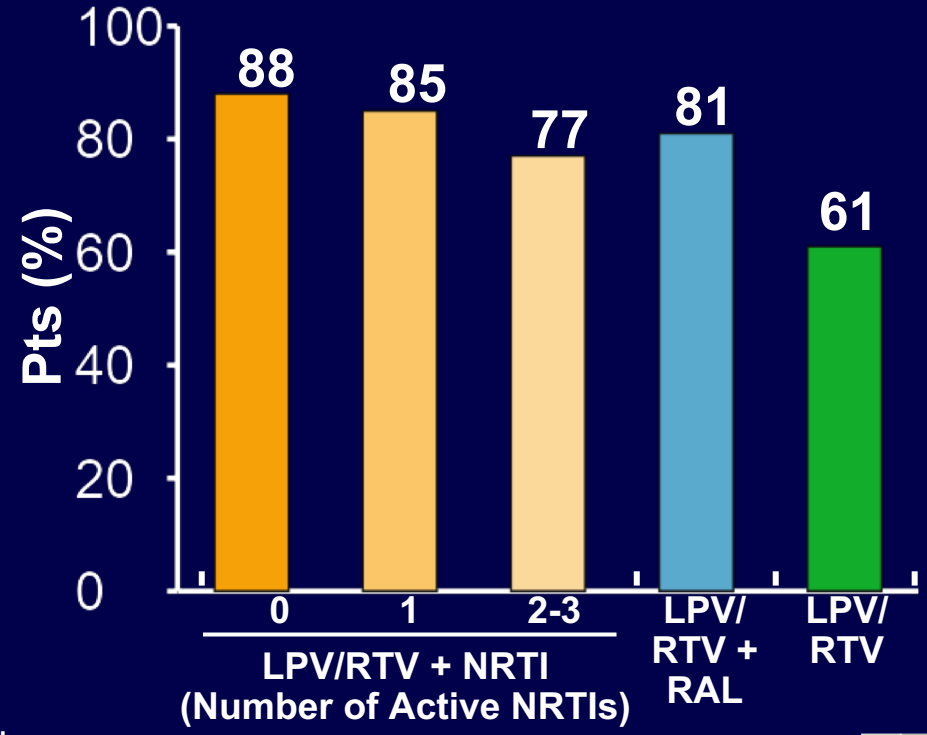
EARNEST: Boosted PIs Effective Even With Partially Active Background Regimen

- Randomized, open-label phase III trial in which pts in sub-Saharan Africa with virologic failure on NNRTI + 2 NRTIs treated with LPV/RTV + RAL, LPV/RTV + 2-3 NRTIs, or LPV/RTV monotherapy* (N = 1277)

HIV-1 RNA < 50 copies/mL, Wk 96[1]



HIV-1 RNA < 400 copies/mL, Wk 144[2]

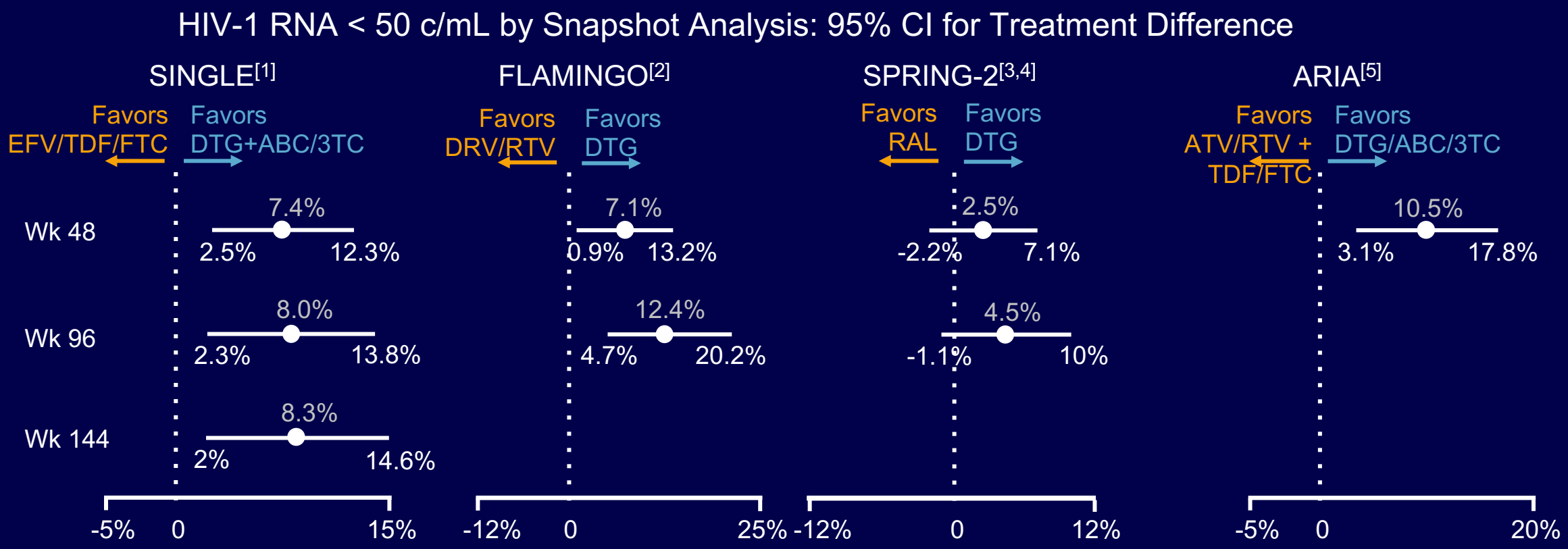


*Pts had no prior PIs; pts receiving monotherapy received 12 wks of LPV/RTV + RAL.

Paton NI, et al. N Engl J Med. 2014;371:234-247. Paton, NI, et al. ACHA 2015.

Slide credit: clinicaloptions.com

DTG + NRTIs: High Barrier to Resistance in Treatment-Naive Pts

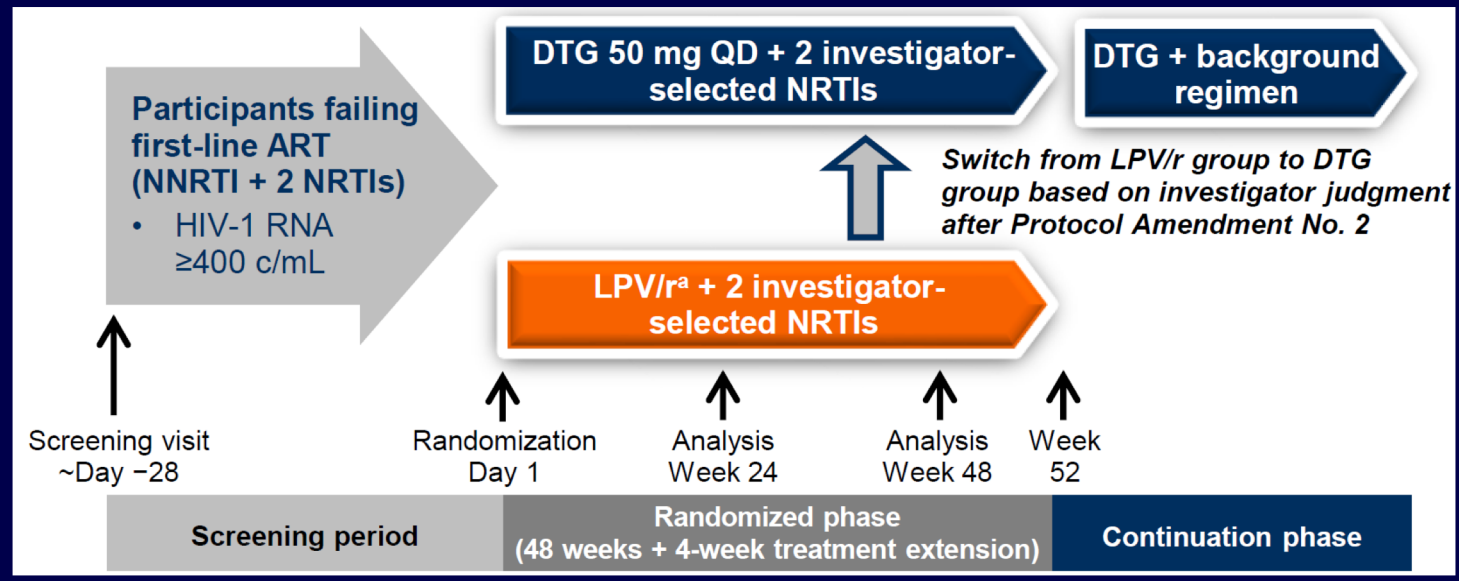


No emergent resistance in any recipients of DTG-based regimens

1. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70:515-519. 2. Molina JM, et al. Lancet HIV. 2015;2:e127-e136. 3. Raffi F, et al. Lancet. 2013;381:735-743. 4. Raffi F, et al. Lancet Infect Dis. 2013;13:927-935.
5. Orrell C, et al. AIDS 2016. Abstract THAB0205LB.

DAWNING: DTG Effective Even With Partially Active Background Regimen

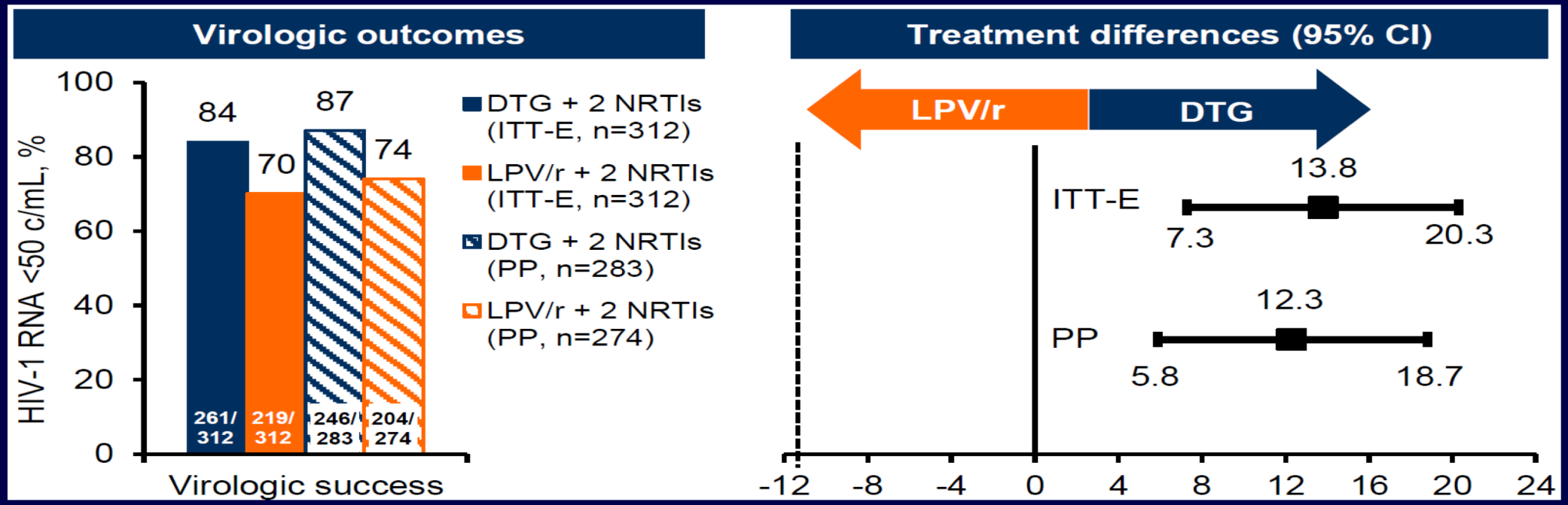
- Randomized, open-label phase IIIb study in which pts in resource-limited settings with virologic failure on NNRTI + 2 NRTIs treated with DTG + 2 NRTIs or LPV/RTV + 2 NRTIs (N = 627)
  - Pts could not have primary resistance to INSTIs or PIs; pts required to receive 1 fully active NRTI
  - Baseline NRTIs, %: ZVD + 3TC, 40; TDF + 3TC or FTC, 42; TDF + ZDV, 12; ABC + 3TC, 2



Aboud et al. 22nd International AIDS Conference; Amsterdam, the Netherlands. Poster THPEB040.

Snapshot Outcomes at Week 48: ITT-E and PP Populations

- In the intention-to-treat exposed (ITT-E) analysis, proportion of participants with HIV-1 RNA <50 c/mL at Week 48 was significantly higher in the DTG + 2 NRTIs group (84%) compared with the LPV/r + 2 NRTIs group (70%; treatment difference [95% CI], 13.8% [7.3%-20.3%]; *P*<0.001 for superiority)

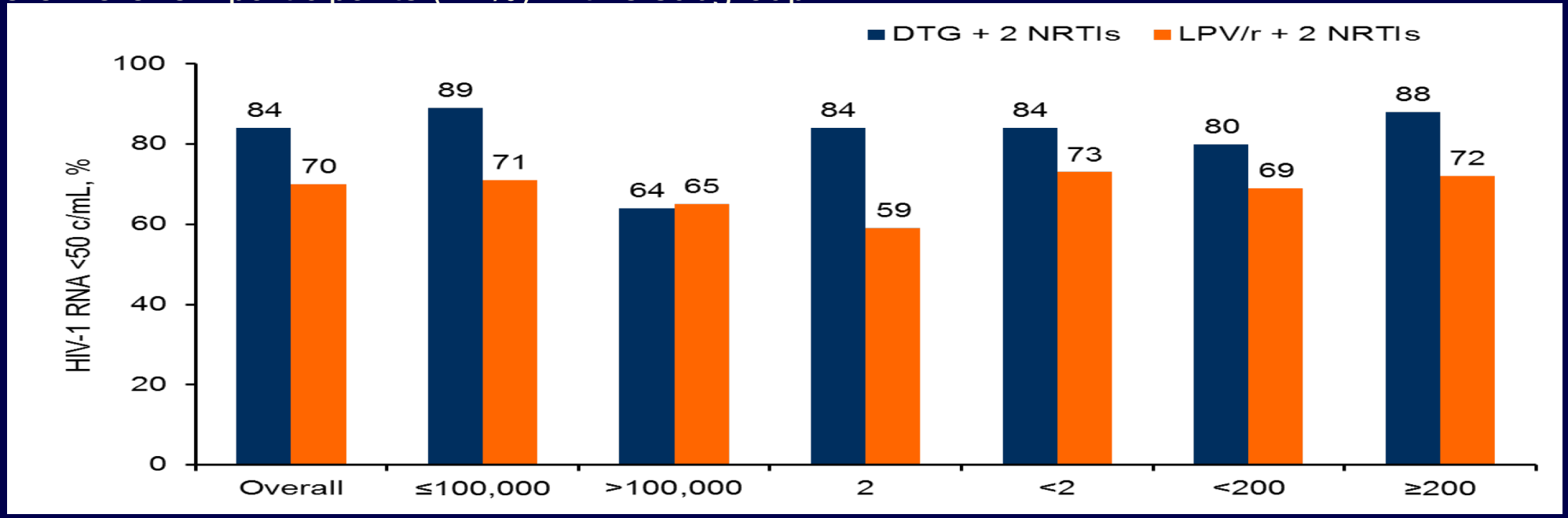


DTG, dolutegravir; ITT-E, intention-to-treat exposed; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; PP, per protocol.

Aboud et al. 22nd International AIDS Conference; Amsterdam, the Netherlands. Poster THPEB040.

Snapshot Outcomes in the ITT-E Population at Week 48 by Key Baseline Subgroups

- Overall, 273 (88%) participants in the DTG + 2 NRTIs group and 247 (77%) in the LPV/r + 2 NRTIs group achieved the secondary efficacy endpoint of HIV-1 RNA <400 c/mL at Week 48
- Efficacy of DTG + 2 NRTIs was generally consistent across key baseline subgroups
- Treatment responses were similar for the groups with baseline plasma HIV-1 RNA >100,000 c/mL, but there were few participants (21%) in this subgroup



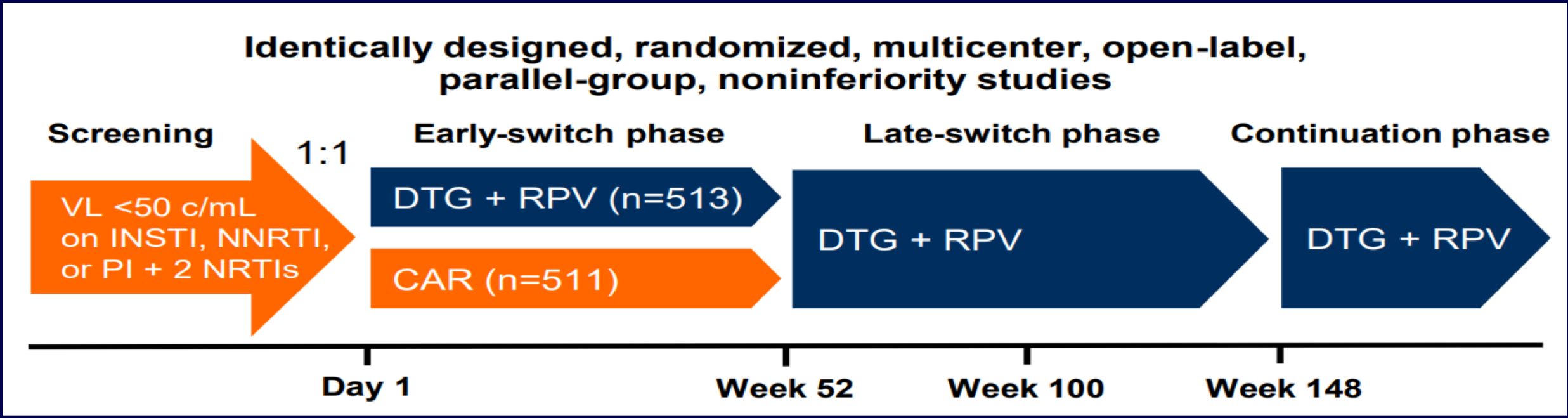
DTG, dolutegravir; ITT-E, intention-to-treat exposed; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor.

Aboud et al. 22nd International AIDS Conference; Amsterdam, the Netherlands. Poster THPEB040.

SWORD

Study Design

- SWORD-1 and SWORD-2 are identically designed, randomized, multicenter, open-label, parallel-group, noninferiority phase III studies



Llibre et al. Lancet. 2018;391:839-849.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Slides THPEB047.

Resistance Data

- Through Week 100 - low number of confirmed virologic withdrawals (CVWs) across study populations (1%; 10/990)
- CVWs with resistance-associated treatment-emergent mutations were low across both groups and detected in 3 participants, all receiving DTG + RPV (0.3%; 3/990)
  - In all 3 participants, at least 1 NNRTI resistance–associated mutation was detected

DTG + RPV: Low Rates of CVW Through Week 100

Week of failure	Previous regimen	Viral loads, copies/mL[b]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[c])	CVW	
Week 24	EFV/TDF/FTC	88; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	1,059,771; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64[d]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	———
Week 76[d]	ATV, ABC/3TC	79; 162; 217	———	Test not performed[e]	———
Week 88	DTG/ABC/3TC	278; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	147; 289	———	Test not performed[e]	———
Week 100	EFV/TDF/FTC	651; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	280; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	———

[a]Shading represents participants with treatment-emergent NNRTI resistance–associated mutations. [b]Underlined value denotes viral load when participant met virologic withdrawal.

[c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing.

[d]Participants in the late-switch group. eResistance testing not performed because of low viral load.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Slides THPEB047.

Bictegravir has a Favorable Cross-Resistance Profile

Comparison of INSTI cross-resistance using a representative panel of HIV with integrase mutants from clinical isolates and site directed mutations

Single Primary Mutations				
IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
E92Q	1.2	1.6	60	18
T97A	0.7	0.9	10	1.8
F121Y*	0.4	0.6	16	5.3
Y143C*	0.9	0.9	2.2	4.3
Y143R	1.4	1.4	2.2	16
Q148H*	0.7	0.8	8.7	4.3
Q148K*	0.8	0.7	108	43
Q148R*	0.7	0.7	117	40
N155H*	1.4	1.5	41	17
R263K*	1.7	1.7	4.5	1.2

More Complex Resistance Patterns				
IN Genotype	Fold Change vs WT			
	BIC	DTG	EVG	RAL
T97A, N155H	1.0	1.5	95	53
E138K, Q148R	1.7	2.2	>150	54
G140A, Q148R	2.0	2.2	>150	88
G140S, Q148H	2.5	5.6	>150	>143
G140S, Q148H, G163K	2.5	5.7	>150	>143
L74M, G140C, Q148R	8.4	9.1	>150	>143
T97A, G140S, Q148H	4.4	15	>150	>143
E138K, G140S, Q148H	2.5	5.3	>150	>143
E138A, G140S, Q148H	7.2	10	>150	>143
E138K, G140A, Q148K	19	63	>150	>143

* Site directed mutants

BIC resistance *in vitro* is possible but requires complex resistance patterns

BIC or EVG < 2.5
RAL <1.5
DTG <4

BIC or EVG 2.5-10
RAL 1.5-10
DTG 4-13

BIC or EVG ≥ 10
RAL >10
DTG >13

‡

Case Study:
B/F/TAF in Setting of Transmitted INSTI Resistance

- 1 participant with transmitted INSTI resistance at G140S + Q148H
  - Phenotypically sensitive to BIC and partially sensitive to DTG
  - RT mutations: K70R and K103N

GENESEQ™	ASSESSMENT*		PHENOSENSE® SUSCEPTIBILITY			ASSESSMENT	
Drug Resistance Mutations Detected	Drug		Cutoffs (Lower - Upper)	Fold Change	Increasing ... Drug Susceptibility ... Decreasing (1, 10, 100)	Drug	
			(2.5)	2.14		BIC	Sensitive
G140S, Q148H	DTG	Resistance Possible	(4 - 13)	4.45		DTG	Partially Sensitive
G140S, Q148H	EVG	Resistant	(2.5)	>MAX		EVG	Resistant
G140S, Q148H	RAL	Resistant	(1.5)	>MAX		RAL	Resistant

‡

Case Study:
B/F/TAF in Setting of Transmitted INSTI Resistance

- 1 participant with transmitted INSTI resistance at G140S + Q148H
  - Phenotypically sensitive to BIC and partially sensitive to DTG
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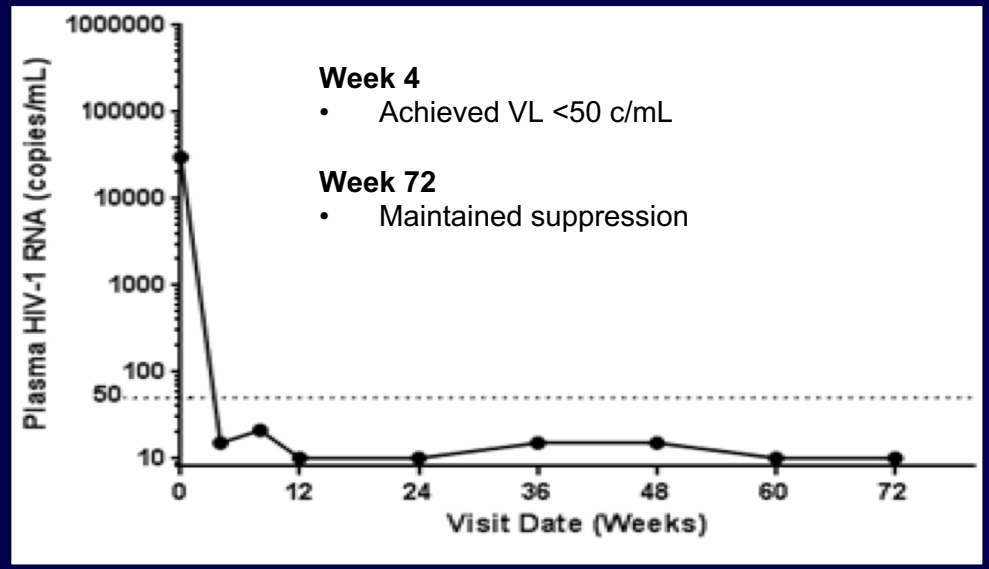
GENESEQ™ ASSESSMENT*			PHENOSENSE® SUSCEPTIBILITY			ASSESSMENT	
Drug Resistance Mutations Detected	Drug		Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (.1, 1, 10, 100)	Drug	
			(2.5)	2.14		BIC	Sensitive
G140S, Q148H	DTG	Resistance Possible	(4 - 13)	4.45		DTG	Partially Sensitive
G140S, Q148H	EVG	Resistant	(2.5)	>MAX		EVG	Resistant
G140S, Q148H	RAL	Resistant	(1.5)	>MAX		RAL	Resistant



Week 4
- Achieved VL <50 c/mL

Week 72
- Maintained suppression

‡

Case Study:
B/F/TAF in Setting of Transmitted INSTI Resistance

- 1 participant with transmitted INSTI resistance at G140S + Q148H
  - Phenotypically sensitive to BIC and partially sensitive to DTG
  - RT mutations: K70R and K103N

GENESEQ™	ASSESSMENT*		PHENOSENSE® SUSCEPTIBILITY			ASSESSMENT	
Drug Resistance Mutations Detected	Drug		Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (.1, 1, 10, 100)	Drug	
			(2.5)	2.14		BIC	Sensitive
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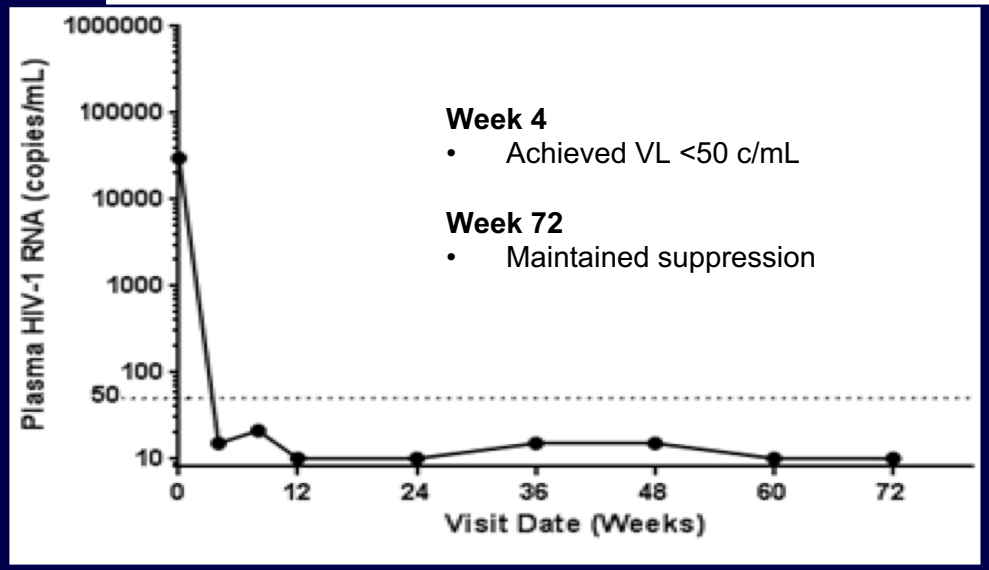
G140S, Q148H	EVG	Resistant	(2.5)	>MAX		EVG	Resistant
G140S, Q148H	RAL	Resistant	(1.5)	>MAX		RAL	Resistant



In this first case of an ART-naïve patient with transmitted integrase resistance (G140S + Q148H) on B/F/TAF.

Virologic suppression was rapid and maintained from Week 4 to 72.

White K, et al . CROI 2018, Boston, MA. Poster 532.

Barrier to Resistance With Recommended INSTI-Based Regimens

Regimen	Barrier to Resistance	Comments	Mutations Highly Reducing Susceptibility[2]*
DTG/3TC/ABC DTG + FTC/TDF *or* FTC/TAF	**High**	▪ Resistance to DTG emerges slowly; multiple mutations required for resistance[1,2] ▪ **DTG + FTC/TDF *or* FTC/TAF recommended by DHHS if must treat before resistance results available**[1]	--
EVG/COBI/FTC/TDF EVG/COBI/FTC/TAF	**Low/Moderate**	▪ Few EVG mutations required for resistance[2]	T66I/A/K E92Q S147G Q148H/R/K N155H
RAL + FTC/TDF *or* FTC/TAF	**Low/Moderate**	▪ Few RAL mutations required for resistance[2]	Y143C/R/H Q148H/R/K N155H

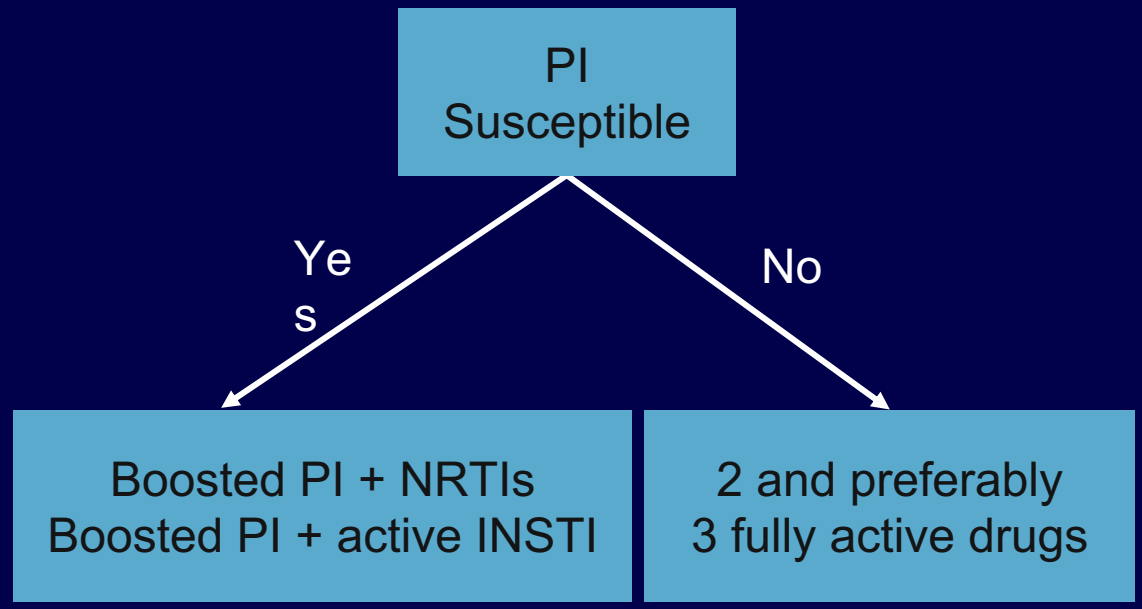
*NRTI backbone mutations not shown in column: FTC/TDF, M184V/I, K65R, T69ins; ABC/3TC, M184V/I, K65R, L74V/I, T69ins, Y115F, Q151M.

References in slidenotes.

Slide credit: clinicaloptions.com

DHHS: Management of ART Failure Second-line ARV Failure

- Goal: fully suppressive ARV regimen
- If susceptible to boosted PI, regimen can be similar to those for first-line failure
- If not susceptible to boosted PI, new regimen should have a minimum of 2 (preferably 3) fully active drugs if possible
  - Susceptibility to drug predicted from pt treatment history, prior and current resistance and tropism testing, MoA of novel drug class
- Not recommended to add single agent to failing regimen due to risk of developing resistance to entire regimen



DHHS Guidelines.

Slide credit: clinicaloptions.com

DHHS: Treatment of Pts With MDR HIV for Whom Optimal Virologic Suppression Is Not Possible

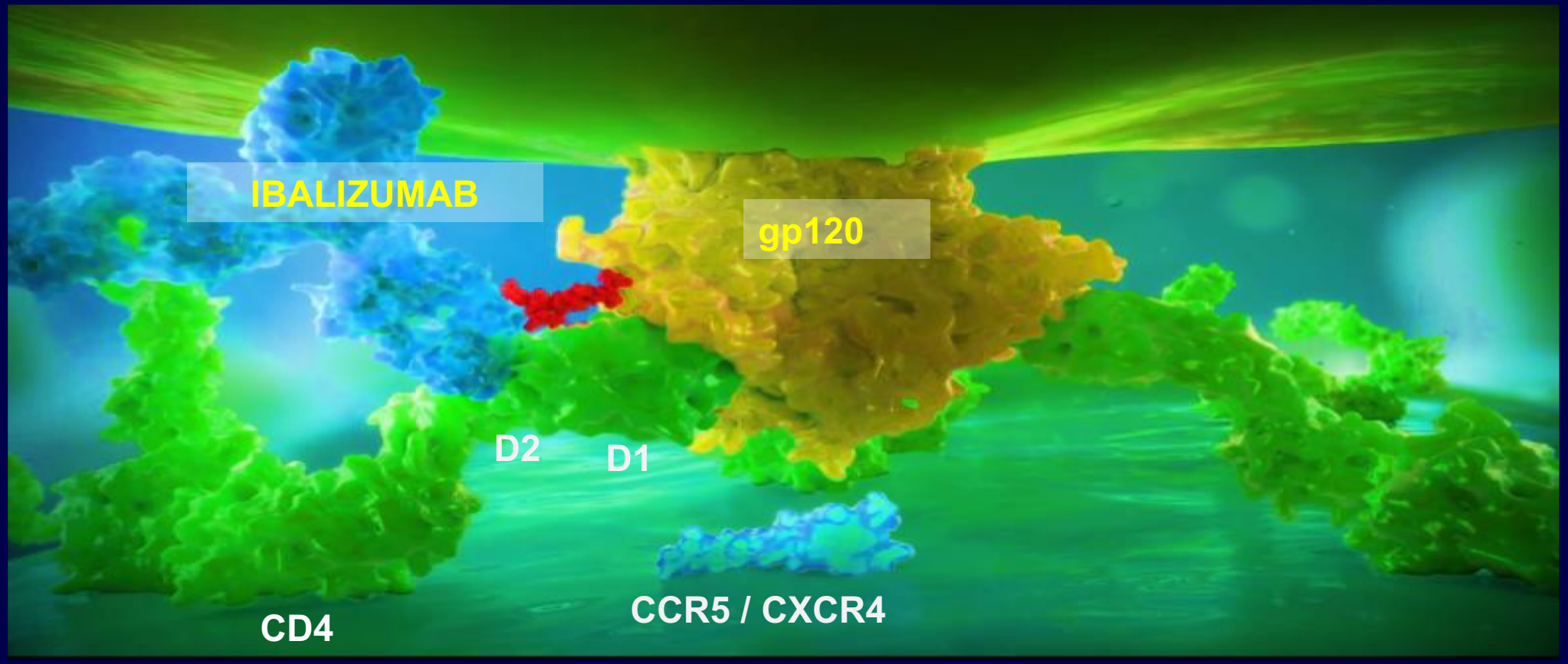
- **Goals:** minimize toxicity, preserve immunologic function, delay clinical progression, minimize further resistance
  - Reduction of HIV-1 RNA > 0.5 $\log_{10}$ copies/mL correlated with clinical benefit
  - If resistant, rarely a reason to continue NNRTIs, ENF, EVG, or RAL: no evidence of clinical benefit; may promote further resistance, limit future treatment options
- Consider enrolling pt in clinical study, expanded access program, or FDA single-pt access to investigational agent

DHHS Guidelines.

Ibalizumab - developed for the treatment of MDR HIV-1 infection

- New mechanism of action
  - **Humanized monoclonal antibody – which blocks the entry of HIV into CD4**
- Binds to the second extracellular domain of the CD4+ T cell receptor
  - Away from major histocompatibility complex molecule binding sites
  - Interferes HIV from infecting CD4+ immune cells while preserving normal immunological function.
- 2014: FDA also granted Orphan Drug designation
- 2015: FDA gave “Priority Review Status” accelerating approval time
- 2016: FDA granted a “Breakthrough Therapy” designation,
- 2018: FDA approval for heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

Ibalizumab – Mechanism of Action



https://www.youtube.com/watch?v=Sq35fn6COQU

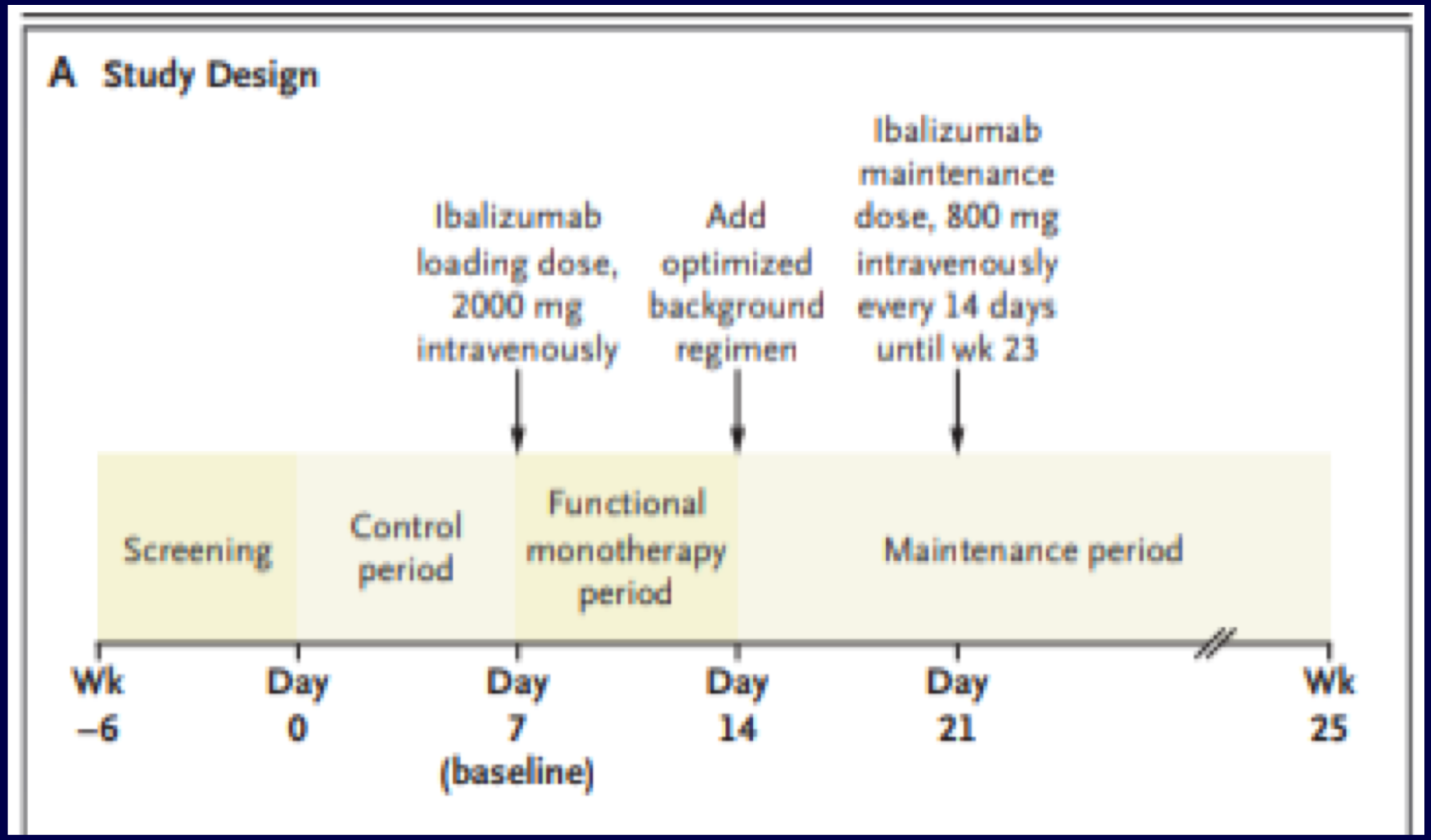
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

Brinda Emu, M.D., Jeffrey Fessel, M.D., Shannon Schrader, M.D.,
Princy Kumar, M.D., Gary Richmond, M.D., Sandra Win, M.D.,
Steven Weinheimer, Ph.D., Christian Marsolais, Ph.D., and Stanley Lewis, M.D.

N Engl J Med 2018;379:645-54



Ibalizumab for Multidrug-Resistant HIV
N Engl J Med 2018;379:645-54

Table 1. Demographic and Clinical Characteristics of the 40 Study Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	53 (23–65)
Male sex — no. (%)	34 (85)
Race — no. (%)†	
White	22 (55)
Black	13 (33)
Asian	4 (10)
Unknown	1 (3)
No. of years since HIV diagnosis	
Mean	20±8
Median (range)	23 (2–30)
Viral load — $\log_{10}$ copies/ml	
Mean	4.5±0.8
Median (range)	4.6 (2.5–5.9)
Patients with viral load of >100,000 copies/ml — no. (%)	7 (18)
CD4 count	
Mean — no. of cells/μl	150±182
Median (range) — no. of cells/μl	73 (0–676)
Distribution — no. of patients (%)	
<10 cells	12 (30)
<50 cells	17 (43)
50–200 cells	10 (25)
>200 cells	13 (33)
Total no. of antiretroviral medications received	
Mean	11±5
Median (range)	10 (3–22)
Known resistance to ≥1 drug in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	37 (93)
Non-nucleoside reverse-transcriptase inhibitor	37 (93)
Protease inhibitor	36 (90)
Integrase inhibitor	27 (68)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)
Known resistance to all drugs in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	26 (65)
Non-nucleoside reverse-transcriptase inhibitor	26 (65)
Protease inhibitor	25 (63)
Integrase inhibitor	19 (48)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was reported by the patients.
‡ Because of an inability to phenotype two samples, data were available for 38 patients.

Ibalizumab for Multidrug-Resistant HIV
N Engl J Med 2018;379:645-54

Table 2. Virologic Response before and after Loading Dose of Ibalizumab and at 25 Weeks in the 40 Study Patients.*

Response	Before and after Loading Dose			Week 25
	Control Period	Functional Monotherapy Period	P Value	
Decrease in viral load of ≥0.5 $\log_{10}$ copies/ml — no. (%)	1 (3)†	33 (83)	<0.001	25 (63)
Decrease in viral load of ≥1.0 $\log_{10}$ copies/ml — no. (%)	0	24 (60)	NA	22 (55)
Mean change in viral load from baseline — $\log_{10}$ copies/ml	0.0±0.2	−1.1±0.6	<0.001	−1.6±1.5

* Plus–minus values are means ±SD. The virologic response during the control period (days 0 to 6) was compared with the response after the administration of an intravenous bolus of 2000 mg of ibalizumab on day 7 during the functional monotherapy period (days 7 to 13). During the maintenance period (day 14 to week 25), patients initiated an optimized background regimen on day 14 and received an intravenous dose of 800 mg of ibalizumab every 14 days, starting on day 21. NA denotes not applicable because the control value is 0.

† One patient initiated the optimized background regimen prematurely during the control period.

Ibalizumab for Multidrug-Resistant HIV
N Engl J Med 2018;379:645-54

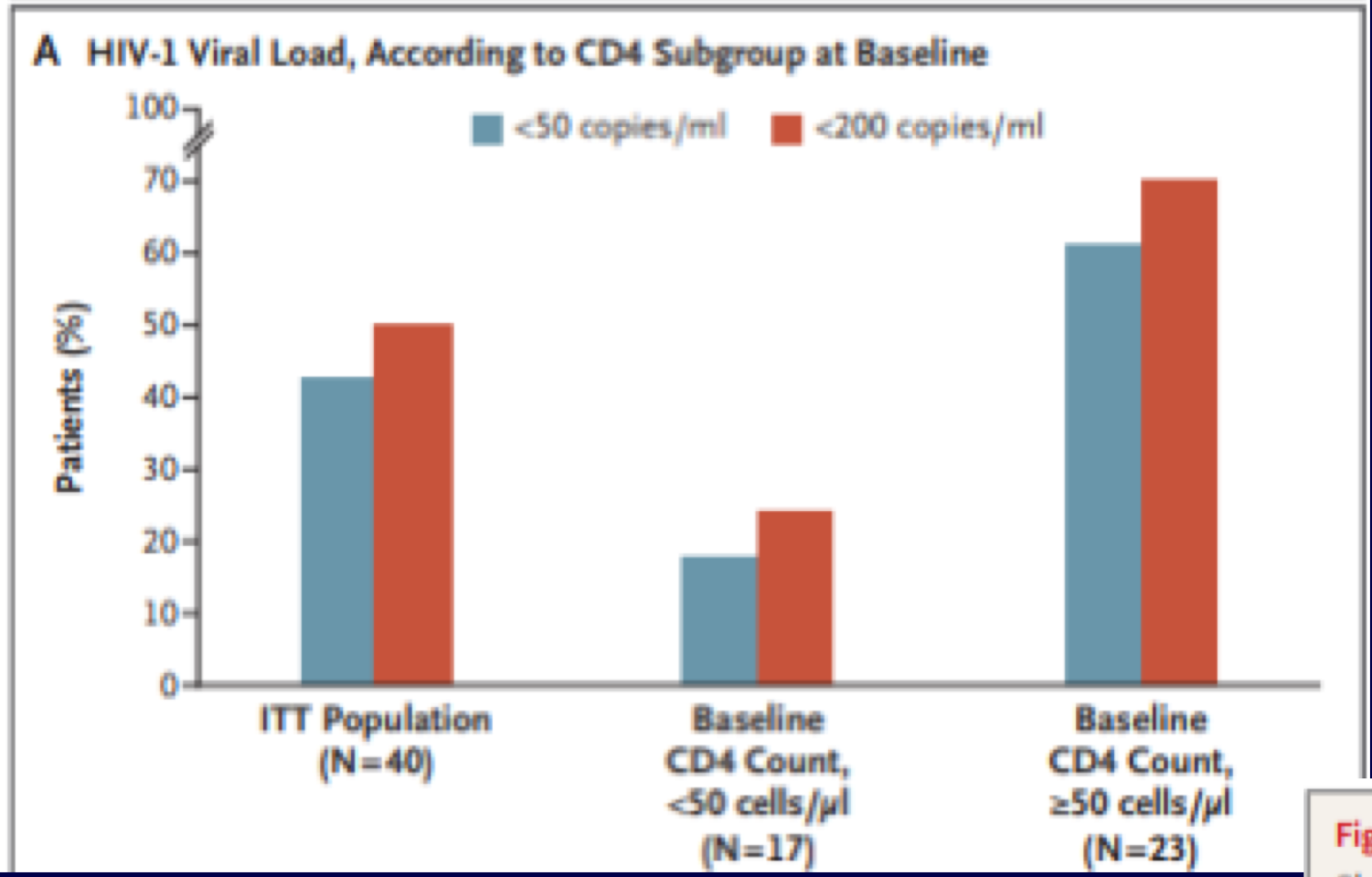
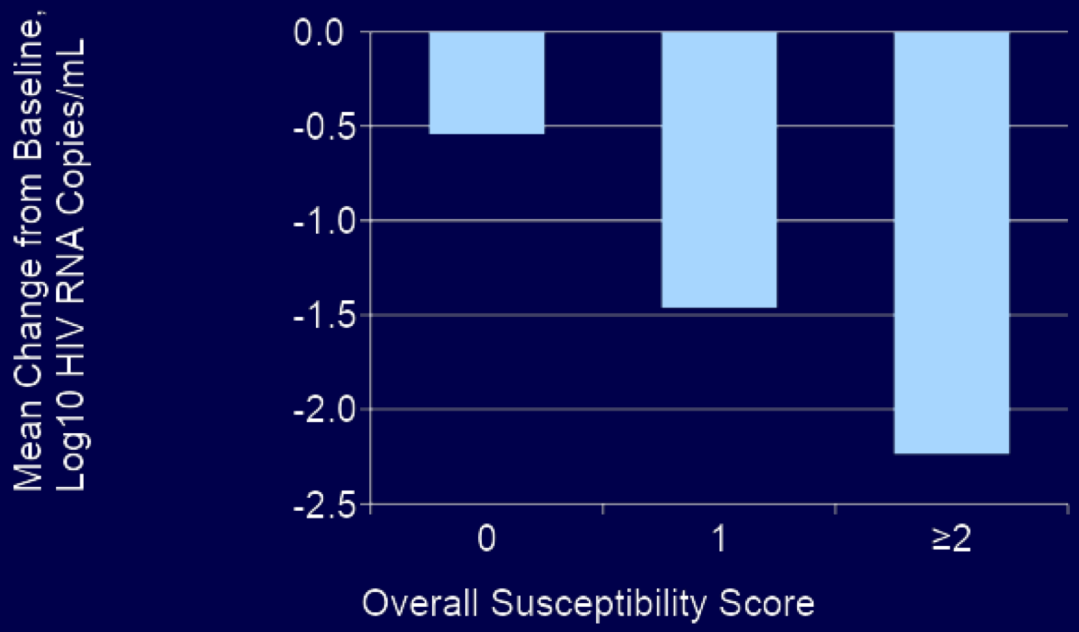


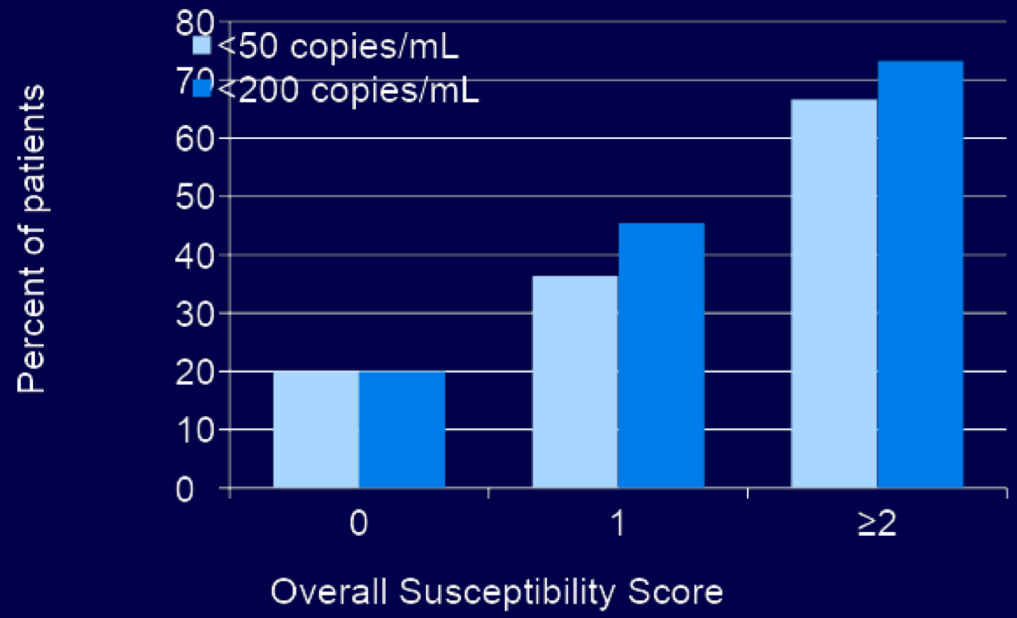
Figure 2. Virologic and CD4 T-Cell Responses at Week 25.

Shown are values for the HIV-1 viral load and CD4 count in the overall intention-to-treat (ITT) population and in subgroups according to the patients' CD4 count at baseline (<50 cells or ≥50 cells per microliter). Panel A shows the proportion of patients with a viral load of less than 50 HIV-1 RNA copies per milliliter or less than 200 copies per milliliter at week 25, with baseline observations carried forward to replace missing data.

Ibalizumab for Multidrug-Resistant HIV
N Engl J Med 2018;379:645-54

Virologic Response at Wk 24 (by OSS)





- More durable responses were observed with the addition of 1 or more fully active OBR agents
  - Only 1 patient had an OSS >2

ITT

Ibalizumab (TMB-311 Expanded Access): Patient Characteristics

- All patients who completed Week 24 endpoint in US were enrolled in TMB-311 (N=27)

- Patients continue to receive 800 mg ibalizumab IV every 2 weeks for an additional 24 weeks
- Gender — 85% Male
- Race — 41% Non-White
- Median VL — 4.3 log10 copies/mL
- Median CD4+ T cell count — 102 cells

- Highly resistant virus species
  - 16 (59%) patients had exhausted ≥3 ARV classes
  - 9 (33%) patients had exhausted ≥4 ARV classes
  - 4 (15%) patients resistant to all approved ARVs

Ibalizumab Expanded Access: Efficacy at 48 weeks

- Potent VL suppression sustained through Week 48
  - Median VL reduction was 2.5 log10 at Week 24
  - Median VL reduction was 2.8 log10 at Week 48

- 16 of 27 (59%) had VL <50 copies/mL
  - All 15 patients with VL <50 copies/mL at Week 24 maintained viral suppression to Week 48
  - Another patient reached VL <50 copies/mL at Week 48 (did not have VL <50 copies/mL at Week 24)

- 17 of 27 (63%) had VL <200 copies/mL

- CD4 counts were maintained from Baseline to week 48
  - CD4 value at Baseline: 157
  - CD4 value at Week 48: 167
    - Results confound by missing lab value

Forty-eight-Week Safety and Efficacy On-Treatment Analysis of Ibalizumab in Patients with Multi-Drug Resistant HIV-1. Open Forum Infect Dis. 2017 Fall; 4(Suppl 1): S38–S39.

Ibalizumab Conclusions

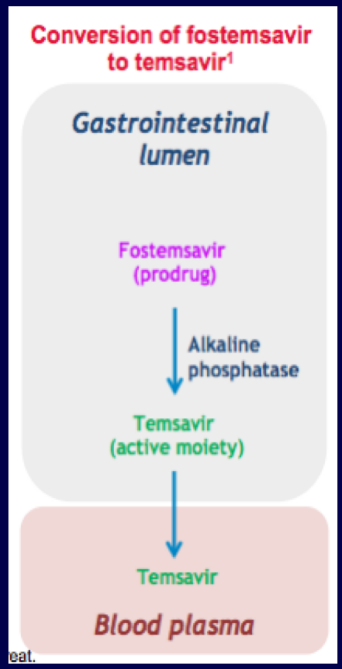
- First long-acting, intravenous monoclonal antibody for treatment of HIV infection presented for FDA approval
  - IV infusion every 2 weeks
- Novel Mechanism of Action
  - Monoclonal antibody targeting CD4
  - Activity against CXCR4 and CCR5 tropic virus
  - No known cross-resistance
- Appears safe and well tolerated
- Significant antiretroviral activity in Drug-resistant HIV
  - After 7 days, Mean VL reduction of 1.1 log10 copies
  - At 24 weeks, 43% of patients with VL<50 copies /mL
  - At 48 weeks, VL suppression maintained from Week 24
- Main concern is the cost ($$$$$) and need for IV infusion

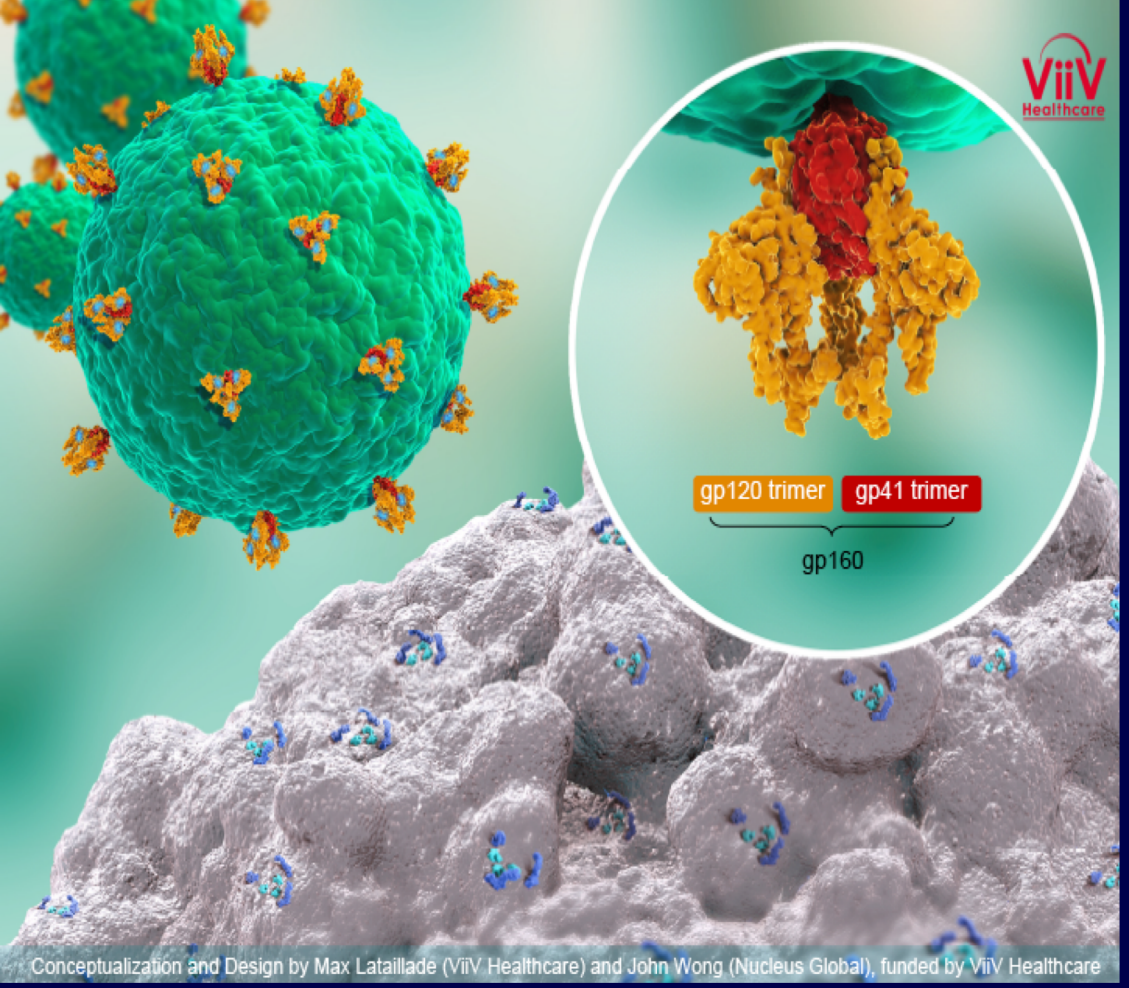
Phase 3 Study of Fostemsavir in Heavily Treatment-Experienced HIV-1-Infected Participants: Day 8 and Week 24 Primary Efficacy and Safety Results (BRIGHTE Study, Formerly 205888/AI438-047)

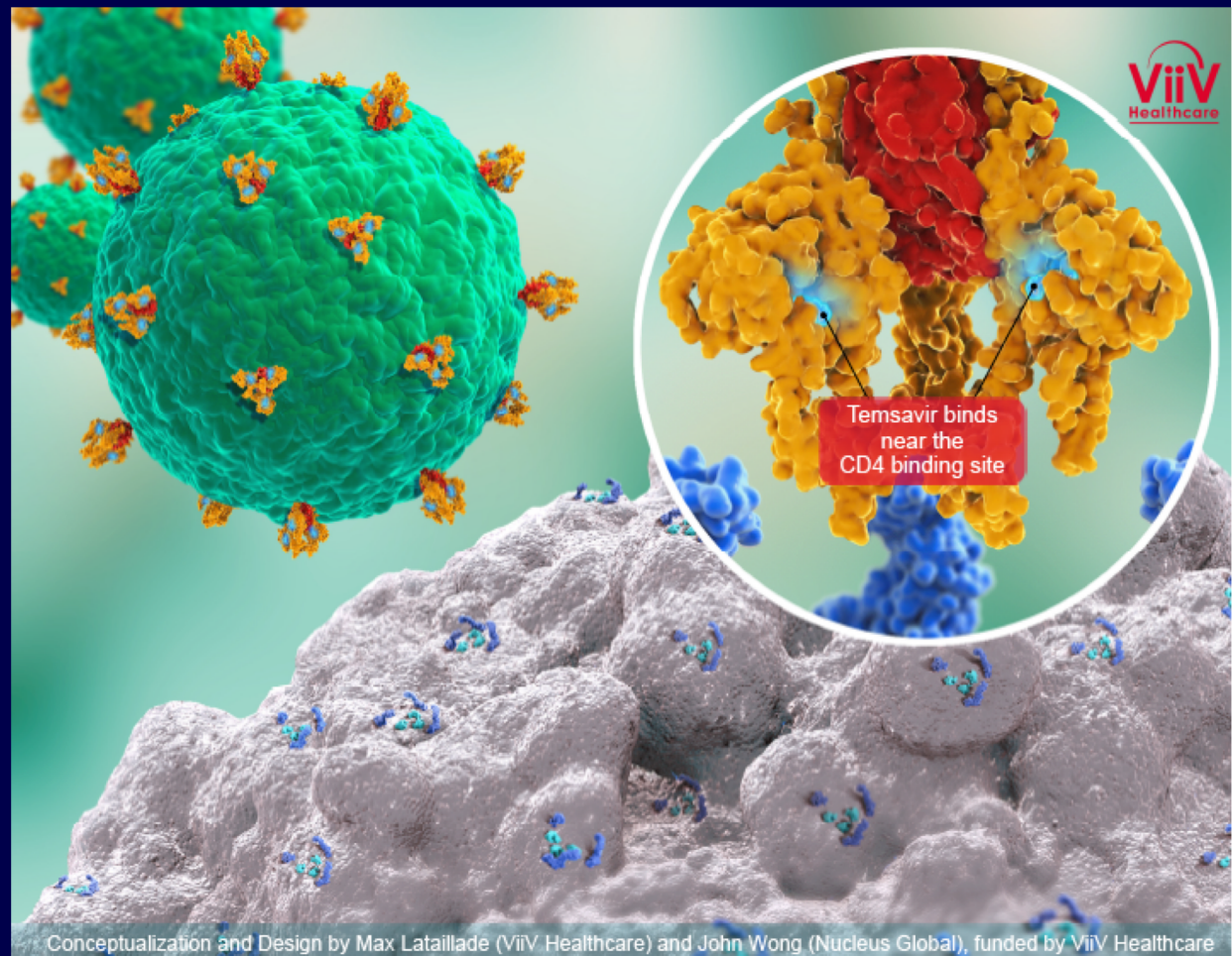
M. Kozal[1], J. Aberg[2], G. Pialoux[3], P. Cahn[4], M. Thompson[5], J.-M. Molina[6], B. Grinsztejn[7], R. Diaz[8], A. Lazzarin[9], M. Gummel[10], A. Pierce[11], P. Ackerman[12], C. Llamoso[12], M. Lataillade[12]

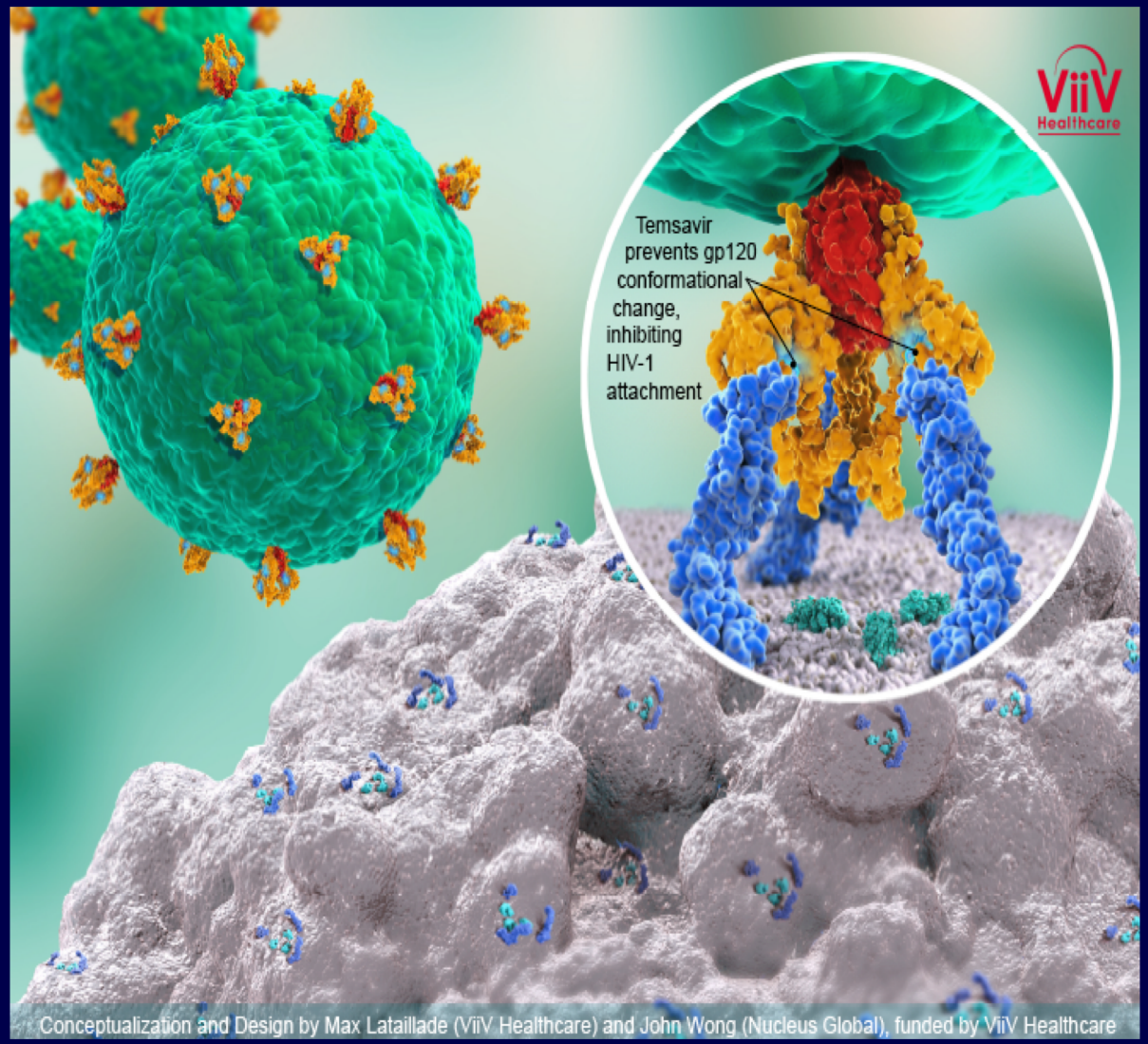
Overview of Fostemsavir

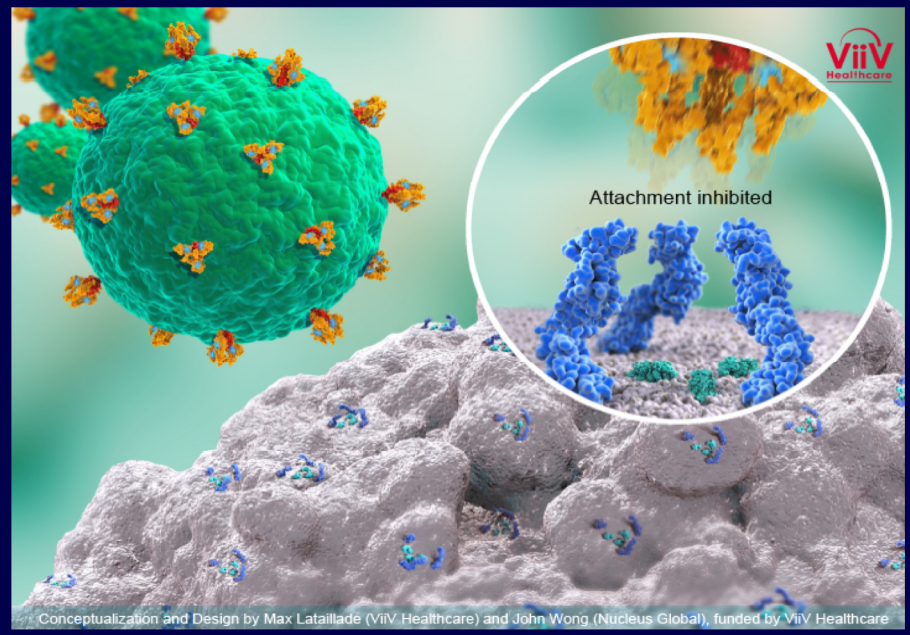
- Fostemsavir (FTR) is a prodrug metabolised to temsavir (TMR),[1] a first-in-class, investigational attachment inhibitor that is currently being evaluated in HIV-1-infected HTE patients
- Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1[2–5]
- Unique resistance profile with no *in vitro* cross-resistance to other classes of ARVs[2,5]

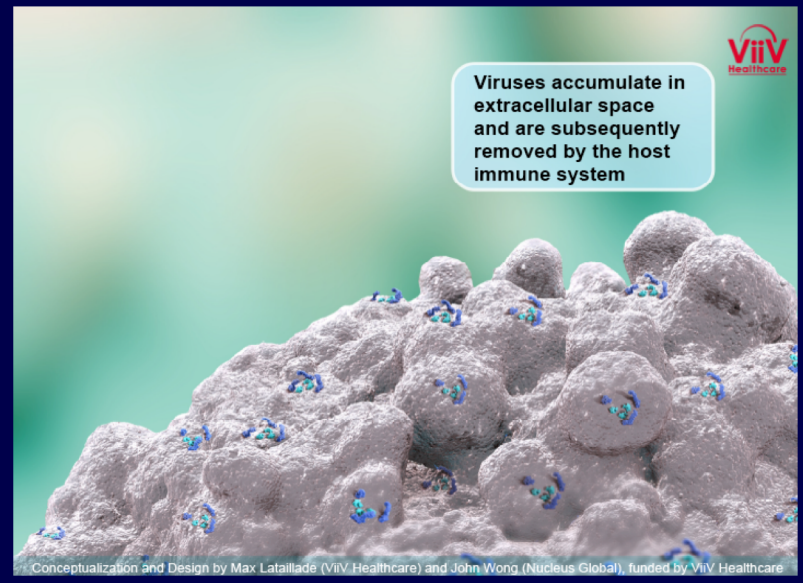



ViiV Healthcare
gp120 trimer
gp41 trimer
gp160
Conceptualization and Design by Max Lataillade (ViiV Healthcare) and John Wong (Nucleus Global), funded by ViiV Healthcare


ViiV Healthcare
Temsavir binds near the CD4 binding site
Conceptualization and Design by Max Lataillade (ViiV Healthcare) and John Wong (Nucleus Global), funded by ViiV Healthcare


ViiV Healthcare
Temsavir prevents gp120 conformational change, inhibiting HIV-1 attachment
Conceptualization and Design by Max Lataillade (ViiV Healthcare) and John Wong (Nucleus Global), funded by ViiV Healthcare


ViiV Healthcare
Attachment inhibited
Conceptualization and Design by Max Lataillade (ViiV Healthcare) and John Wong (Nucleus Global), funded by ViiV Healthcare


ViiV Healthcare
Viruses accumulate in extracellular space and are subsequently removed by the host immune system
Conceptualization and Design by Max Lataillade (ViiV Healthcare) and John Wong (Nucleus Global), funded by ViiV Healthcare

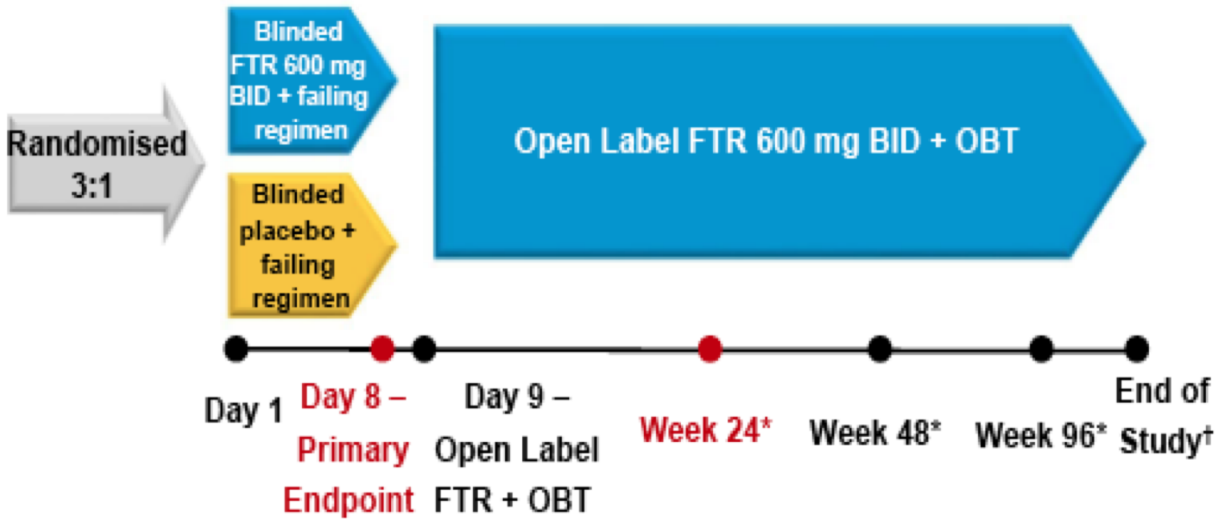
Study Design

BRIGHTE

BRIGHTE is an ongoing Phase 3 randomised, placebo-controlled, double blind trial

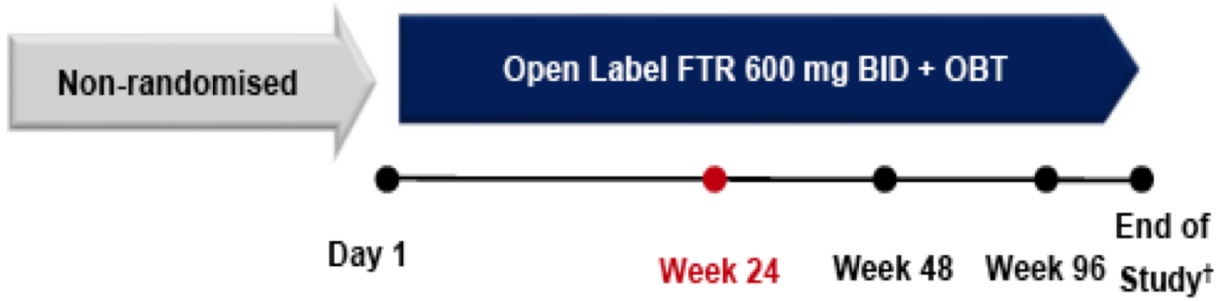
Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-randomised Cohort §:
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 0 ARV classes remaining and no remaining fully active approved agents‡

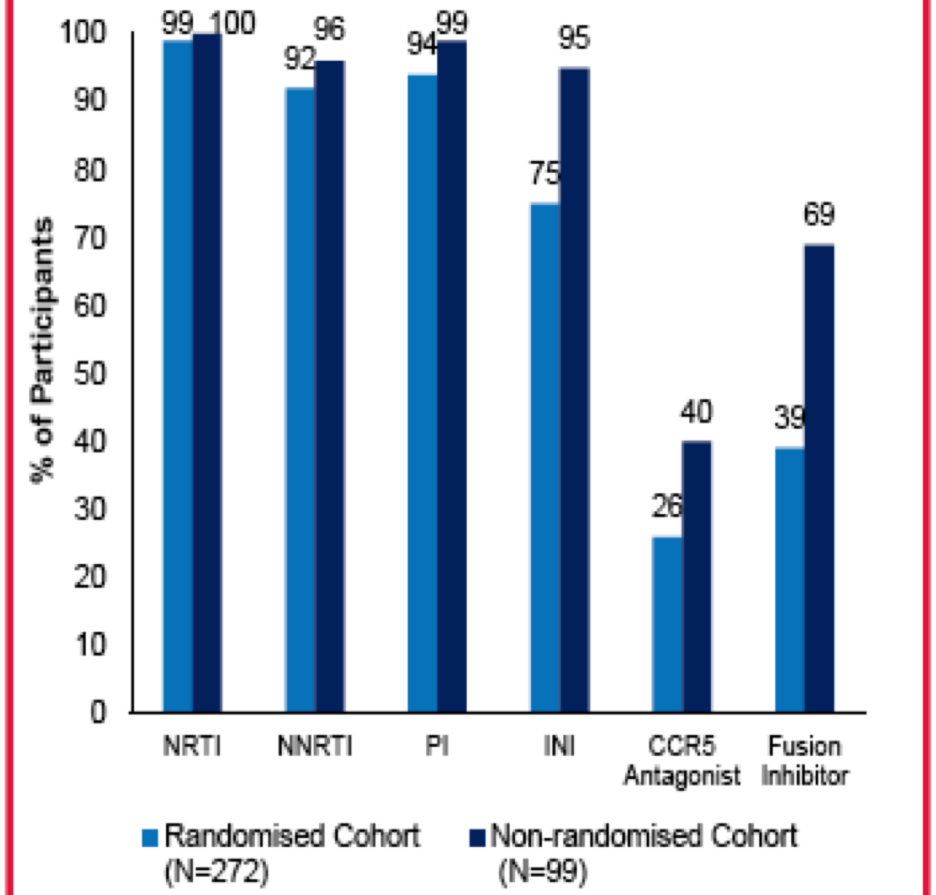


*Measured from the start of open label FTR 600 mg BID + OBT; †The study is expected to be conducted until an additional option, rollover study or marketing approval, is in place; ‡Use of investigational agents as part of OBT was permitted; §There was no screening FTR IC_{50} criteria.
BID, twice-daily; OBT, optimised background therapy.

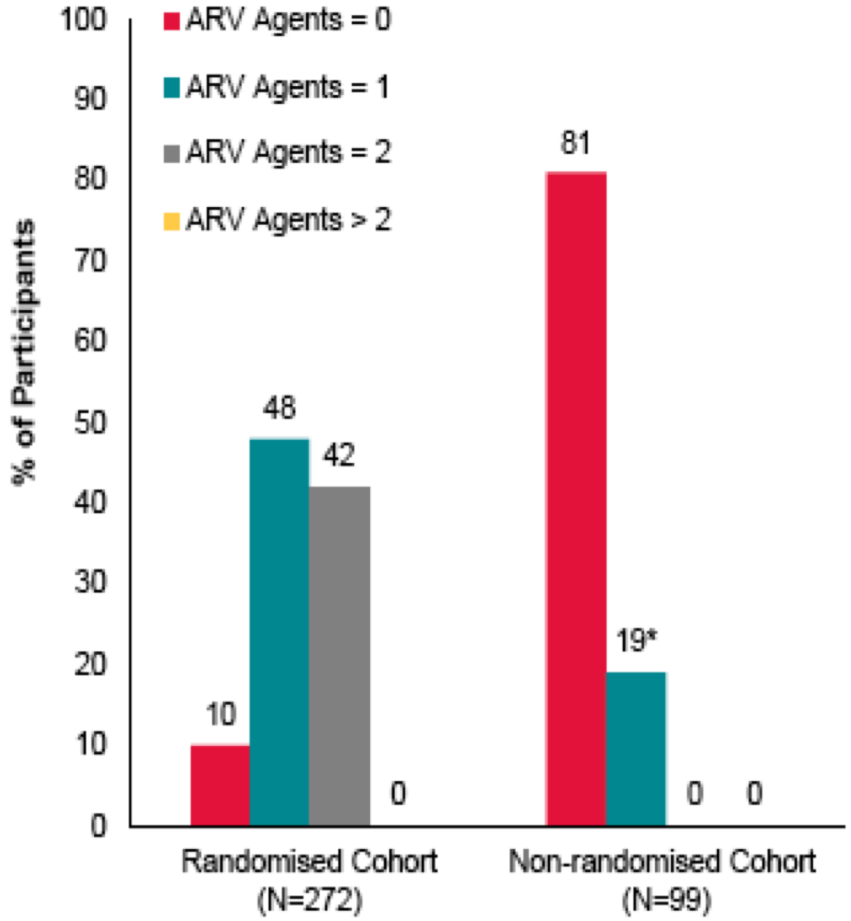
Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Prior ARV Exposure and Initial OBT

Prior Exposure to ARVs



Fully Active and Available ARV Agents in Initial OBT

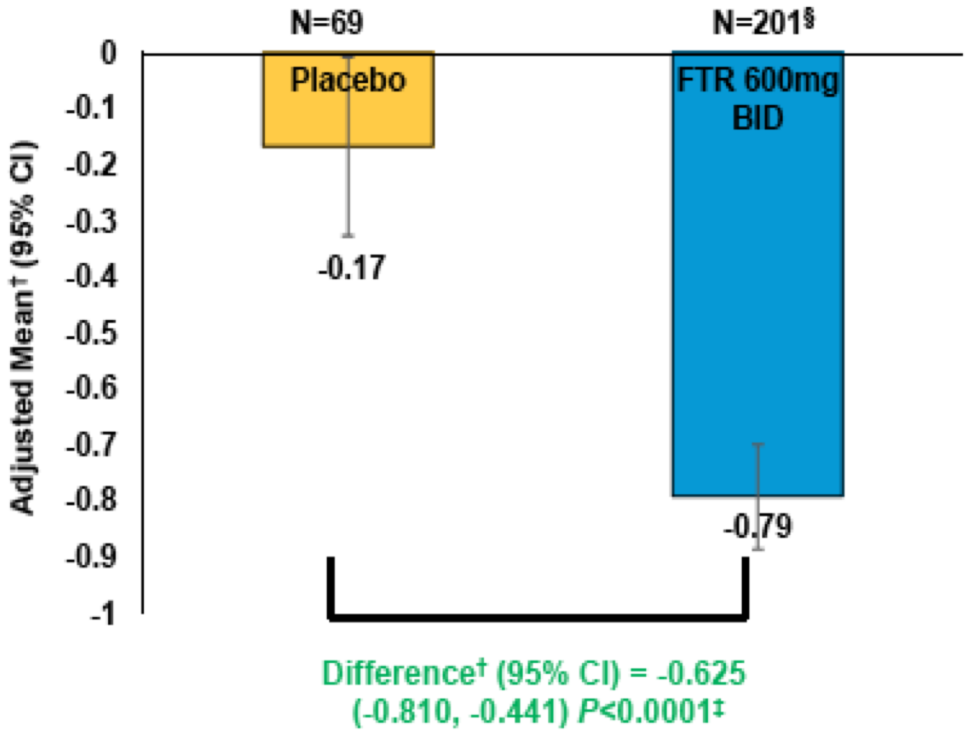


Baseline and emergent resistance analysis are currently ongoing; *13/19 received investigational ARV Ibalizumab. INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; PI, protease inhibitor.

Primary Endpoint:

Adjusted Mean HIV-1 RNA log_{10} Change at Day 8

The primary endpoint was the adjusted mean plasma HIV-1 RNA log_{10} change from Day 1 at Day 8* in the Randomised Cohort (ITT-E)



FTR participants (ITT-E)

- >0.5 log_{10} decrease - **65%**
- >1 log_{10} decrease - **46%**

Subgroup: Baseline HIV-1 RNA >1000 c/mL (n=182), FTR demonstrated:

- Median decrease of **1 log_{10}**
- Adjusted mean decrease of **0.9 log_{10}**
- >0.5 log_{10} decrease - **68%**
- >1 log_{10} decrease - **50%**

*Day 8 window includes viral load between Day 6 to Day 10; participants who did not have a result in the Day 8 window had their last on treatment result carried forward (1 participant receiving FTR) or their Day 1 result carried forward (9 participants; 4 receiving placebo and 5 receiving FTR); †Mean adjusted by Day 1 log_{10} HIV-1 RNA; ‡hypothesis test: μFTR - μ placebo; *P* from Levene's test of homogeneity of variance 0.2082; §Two participants in the FTR arm, who had missing Day 1 HIV-1 RNA values, were not included in the analysis for the HIV-1 RNA log_{10} least squares mean change at Day 8. ITT-E, intent to treat-exposed.

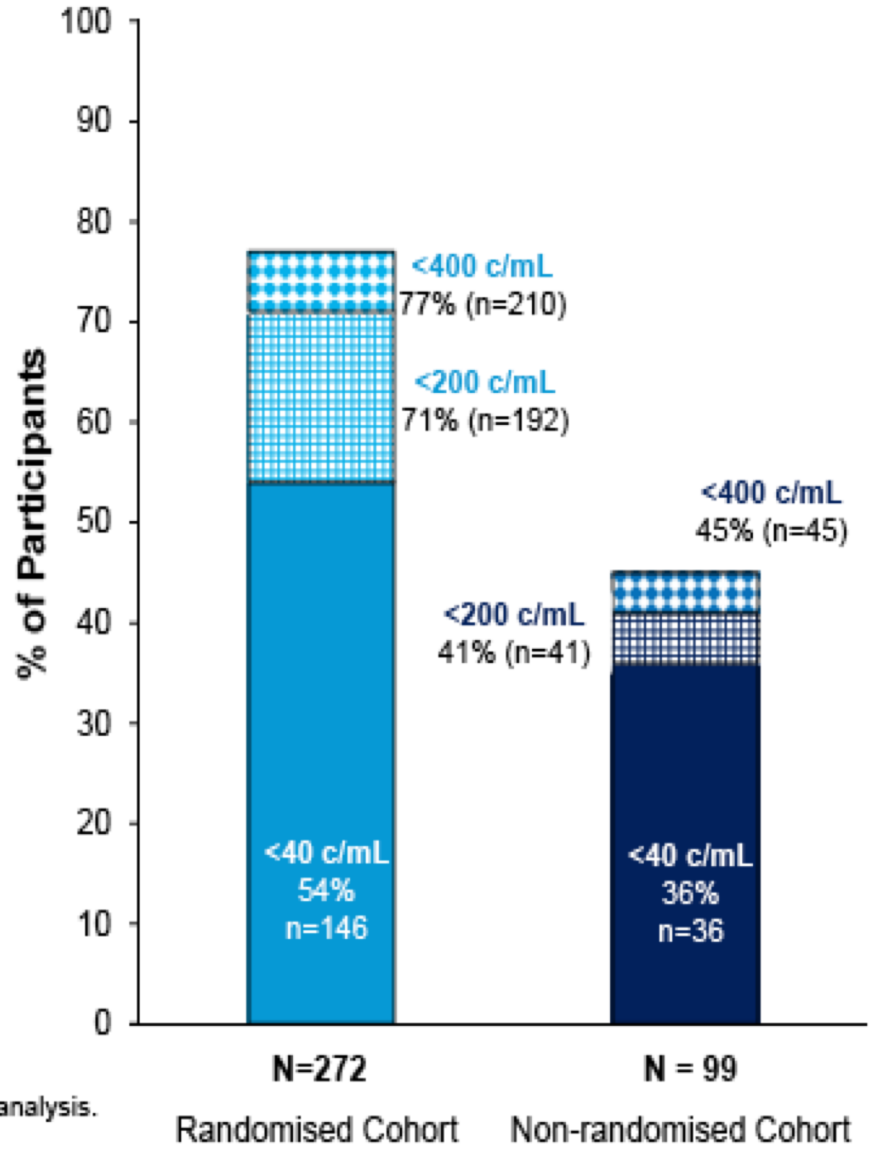
Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Virologic Response at Week 24 (Snapshot Analysis)

Outcome	Randomised Cohort (N=272)	Non-Randomized Cohort (N=99)
Virologic Success (<40 c/mL), n (%)	146 (54)	36 (36)
Virologic Failure, (≥40 c/mL), n (%)	108 (40)	55 (56)
Data in window not below threshold	87 (32)	44 (44)
D/C for lack of efficacy	1 (<1)	0
D/C for other reason while not below threshold	5 (2)	2 (2)
Change in ART*	15 (6)	9 (9)
No Virologic Data	18 (7)	8 (8)
D/C study due to AE or Death	11 (4)	4 (4)
D/C study for Other Reasons	4 (1)	0
Missing data during window but on study	3 (1)	4 (4)

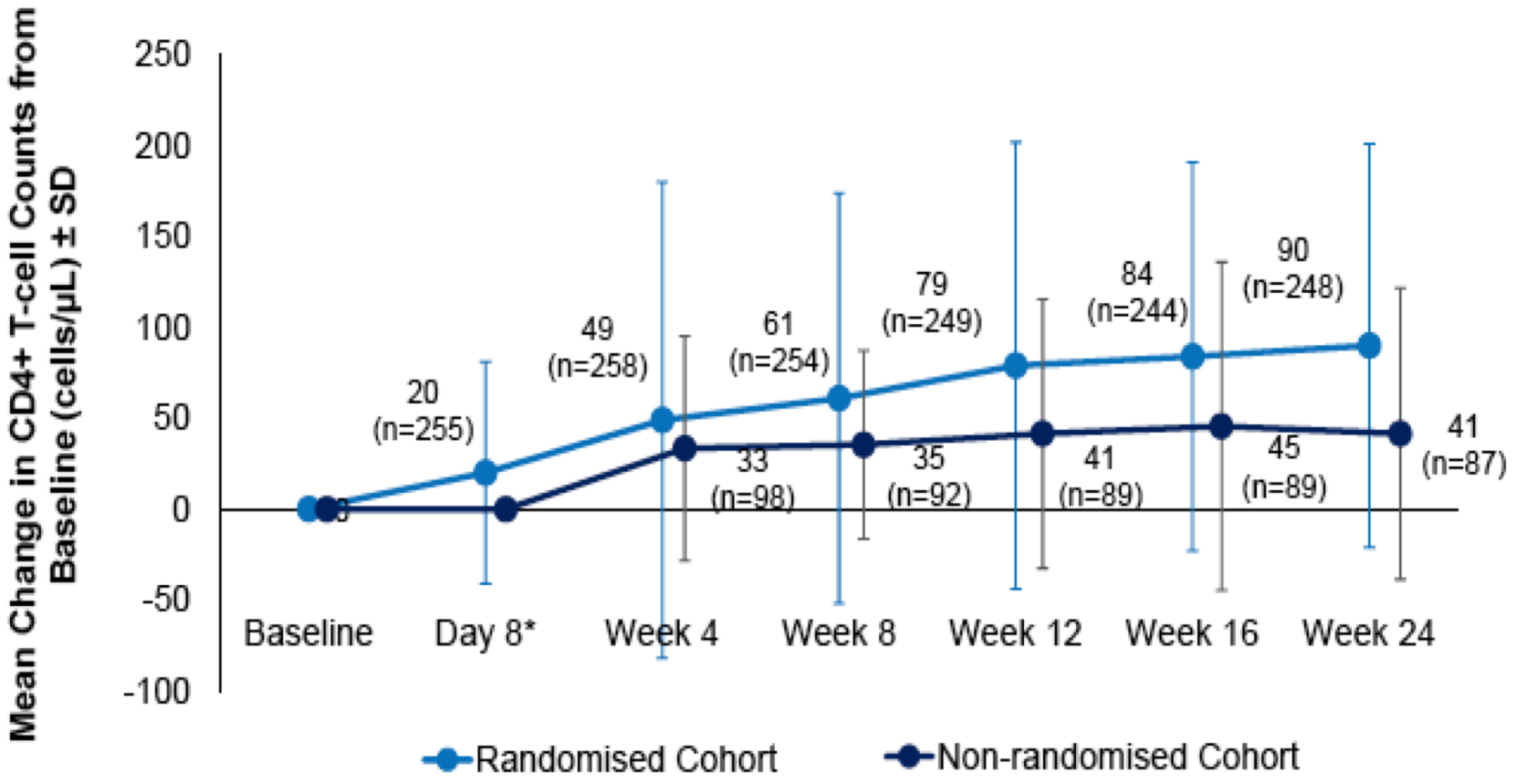
*Change in OBT for efficacy reasons were considered virologic failures in this analysis.

ART, antiretroviral therapy; D/C, discontinued.



Mean Change in CD4+ T-cell Counts from Baseline through Week 24: Observed Analysis

Mean CD4+ T-cell count at baseline was 153 cells/μL (SD=182) for the Randomised Cohort and 99 cells/μL (SD=131) for the Non-randomised Cohort



*The Non-randomised Cohort did not have a Day 8 visit.

SD, standard deviation.

Conclusions

- FTR achieved its primary endpoint of superior efficacy relative to placebo in HTE, HIV-1-infected participants, with an adjusted mean decline of 0.79 $\log_{10}$ HIV-1 RNA through 8 days of FTR functional monotherapy (Treatment Difference = -0.625, $P<0.0001$)
  - In a subgroup of participants with baseline HIV-1 RNA >1000 c/mL, FTR demonstrated median decrease of 1 $\log_{10}$ at Day 8
- At Week 24
  - 54% of randomised participants receiving FTR+OBT achieved HIV-1 RNA <40 c/mL (Snapshot)
    - 71% and 77% achieved HIV-1 RNA <200 c/mL and <400 c/mL, respectively
  - 36% of non-randomised participants (81% of whom had FTR as the only fully active ARV) achieved HIV-1 RNA <40 c/mL (Snapshot)
    - 41% and 45% achieved HIV-1 RNA <200 c/mL and <400 c/mL, respectively
- FTR-containing regimens were generally well tolerated:
  - The most common safety events were consistent with those seen during Phase 2b study
  - Significant AEs were generally reflective of the advanced disease state in the study population
- These results support continued development of FTR as an important treatment option for HTE patients

Summary

- **Evaluation of virologic failure should include an assessment of adherence, drug-drug or drug-food interactions, drug tolerability, HIV RNA and CD4 cell count, ART history, and prior and current drug-resistance testing results.**

- Drug-resistance testing should be performed while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation. Even if more than 4 weeks have elapsed since ARVs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations.

- A new regimen should include at least two, and preferably three, fully active agents.

- In general, adding a single ARV agent to a virologically failing regimen **is not recommended** because this may risk the development of resistance to all drugs in the regimen.

Summary

- When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may cause serious hepatocellular damage resulting from reactivation of HBV.
- For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.
- When it is not possible to construct a viable suppressive regimen for a patient with multidrug resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.

- No need to change ARV therapy for persistent low level viremia (<200 copies)
- If resistant, rarely a reason to continue NNRTIs, ENF, EVG, or RAL: no evidence of clinical benefit; may promote further resistance, limit future treatment options
- NRTI's retained substantial virological activity when given with a boosted PI even in the setting of resistance
- Presence of M184V does not effect initial Rx much (except for use of ABC at higher viral load)
- Even partial virological suppression of HIV RNA to >0.5 log10 copies/mL from baseline correlates with clinical benefit in patients with MDR
- Newly approved/Investigational agents with novel MoAs may provide options for pts with MDR HIV
  - Fostemsavir (gp120 binder; prevents CD4+ cell attachment), ibalizumab (anti-CD4 receptor mAb), PRO 140 (anti-CCR5 mAb)
- Adherence is the Achilles heel

Questions