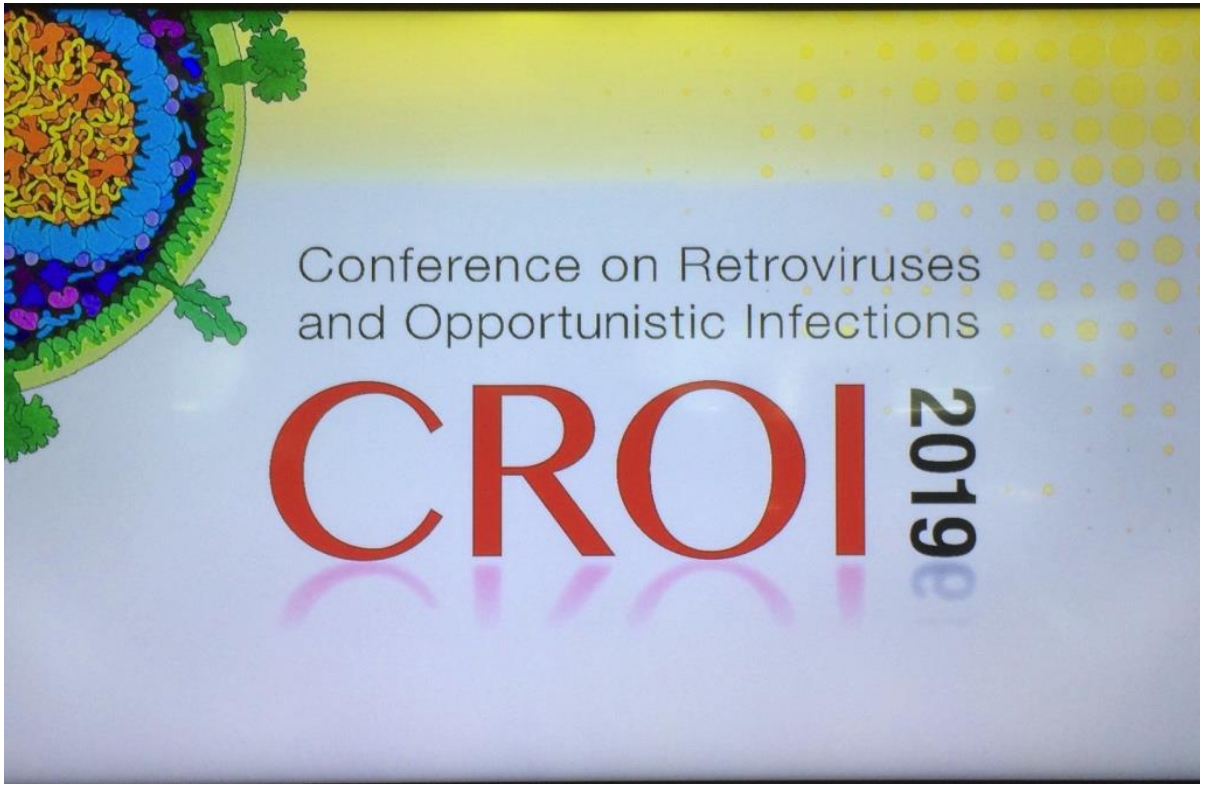
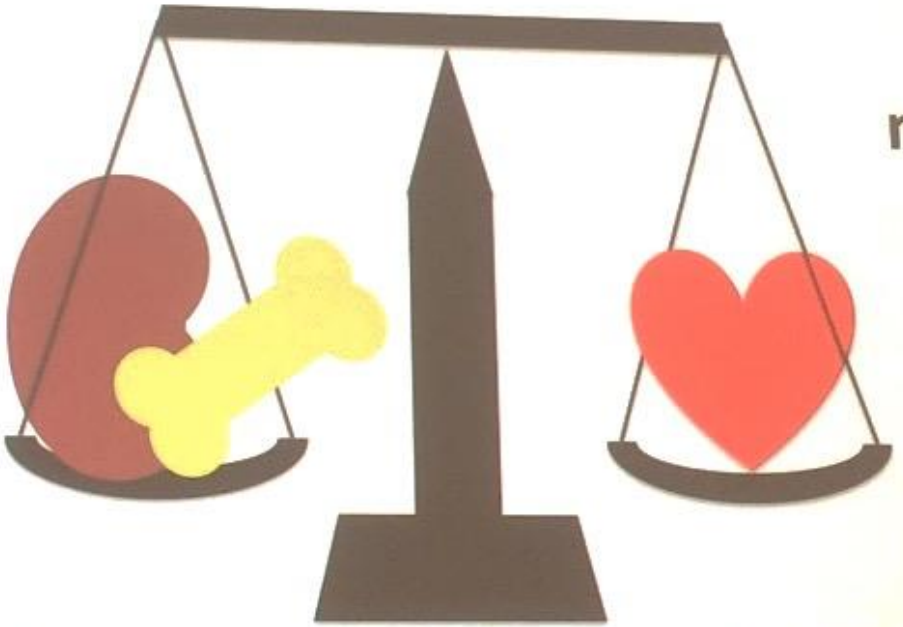

Conference on Retroviruses
and Opportunistic Infections
CROI
2019

P de Truchis

New ARVs

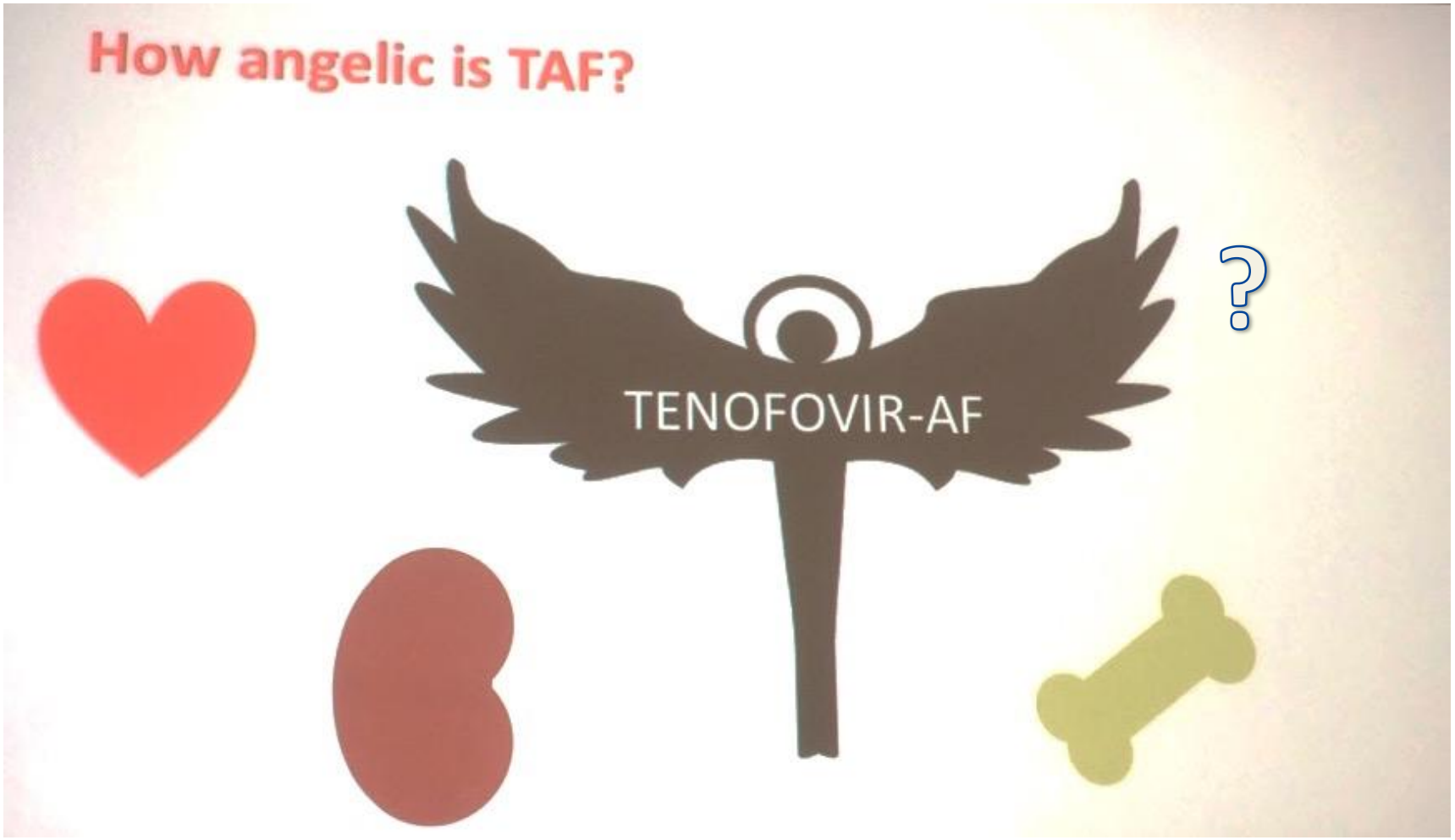
NRTI: tenofovir-DF vs abacavir

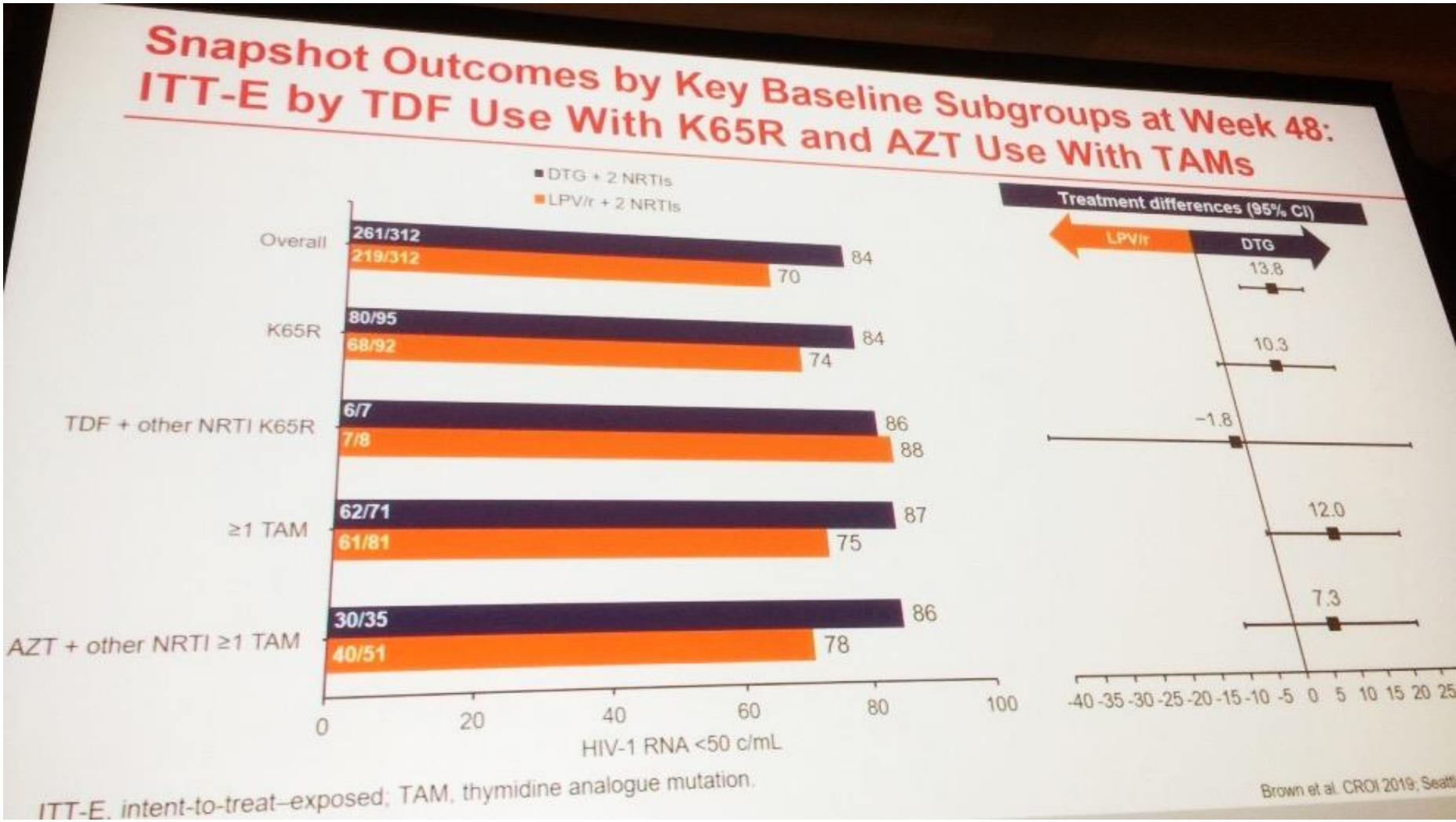
mtDNA

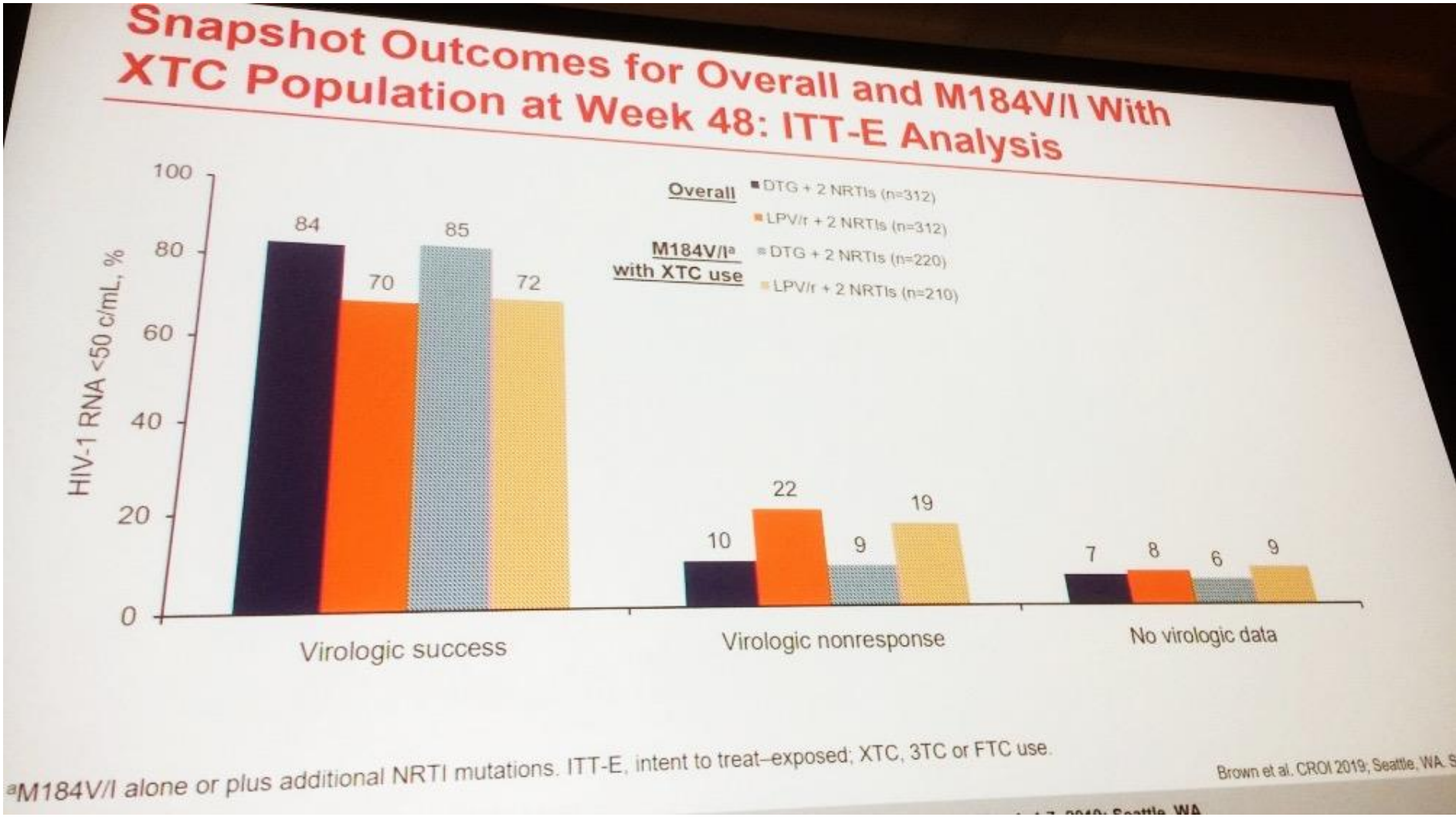


DNA methylation

Telomerase & telomere length


How angelic is TAF?
TENOFOVIR-AF
?


Snapshot Outcomes by Key Baseline Subgroups at Week 48: ITT-E by TDF Use With K65R and AZT Use With TAMs
DTG + 2 NRTIs
LPV/r + 2 NRTIs
Overall
261/312
84
219/312
70
K65R
80/95
84
68/92
74
TDF + other NRTI K65R
6/7
86
7/8
88
≥1 TAM
62/71
87
61/81
75
AZT + other NRTI ≥1 TAM
30/35
86
40/51
78
0
20
40
60
80
100
HIV-1 RNA <50 c/mL
Treatment differences (95% CI)
LPV/r
DTG
13.8
10.3
−1.8
12.0
7.3
-40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25
ITT-E, intent-to-treat–exposed; TAM, thymidine analogue mutation.
Brown et al. CROI 2019; Seattl


Snapshot Outcomes for Overall and M184V/I With XTC Population at Week 48: ITT-E Analysis
HIV-1 RNA <50 c/mL, %
100
80
60
40
20
0
Overall
DTG + 2 NRTIs (n=312)
LPV/r + 2 NRTIs (n=312)
M184V/I[a] with XTC use
DTG + 2 NRTIs (n=220)
LPV/r + 2 NRTIs (n=210)
84
70
85
72
10
22
9
19
7
8
6
9
Virologic success
Virologic nonresponse
No virologic data
[a]M184V/I alone or plus additional NRTI mutations. ITT-E, intent to treat–exposed; XTC, 3TC or FTC use.
Brown et al. CROI 2019, Seattle, WA.

Résistance aux INI

Table 2A. Detailed HIV-1 Integrase Genotypic and Phenotypic Analysis (No G140A/C/S + Q148H/R/K) (n=11)

Patient #	ART at Sample Collection[b]	Previous INSTI Failures[b]	Substitutions in IN: IN Resistance Substitutions	Substitutions in IN: Other IN Substitutions	Drug Susceptibility (Fold Change from WT)[a]: BIC	DTG	EVG	RAL
1329	3TC+DRV/r	RAL	None	E11D, R20R/K, V32I, V37I, V72I, L101I, T112A, V113I, T122I, T125A, V165I, V201I, K211K/R, V234L, S283S/G	0.98	1.17	1.84	1.32
1329	DRV/r+ETV+MCV+DTG	RAL, DTG	None	E11D, V32I, V37I, V72I, L101I, T112A, V113I, T122I, T125A, V165I, V201I, V234L	0.83	0.96	1.57	1.07
3919	3TC/ABC+DRV/r+ETV	RAL	None	S17N, R20K, V72I, T124N, T125A/V, M154L, T206S, V234L, D256E	0.92	0.93	1.43	0.88
1631	TDF/FTC+DRV/r	RAL	None	V31I, D41D/N, V54I, V72I, T124A, T125A, V201I, K215N, V234L, S283G, D286D/N	0.96	1.16	1.56	1.01
25	TDF/FTC+DRV/r+ETV	RAL	None	D6N, K7E, L28I, P30A, V72I, V113I, T206T/S, K211R, V234L, D286N	0.97	1.02	1.94	1.00
3211	ATV+RAL+MCV	None	None	K111T, Q216H, D232D/E, V234L, D256D/E	1.10	1.12	1.27	0.83
1218	TDF/FTC+DRV/r	RAL	S119P	S17N, V31I, V72V/I, L101I, T112I, V113I/L, T122I, T124N, F139F/L, T206S, T216S, Y227F, V234L, S255S/N, D256E, D279D/N	0.92	0.92	1.40	0.82
5554	3TC+DRV/r	RAL	None	P30S, V31V/I, V72I, L101I, V113I, G163K/E, K173R, V201I, T206S, Y227F, V234L, D253Y, D256E	1.04	1.17	1.35	1.18
817	DRV/r+RAL+MVC+ENF	RAL	S119T, Y143Y/R/H/C	K14R, S17S/N, R20R/K, S24N, D25D/E, V72I, P109P/S, T124A, T125A, V165I, V201V/I, T206S, Q216H, V234L, D278D/N, R284R/G, E287E/K	0.94	1.00	2.66	2.11
5296	TDF+MCV+RAL	None	T97A, Y143R, G163R	S17N, S24N, L101I, G106A, T112A, V113I, S119G, T122I, T125A, V165I, V201I, K211R, T218I, Q221G, D256E	0.59	0.80	35	>100
2552	RAL+MCV	None	N155H, G163R	D6E, E11D, S24G, V32I, V72I, A80S, L101I, S119A, T124N, T125V, K173R, D232E, V234L	1.36	1.52	33	27
				Mean (Median) FC Values	0.96 (0.96)	1.07 (1.02)	6.9 (1.57)	20 (1.07)

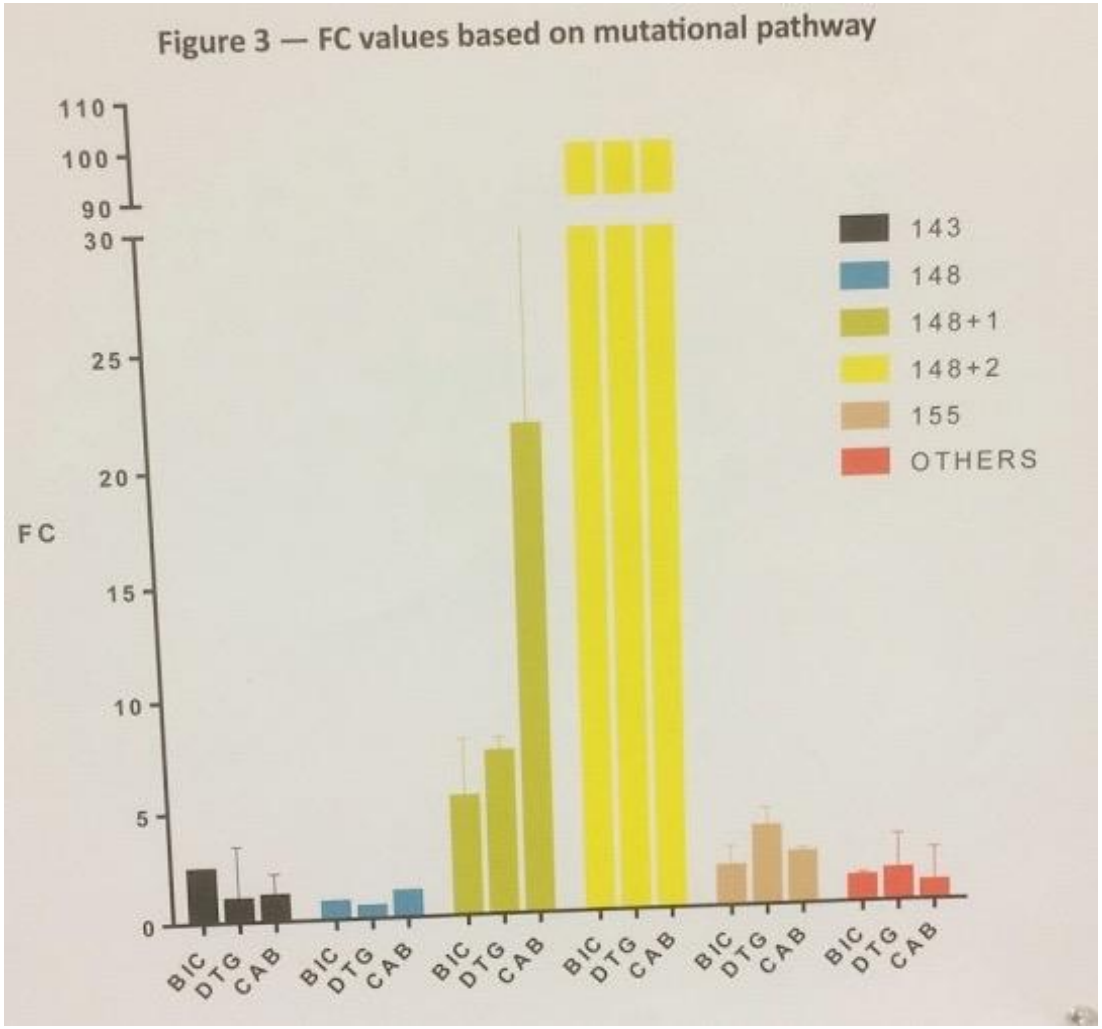
[a] Estimated by PhenoSenseIN assay (Monogram Biosciences, South San Francisco, CA; https://www.monogrambio.com/hiv-tests/phenotype-assays/phenosense-integrase)
[b] All INSTI were BID

Table 2B. Detailed HIV-1 Integrase Genotypic and Phenotypic Analysis (With G140A/C/S + Q148H/R/K) (n=11)

Patient #	ART at Sample Collection[b]	Previous INSTI Failures[b]	Substitutions in IN: IN Resistance Substitutions	Substitutions in IN: Other IN Substitutions	Drug Susceptibility (Fold Change from WT)[a]: BIC	DTG	EVG	RAL
1565	RAL+ETV	None	G140S, Q148H	V72I, L101I, V113I, T122I, T124N, T125T/A, M154M/I/L, F181F/L, V201I, V234L	2.28	4.85	>100	>100
1767	FPV+DRV/r+RAL	None	G140S, Q148H	D3D/E, K14R, S17C, L45V, L63L/I, V72I, G106A, V113I, T124A, T125T/A, F139F/Y, V165I, F185Y, V201V/I, I203I/M, T218T/S, K219N, N222K, V234L	2.64	5.56	>100	>100
4932	TDF/FTC+ATV+RAL+MCV+ENF	RAL	S119P, G140S, Q148H	K14R, A23V, S24G, D25E, L28I, S39C, G59G/E, V72I, L101I, T112V, V113I, T125T/I, V165I, V201I, T218S, V234L	2.99	4.44	>100	>100
1298	ETV+RAL+MVC	RAL	G140S, Q148H	E10D, R20R/K, V72I, L101I, V113I, S119G, T122I, T124N, T125A, G163Q/E, V234L, D256E	3.02	6.62	>100	>100
252	3TC+TDF+DRV/r+ETV+RAL+ENF	RAL	G140S, Q148H	K7Q, E11D, S24N, V72I, L101I, T112T/I/M/S/L, V113I, T124N, T125T/A, G193R, I203I/M, T206S, T216S, V234L, D256D/E	3.15	6.01	>100	>100
4084	3TC+RAL+ETV	None	G140S, Q148H	S17N, S24N, V72I, L101I, K111Q, V113I, T124N, T125A, M154I, V165I, V201I, V234L	3.18	6.19	>100	>100
4092	TDF+DRV/r+RAL	RAL	E138A, G140S, Q148H	E10E/G, K14R, V31I, M50R, V72I, L101I, K111T, V113I, T124A, F139Y, G193E, V201I, I220M, V234L, D253E, S255R	3.38	7.42	>100	>100
4932	TDF/FTC+ATV+DTG+MCV+ENF	RAL	T97T/A, S119P, E138E/K, G140S, Q148H	K14R, A23V, S24G, D25E, L28I, S39C, G59G/E, V72I, L101I, T112V, V113I, V165I, V201I, T218S, V234L	5.33	6.29	>100	>100
4932	TDF/FTC+MCV+ENF+DTG	RAL, DTG	T97T/A, S119P, E138E/K, G140S, Q148H	K14R, A23V, S24G, D25E, L28I, S39C, G59G/E, V72I, L101I, T112V, V113I, T125T/I, V165I, V201I, T218S, V234L	8.63	11	>100	>100
817	3TC+DRV/r+ETV+DTG+ENF	RAL, DTG	L74M, T97T/A, S119T, E138E/K, G140S, Y143R, Q148Q/H	K14R, S24N, L63L/I, V72I, T124A, T125A, K136K/E, V165I, V201V/I, I203I/M, T206S, Q216H, V234L, D278D/N, R284R/G	26	52	>100	>100
1631	TDF+MCV+DTG+ENF	RAL	L74M, E138E/K, G140S, Q148H	V31I, D41N, V72I, L101L/F, T112T/K, V113L, T124A, T125A, G149A, V201I, K215N, V234L, S283G	50	>100	>100	>100
				Mean (Median) FC Values	12 (3.2)	30 (6.3)	>163 (>164)	>189 (>188)

[a] Estimated by PhenoSenseIN assay (Monogram Biosciences, South San Francisco, CA; https://www.monogrambio.com/hiv-tests/phenotype-assays/phenosense-integrase)
[b] All INSTI were BID

Résistance aux INI



CROI 2019
Seattle, WA

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Activity of Bictegravir Against HIV-2 Isolates and INI-resistant HIV-2 Mutants

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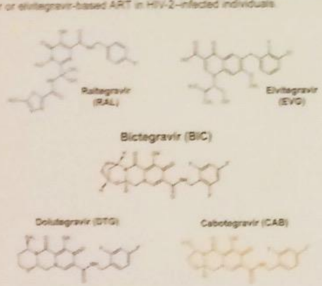
Background

HIV-2 infection is a significant public health problem in West Africa and has been reported in other countries with ties to the region.

Treatment options for HIV-2 are restricted due to intrinsic drug resistance.

The use of regimens containing two NRTI plus an integrase inhibitor (INI) for HIV-2 is supported by cohort-based studies, and by the outcomes of recent clinical trials of raltegravir or elvitegravir-based ART in HIV-2–infected individuals.



BIKTARVY® (bictegravir/emtricitabine/tenofovir alafenamide; Gilead Sciences, Inc.) is a fixed-dose, single-tablet regimen that was approved by the US FDA for use in HIV-1–infected patients in Feb. 2018.

To date, there are no published case reports or clinical studies describing the use of bictegravir/BIKTARVY® for HIV-2 treatment.

Data describing the *in vitro* susceptibility of HIV-2 to bictegravir are limited. Tsiang *et al.* reported that a group B isolate was susceptible to the drug (EC_{50} 1.7 nM) (1). Le Hingrat *et al.* showed that bictegravir inhibited $HIV\text{-}2_{ROD9}$ and two HIV-2 isolates from treatment-naive patients with EC_{50} values ranging from 0.8 to 3.8 nM (2). Both studies used spreading infections of human PBMC to measure anti–HIV-2 activity.

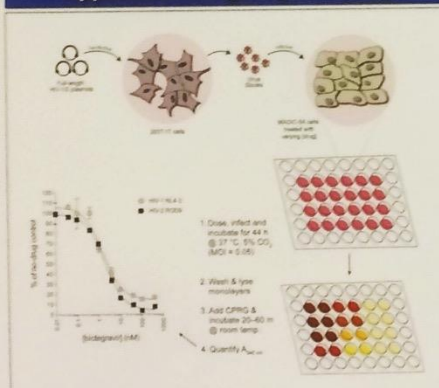
Le Hingrat and colleagues (2) also determined the bictegravir susceptibilities of 10 HIV-2 isolates that were obtained from patients treated with raltegravir (n = 6), elvitegravir (n = 1) or raltegravir followed by dolutegravir (n = 3). Five of these isolates contained canonical INI-associated amino acid changes in integrase (Y143R, T97A/Y143G, E92Q/T97A, E92Q/T97A/N155H, G140S/Q148H), one had no known resistance-associated changes, and four contained novel insertions at integrase codon 231. The G140S/Q148H isolate was 32-fold resistant to bictegravir. Isolates with E92Q/T97A/N155H and certain codon 231 insertions were 2.9 to 8.0-fold resistant to the drug.

REFERENCES
1. Tsiang, M. et al. (2016) Antimicrob. Agents Chemother. 60:7086.
2. Le Hingrat Q. et al. (2018) Clin. Infect. Dis. in press. (doi: 10.1093/cid/ciy940)
3. Smith R.A. et al. (2008) Antimicrob. Agents Chemother. 52:329.
4. Wu, V.H. et al. (2017) Antimicrob. Agents Chemother. 61:e00744.
5. Bancio I. et al. (2018) Antiviral Res. 161:86.
6. Callebaut C. et al. (2015) Antimicrob. Agents Chemother. 59:5909.

Aims

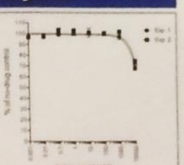
- To compare the activity of bictegravir against HIV-1 and HIV-2 isolates in single round of replication.
- To determine the potency of bictegravir against site-directed HIV-2 mutants that represent the three major pathways to INI resistance.

Approach – Single-cycle Assay

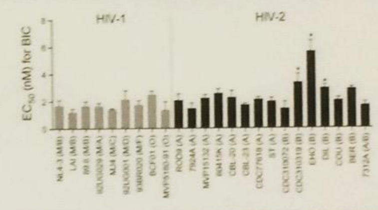


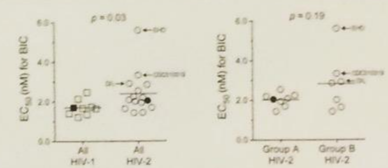
Cytotoxicity Analysis

- MAGIC-5A cells were seeded and dosed with bictegravir in the same manner as the drug susceptibility assay; medium was used in place of the virus inoculum.
- 44 hours after dosing, cell viability was measured using the CellTiter-Glo Luminescence assay (Promega).
- The results show that the CC_{50} for Bictegravir is >10 µM (see right).

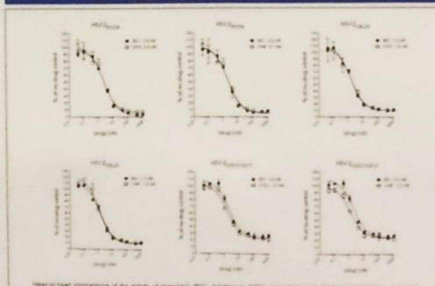


Results – HIV-1 and HIV-2 Isolates





Comparison to DTG & CAB



Results – INI-resistant Mutants

HIV Type	Genotype	EC_{50} (nM)	n	Fold Change
HIV-1	Wild type	1.7 ± 0.38	7	–
	T97A+Y143C	0.95 ± 0.16	3	0.6
	E92Q+N155H	2.0 ± 0.47	3	1.2
	G140S+Q148H	**3.4 ± 0.29**	**3**	**2.0**
	E138K+G140S+Q148R	**3.9 ± 0.42**	**3**	**2.3**
HIV-2	Wild-type	2.0 ± 0.47	12	–
	Q91R+T97A+Y143C	1.3 ± 0.11	3	0.7
	Q91R+T97A+Y143C+A153S	1.4 ± 0.43	3	0.7
	Q91R+E92Q+T97A+Y143G+A153S	2.4 ± 0.55	3	1.2
	G140S+Q148H	**220 ± 69**	**4**	**110**
	G140A+Q148R	**4.7 ± 3.6**	**5**	**2.8**
	G140S+Q148R	**67 ± 9.2**	**3**	**34**
	E92Q+N155H ROD9	**5.1 ± 1.2**	**3**	**3.0**
	E92Q+T97A+N155H	**8.7 ± 2.2**	**3**	**4.4**
	E92Q+A153G+N155H	3.7 ± 1.2	3	1.9
	I84V+E92Q+T97A+A153S+N155H	**9.1 ± 2.7**	**3**	**4.6**

Conclusions

- HIV-1 and HIV-2 show comparable sensitivity to bictegravir in a single cycle of infection. EC_{50} values for both HIV types, including group O isolates of HIV-1, were in the low nanomolar range.
- Bictegravir, dolutegravir, and cabotegravir show equivalent potency against HIV-2 in culture.
- Q148-pathway mutants of HIV-2 are highly resistant to bictegravir. N155H-pathway mutants also show modest decreases in BIC susceptibility (≤5-fold).
- Fold-change values for the site-directed HIV-2 mutants are concordant with those reported for clinical isolates of HIV-2 from INI-treated patients (2).
- All three components of BIKTARVY® are highly active against HIV-2 *in vitro* (see also references 3-6). A clinical trial should be performed in West Africa to evaluate BIKTARVY® as a first-line regimen for all PLWHIV, including those infected with HIV-2.

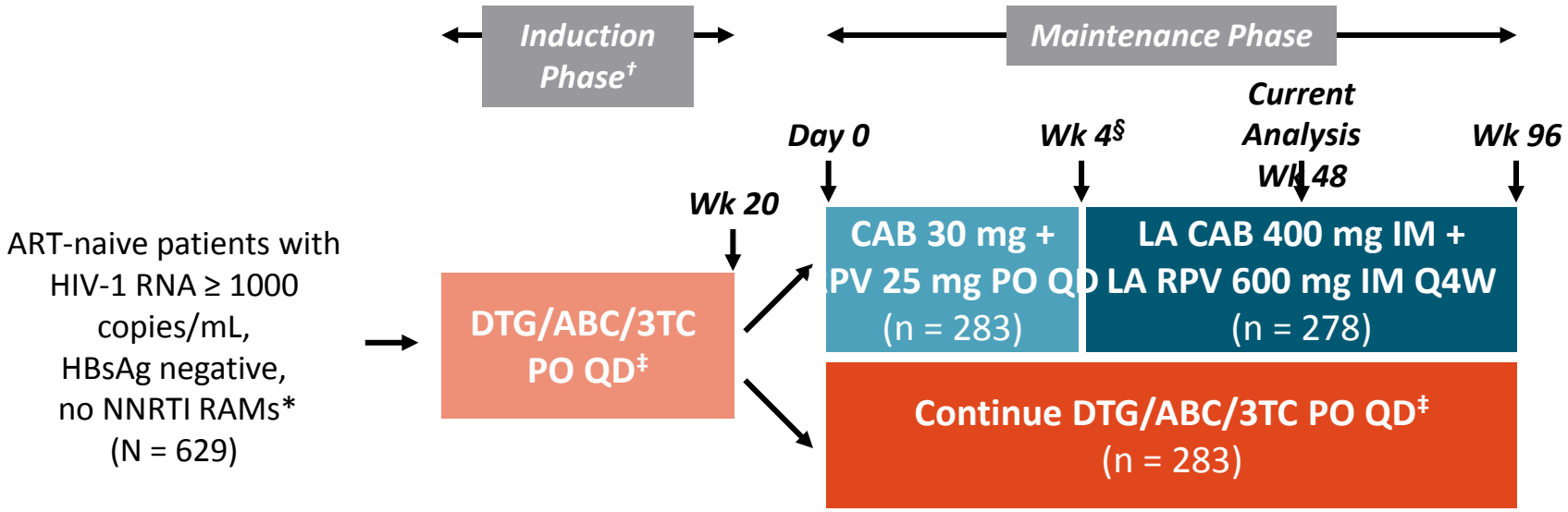
Acknowledgements

Results – INI-resistant Mutants

HIV Type	Genotype	EC_{50} (nM)[a]	n[b]	Fold Change[c]
HIV-1	Wild type	1.7 ± 0.38	7	–
	T97A+Y143C	0.95 ± 0.16	3	0.6
	E92Q+N155H	2.0 ± 0.47	3	1.2
	G140S+Q148H	**3.4 ± 0.29**	**3**	**2.0**
	E138K+G140S+Q148R	**3.9 ± 0.42**	**3**	**2.3**
HIV-2	Wild-type	2.0 ± 0.47	12	–
	Q91R+T97A+Y143C	1.3 ± 0.11	3	0.7
	Q91R+T97A+Y143C+A153S	1.4 ± 0.43	3	0.7
	Q91R+E92Q+T97A+Y143G+A153S	2.4 ± 0.55	3	1.2
	G140S+Q148H	**220 ± 69**	**4**	**110**
	G140A+Q148R	**4.7 ± 3.6**	**5**	**2.8**
	G140S+Q148R	**67 ± 9.2**	**3**	**34**
	E92Q+N155H ROD9	**5.1 ± 1.2**	**3**	**3.0**
	E92Q+T97A+N155H	**8.7 ± 2.2**	**3**	**4.4**
	E92Q+A153G+N155H	3.7 ± 1.2	3	1.9
	I84V+E92Q+T97A+A153S+N155H	**9.1 ± 2.7**	**3**	**4.6**

FLAIR: Study Design

- Multicenter, randomized, open-label phase III noninferiority trial



*K103N permitted. †Patients with HIV-1 RNA < 50 copies/mL from Wk 16 to Wk 20 continued to maintenance phase. ‡Alternative, non-ABC NRTIs permitted for intolerance or HLA-B*5701 positivity. §Loading dose: LA CAB 600 mg IM + LA RPV 900 mg IM; regular dosing begun at Wk 8.

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot (6% noninferiority margin)
- Secondary endpoints: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot, resistance at confirmed virologic failure, safety and tolerability, patient-reported outcomes

Orkin. CROI 2019. Abstr 140LB. NCT02938520.

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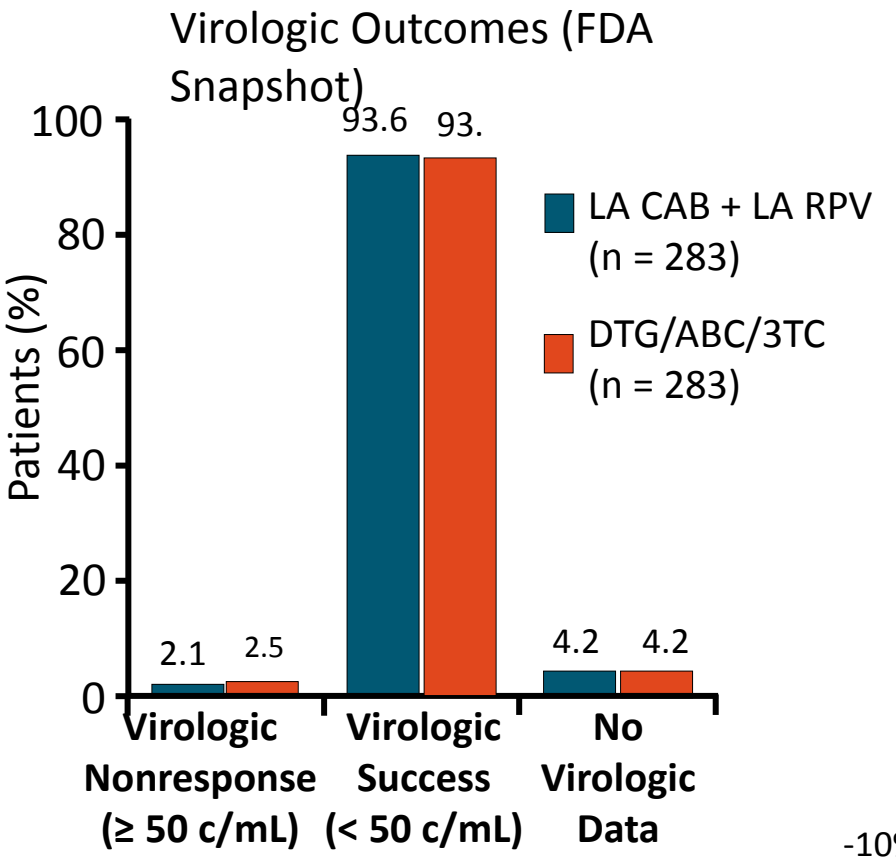
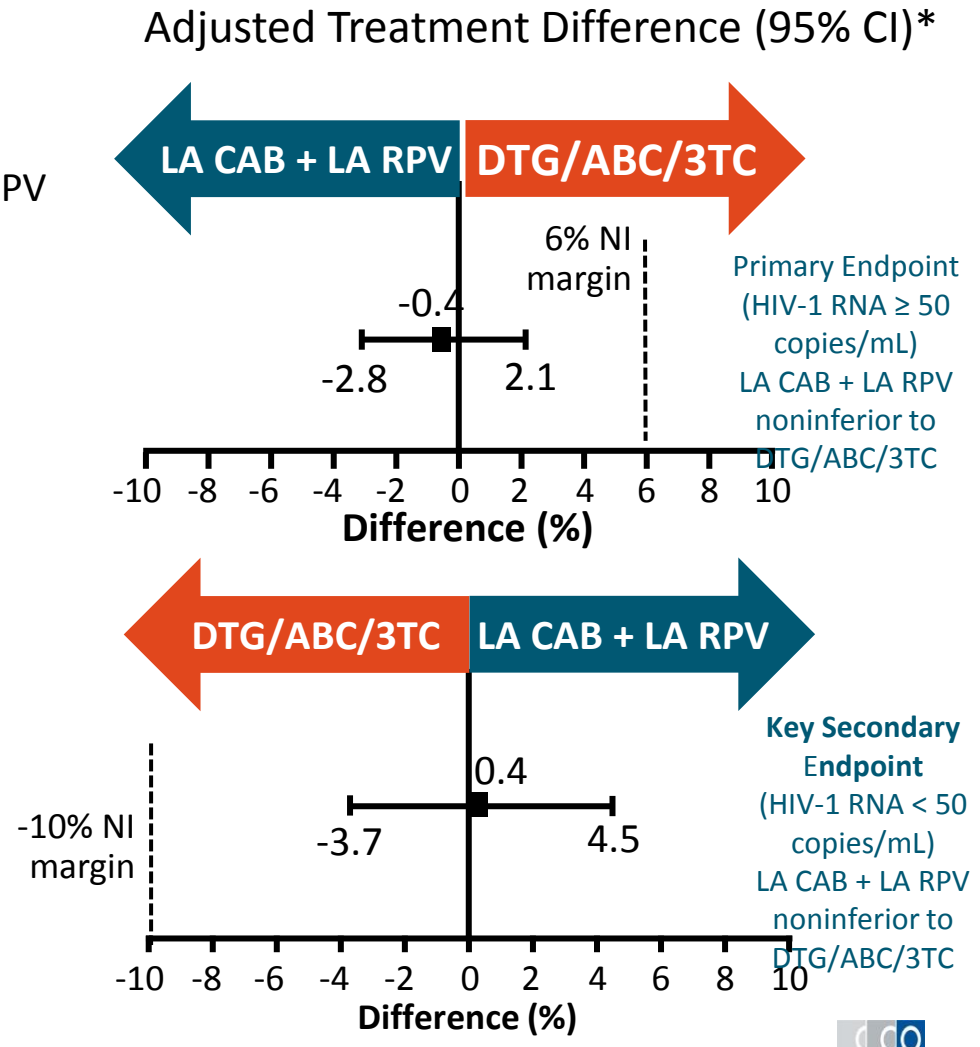
FLAIR: Efficacy at Wk 48 in ITT-E Population





- Confirmed VF: n = 3 per arm; emergent NNRTI + INSTI resistance in all CAB + RPV failures (all HIV-1 subtype A1), no resistance in DTG/ABC/3TC failures

*Adjusted for sex, BL HIV-1 RNA (< vs ≥ 100,000 c/mL).

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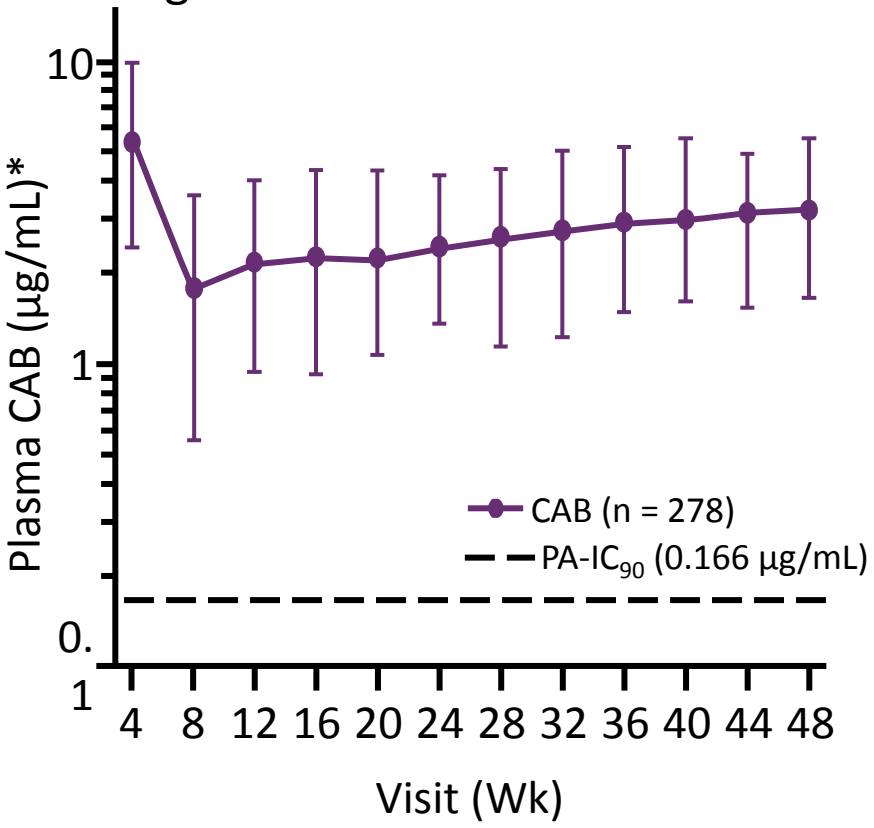
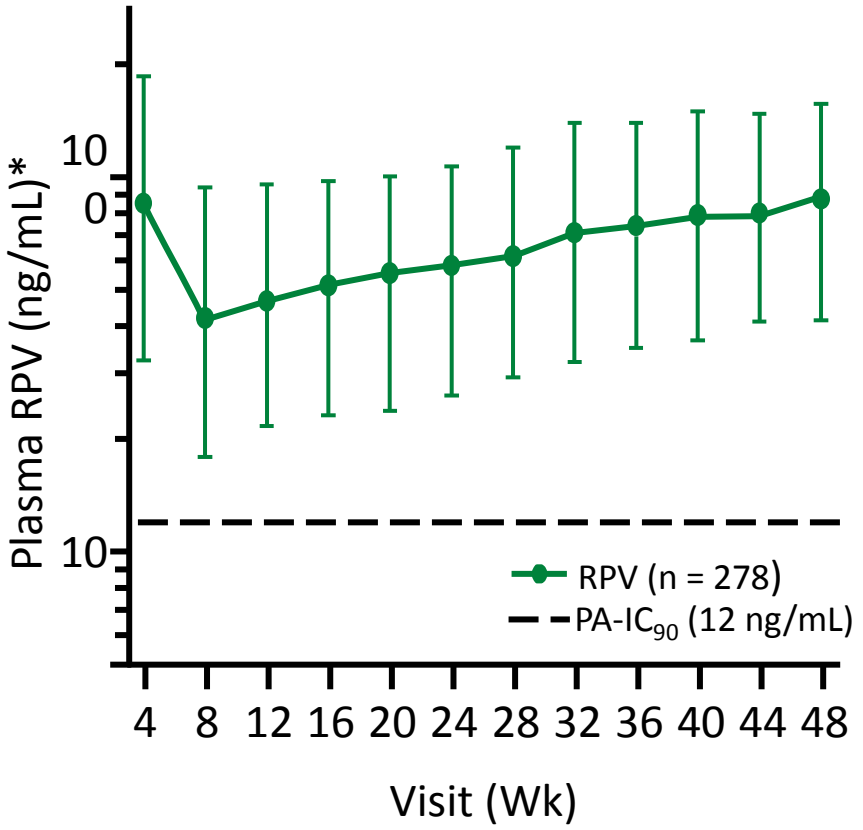
FLAIR: Plasma Trough Concentrations by Visit

- Plasma concentrations with IM CAB and RPV similar to effective PO regimens





*Median (5th, 95th percentile) concentration–time data.

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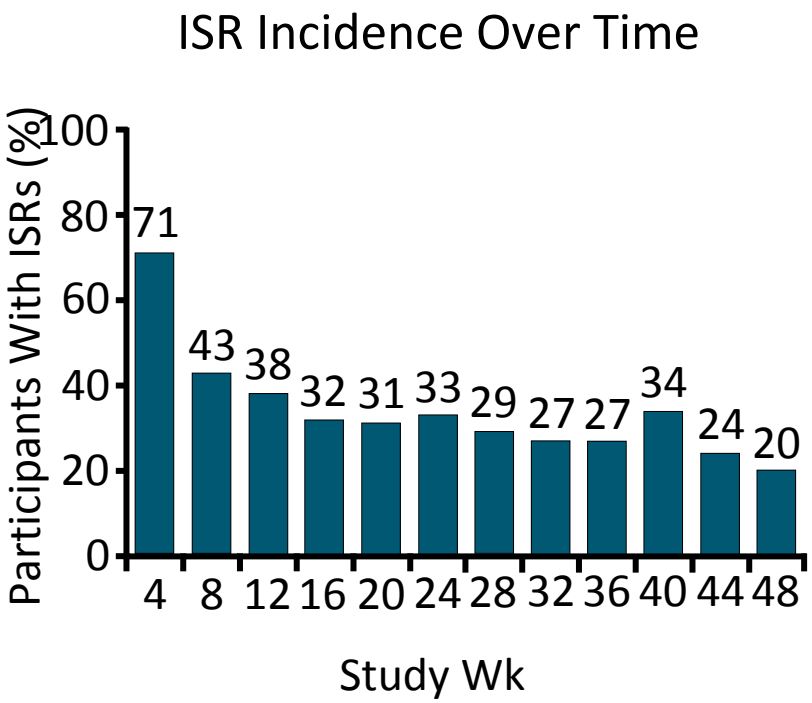
Slide credit: clinicaloptions.com

FLAIR: Injection-Site Reactions



- 99% of ISRs were grade 1/2, 88% resolved within 7 days

Characteristic to Wk 72	LA CAB + LA RPV (n = 283)
Patients receiving injections, n	278
Injections given, n	7704
ISR events, n (%) ▪ Pain ▪ Nodule ▪ Induration ▪ Swelling ▪ Warmth ▪ Grade 3 ISR pain*	2203 (28.6) 1879 (85.3) 86 (3.9) 82 (3.7) 38 (1.7) 38 (1.7) 12 (< 1.0)
Median duration of ISRs, days	3
ISR pain leading to d/c,† n (%)	2 (< 1.0)

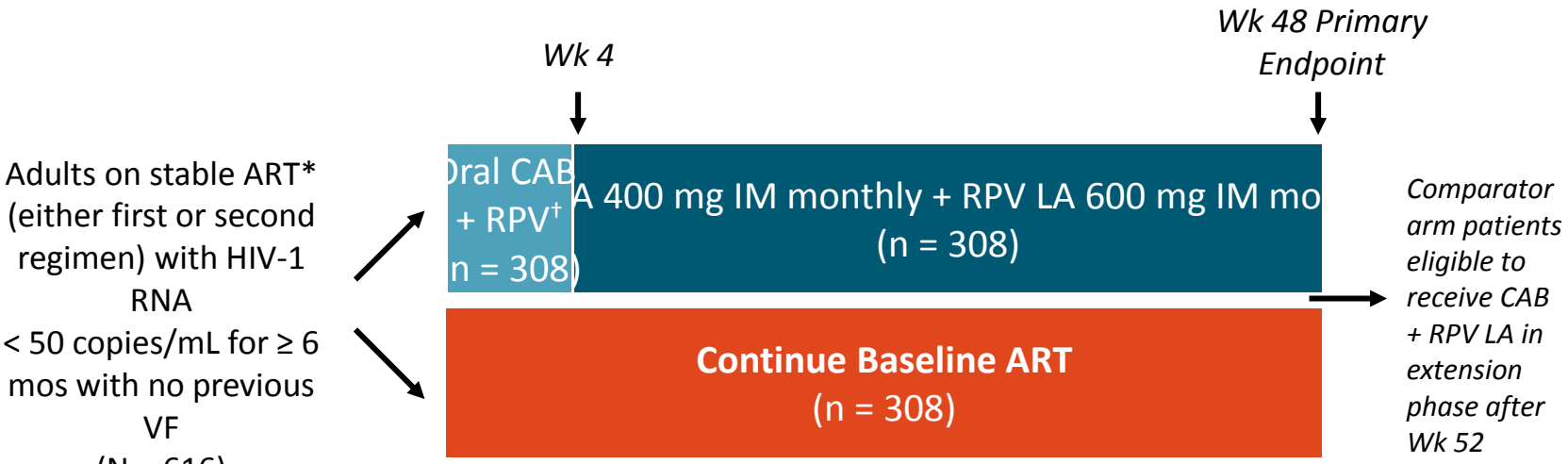
*No grade > 3 events reported. †2 additional patients d/c for injection intolerability.

Orkin. CROI 2019. Abstr 140LB. Reproduced with permission.

Slide credit: clinicaloptions.com

ATLAS: Study Design

- Multicenter, randomized, open-label phase III noninferiority trial



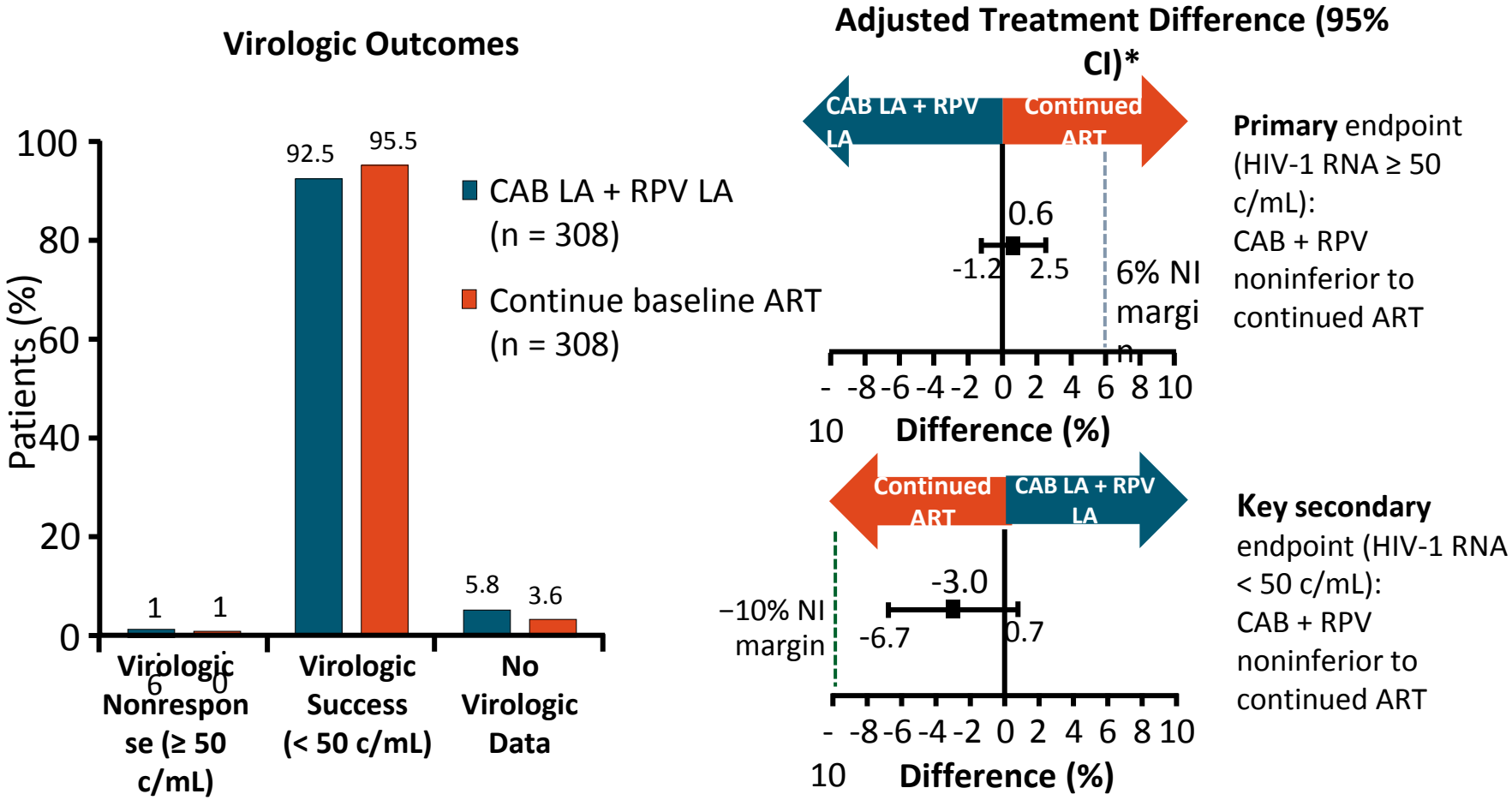
*Permitted baseline regimens: 2 NRTIs + INSTI (except DTG/ABC/3TC), NNRTI, or boosted PI (or unboosted ATV).
†CAB 30 mg + RPV 25 mg orally QD for 4 wks, followed by CAB LA 600 mg IM + RPV LA 900 mg IM at first injection, then CAB LA 400 mg IM + RPV LA 600 mg IM at Wk 8 and every 4 wks thereafter until withdrawal.

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 (FDA snapshot) in ITT-E
  - 6% noninferiority margin for difference in efficacy between arms
- Secondary endpoints: HIV-1 RNA < 50 or < 200 copies/mL at Wk 48, VF, safety, resistance,
  patient-reported outcomes

Swindells. CROI 2019. Abstr 139.

Slide credit: clinicaloptions.com

ATLAS: Virologic Outcomes at Wk 48 (FDA Snapshot)



- In CAB + RPV arm, 2 of the 3 patients with virologic failure had baseline NNRTI RAMs

Swindells. CROI 2019. Abstr 139.

Slide credit: clinicaloptions.com

ATLAS: Injection-Site Reactions

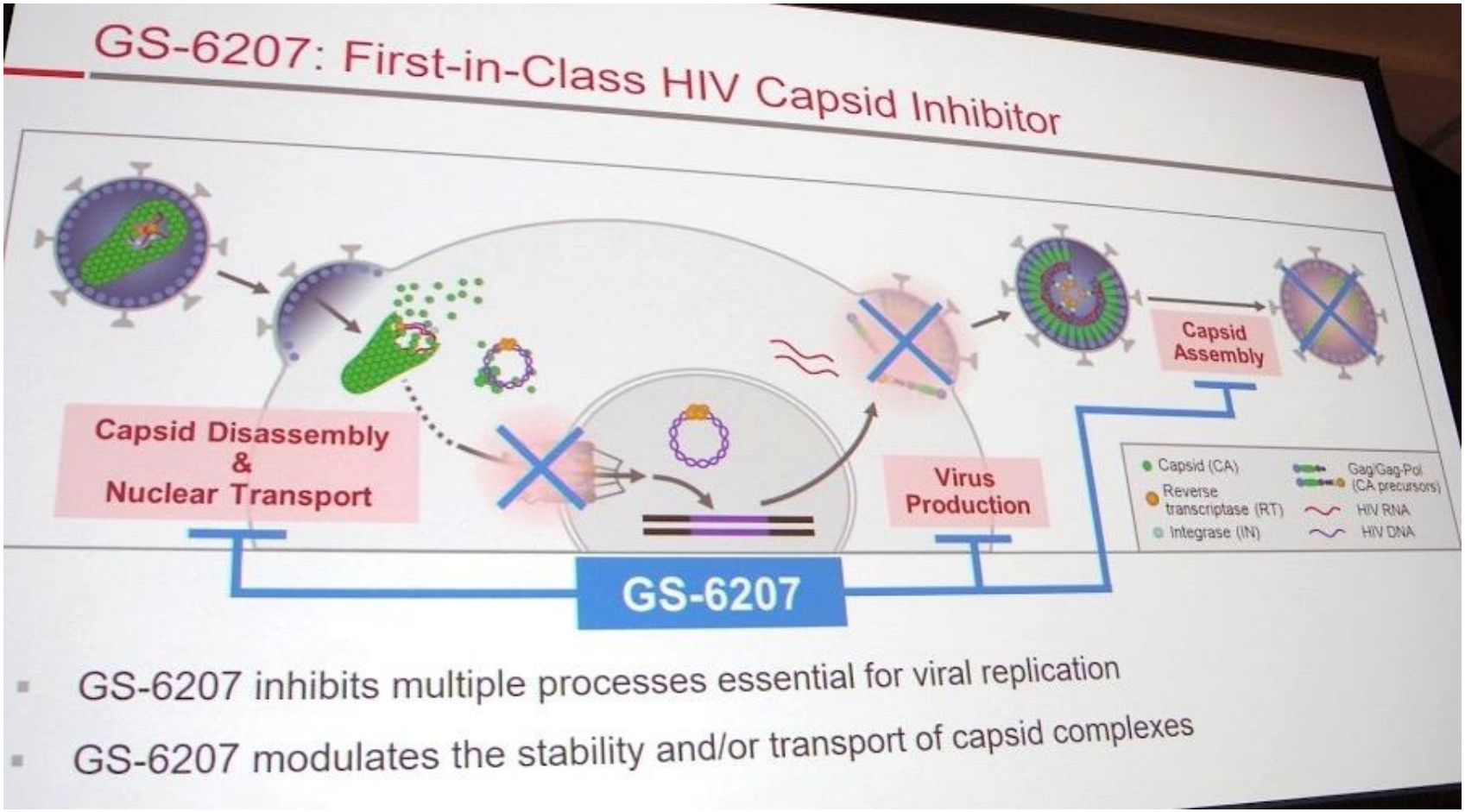
Injection-Site Reactions	Switch to CAB LA + RPV LA (N = 308)
Patients receiving injections, n	303
Injections given, n	6978
ISR events, n (%) ▪ Pain ▪ Nodule ▪ Induration ▪ Swelling ▪ Grade 3 ISR pain	1460 (20.9) 1208 (82.7) 54 (3.7) 54 (3.7) 48 (3.3) 20 (1.7)
Median duration of ISRs, days	3
Patients with ISR leading to discontinuation, n (%)	4 (1.3)

- Most (99%) ISRs were of grade 1/2 severity and 88% resolved within ≤ 7 days

Swindells. CROI 2019. Abstr 139.

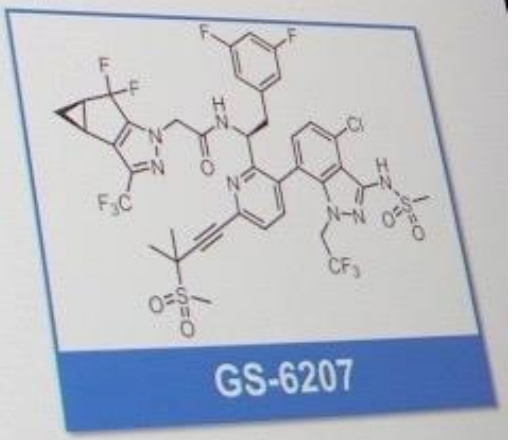
Slide credit: clinicaloptions.

GS6207 Inhibiteur de capside



GS-6207: Overview

- Desirable in vitro pharmacology profile (**Poster 480**[1]):
  - Active against a broad range of HIV-1 isolates*[1]
  - Retains full activity against mutants resistant to existing ARV classes†[1]
- Properties ideal for low-dose long acting injectable
  - Picomolar antiviral potency (≥10x more potent than current ARVs)†
  - Low predicted clearance (~5% of hepatic blood flow)[2]
  - Low aqueous solubility (<1 µg/mL at pH 2–7)[2]
- Demonstrated sustained exposure in preclinical species[2]

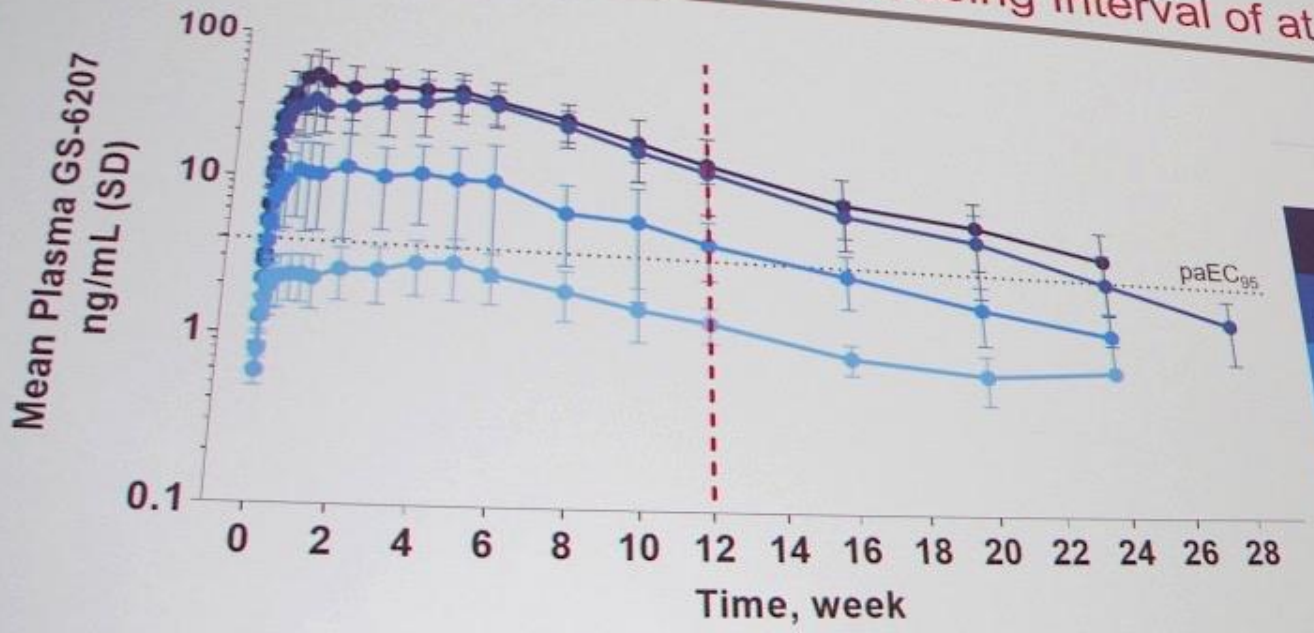


GS-6207

*Panel of 15 HIV Clinical Isolates in Human PBMCs; †MT-4 T-Cell Line. 1. Yant et al. CROI 2019, poster 480; 2. Zheng et al. LEAP 2019.

Results

Sustained Delivery Supports Dosing Interval of at least 12 Weeks



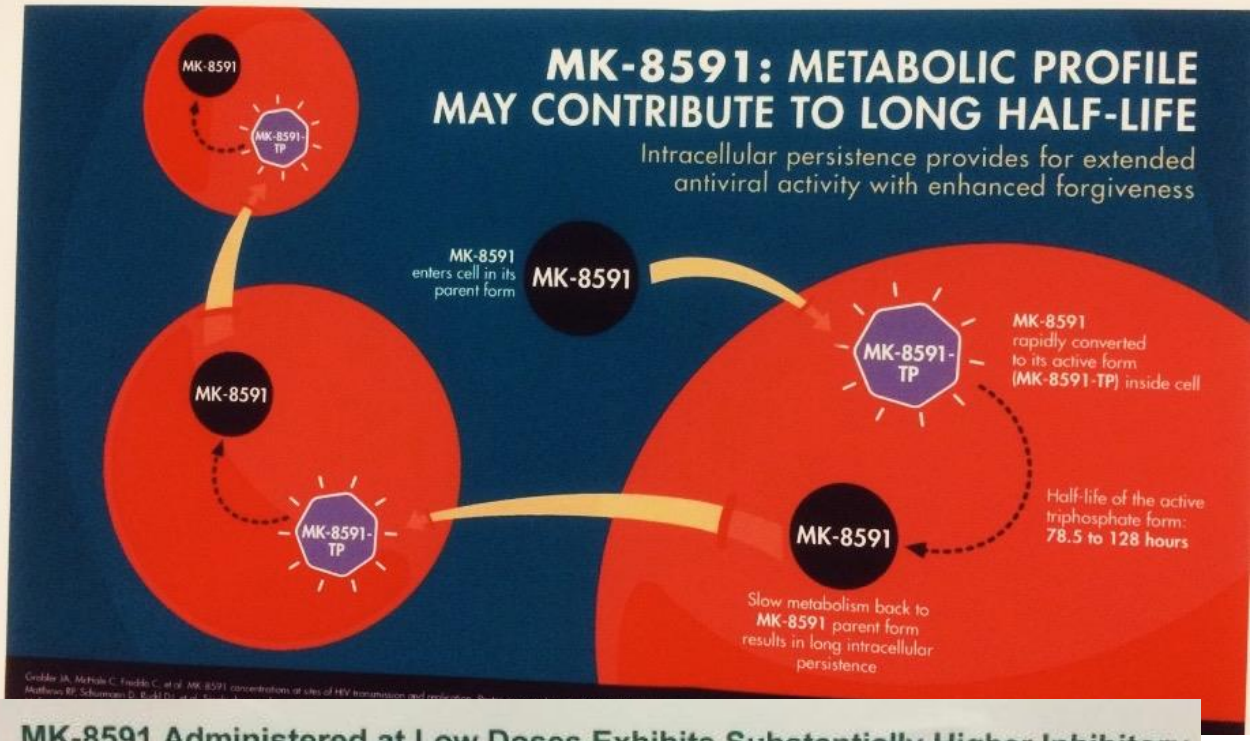
Dose	IQ at week 12
450 mg	4.7
300 mg	4.1
100 mg	1.3
30 mg	0.4

$IQ = C_{w12}/paEC_{95}$

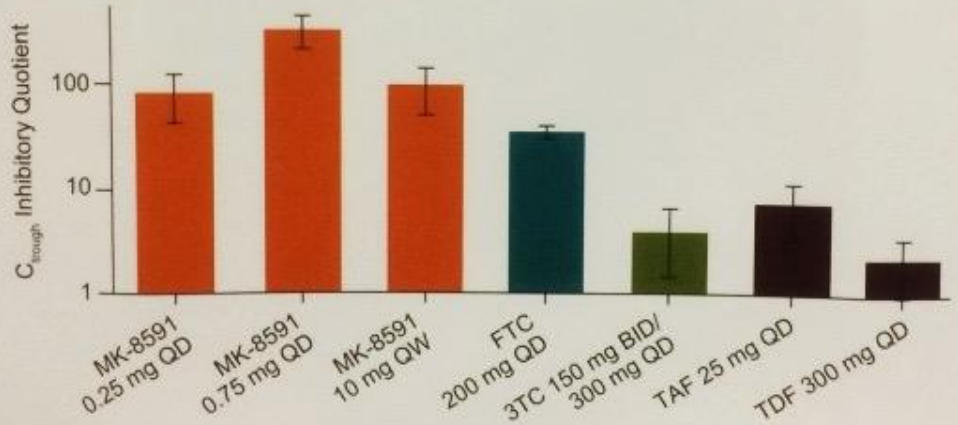
- At doses ≥100 mg, GS-6207 plasma concentrations at 12 weeks were above the $paEC_{95}$ of 3.87 ng/mL

*EC_{95} determined in MT-4 T-Cell Line with WT HIV-1 (IIIB strain). C_{w12}, GS-6207 plasma concentration on Day 84; IQ, inhibitory quotient; $paEC_{95}$, protein adjusted EC_{95}

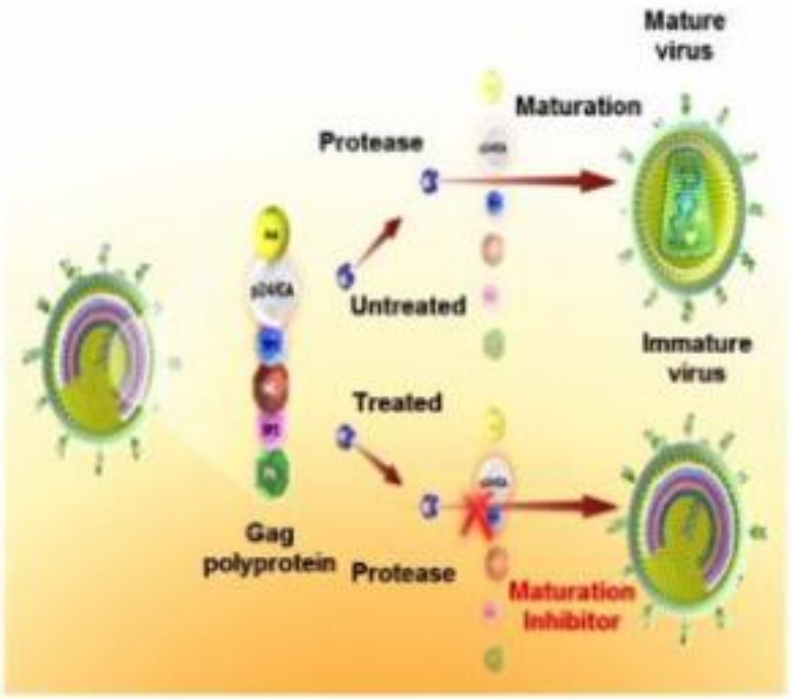
Antiviral Activity of MK-8591 and NRTIs Requires Intracellular Phosphorylation to Their Active Anabolites



MK-8591 Administered at Low Doses Exhibits Substantially Higher Inhibitory Quotients Than Marketed NRTIs



GSK2838232
Mode of Action of Maturation Inhibitors



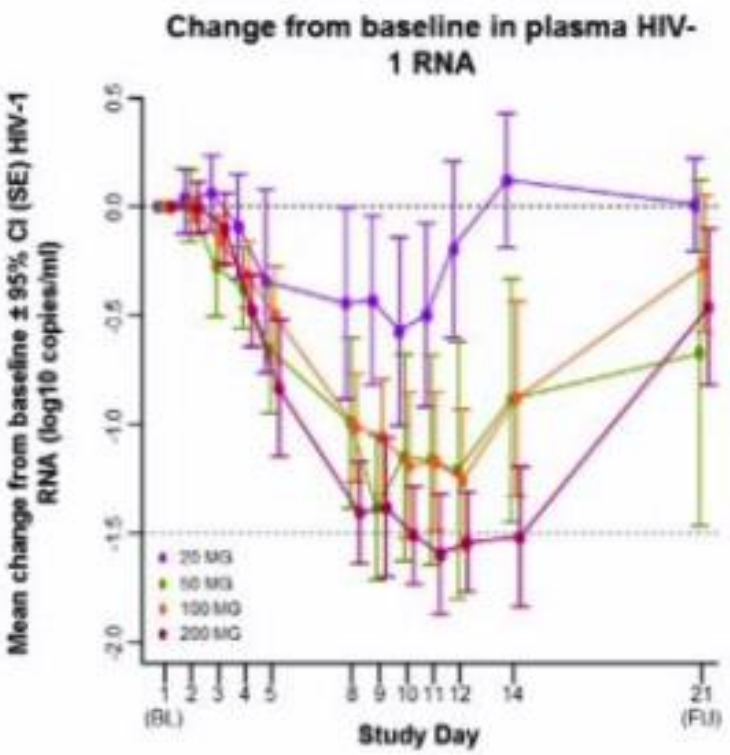
- Maturation Inhibitors bind to the gag protein, inhibiting the last proteolytic cleavage event between the p24 CA and SP1
- Development of previous maturation inhibitors has been halted for various reasons:
  - Bevirimat: naturally occurring polymorphism in HIV-1 Gag at or near its site of activity[1]
  - BMS-955176: issues with resistance and gastrointestinal tolerability[2]

Gag: group-specific antigen; HIV: human immunodeficiency virus
[1]Dybowski JN, et al. BioData Min. 2011;4:26. [2]Morales-Ramirez J, et al. PLoS One. 2018. https://doi.org/10.1371/journal.pone.0205368

DeJesus E, et al. CROI 2019. Abs

Antiviral Activity of Maturation Inhibitor GSK2838232

Robust reductions in 50 mg, 100 mg, and 200 mg cohorts; maximal effect in 200 mg cohort



	20 mg (n=7)	50 mg (n=8)	100 mg (n=10)	200 mg (n=8)
Plasma HIV RNA (copies/mL)				
Max. decline from baseline, mean (SD)	**-42,095** (37,576)	**-49,066** (71,340)	**-32,948** (54,291)	**-33,149** (31,786)
Max. decline from baseline (log $_{10}$-transformed), mean (SD)	**-0.67** (0.41)	**-1.56** (0.67)	**-1.32** (0.44)	**-1.70** (0.38)
>1.5 log$_{10}$ copies/mL decrease from baseline, n (%)	**0**	**2** (25)	**2** ([illegible])	**5** (63)
<400 copies/mL, n (%)	**0**	**2** (25)	**2** (20)	**4** (50)
CD4 count				
Change from baseline, mean (SD)	**-1.4** (95.3)	**52.0** (145.4)	**40.7** (94.5)	**11.1** (75.2)

BL, baseline; CI, confidence interval; FU, follow-up; HIV, human immunodeficiency virus; SD, standard deviation; SE, standard error

IBALIZUMAB: 96-WEEK DATA AND EFFICACY IN PATIENTS RESISTANT TO COMMON ANTIRETROVIRALS

#485

B. EMU[1], J. LALEZARI[2], P. KUMAR[3], S.WEINHEIMER[4], S. LEWIS[4], B. CASH[5], Z. MIAO[6], Z. COHEN[6]

[1]Yale School of Medicine, New Haven, CT, [2]Quest Clinical Research, San Francisco, CA, [3]Georgetown University Medical Center, Washington, DC, [4]TaiMed Biologics, Irvine, CA, [5]Syneos Health, Somerset, NJ, [6]Theratechnologies, Montréal, Canada

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Background

Ibalizumab (IBA) is a long-acting humanized immunoglobulin G4 monoclonal antibody that blocks entry of HIV into CD4+ T cells. Unlike other antiretroviral agents, IBA binds to a conformational epitope on the 2nd extracellular domain of the CD4 receptor, away from MHC II binding sites. It prevents HIV virus from infecting CD4+ immune cells while preserving normal immunological function.

IBA was approved by the FDA in March 2018 for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection failing their current antiretroviral (ARV) regimen.

We report the efficacy outcomes of IBA with OBR in patients resistant and susceptible to two widely used antiretrovirals, dolutegravir (DTG) and darunavir (DRV). Additionally, we report the long-term safety/tolerability and efficacy of IBA with OBR through 96 weeks of treatment.

Methods

TMB-301 is a single arm, 24-week study of IBA plus optimized background regimen (OBR) in treatment-experienced patients infected with MDR HIV-1.

Patients receiving their current failing ARV therapy, or no therapy, were monitored during a 7-day control period. Thereafter, a loading dose of 2,000 mg of intravenous (IV) IBA was the only ARV agent added to their regimen for 7 days. An OBR with at least one additional sensitive agent was added 7 days after loading dose. IBA was continued at doses of 800 mg IV every 2 weeks through 25 weeks on study treatment.

Eligible patients, i.e. patients who completed the 25-week TMB-301 study and enrolled in US and Puerto Rico, continued to receive IBA at 800 mg every 2 weeks under study TMB-311 for up to 96 weeks.

Study Design

TMB-301 → TMB-311

Baseline Characteristics

TMB-301

- N = 40
- Median viral load of 35,350 c/mL
  - 18% with viral load ≥ 100,000 c/mL
- Median CD4+ cell count of 75 cells/µL
  - 17 patients with < 50 cells/µL
    - 12 patients with < 10 cells/µL
  - 10 patients with 50-200 cells/µL
  - 13 patients with > 200 cells/µL
- Median CD4 of 2
- 17 patients received investigational agent (fostemsavir) in OBR

TMB-311

Patients who rolled over from TMB-301

- N = 27
- Median viral load of 21,700 c/mL
  - 19% with viral load ≥ 100,000 c/mL
- Median CD4+ cell count of 102 cells/µL
  - 8 patients with < 50 cells/µL
    - 5 patients with < 10 cells/µL
  - 10 patients with 50-200 cells/µL
  - 9 patients with > 200 cells/µL
- Median CD4 of 2
- 15 patients received investigational agent (fostemsavir) in OBR

Response in DTG Resistance/Susceptible Patients

- 18 patients with DTG resistance
  - 12 of 18 had major DTG resistant mutations (Q148 plus two additional G140/L74/E138 mutations)
- 26 patients incorporated DTG in OBR (16 in susceptible, 10 in resistant group)
- 4 of 5 patients who discontinued early were from DTG resistant group

	DTG Resistant		DTG Susceptible	
	DTG no OBR	DTG in OBR	DTG no OBR	DTG in OBR
Median DSS	1.0	1.0	2.0	3.0
>0.5 $\log_{10}$ VL reduction – Day 14	88% (7/8)	70% (7/10)	100% (6/6)	82% (13/16)
Median VL reduction - Day 14	1.1 $\log_{10}$	1.0 $\log_{10}$	1.1 $\log_{10}$	1.1 $\log_{10}$
>0.5 $\log_{10}$ VL reduction - Week 25	50% (4/8)	40% (4/10)	83% (5/6)	82% (13/16)
Median VL reduction - Week 25	0.6 $\log_{10}$	0.0 $\log_{10}$	1.2 $\log_{10}$	2.9 $\log_{10}$
<50 copies/mL - Week 25	38% (3/8)	10% (1/10)	33% (2/6)	69% (11/16)
<200 copies/mL - Week 25	38% (3/8)	20% (2/10)	50% (3/6)	75% (12/16)

Response in DRV Resistance/Susceptible Patients

- 27 patients with DRV resistance
  - 20 of 27 had major DRV resistant mutations (V32/I47/I50/I54/L76)
- 18 of 27 incorporated DRV/r in OBR and 15 had daily dose ≥ 600 mg
- 5 of 5 patients who discontinued early were from DRV resistant group

	DRV Resistant		DRV Susceptible	
	DRV no OBR	DRV in OBR	DRV no OBR	DRV in OBR
Median DSS	2.0	1.0	2.0	2.5
>0.5 $\log_{10}$ VL reduction – Day 14	78% (7/9)	83% (15/18)	80% (4/5)	88% (7/8)
Median VL reduction - Day 14	0.9 $\log_{10}$	1.4 $\log_{10}$	0.9 $\log_{10}$	1.0 $\log_{10}$
>0.5 $\log_{10}$ VL reduction - Week 25	78% (7/9)	61% (11/18)	60% (3/5)	63% (5/8)
Median VL reduction - Week 25	2.8 $\log_{10}$	0.8 $\log_{10}$	0.7 $\log_{10}$	2.4 $\log_{10}$
<50 copies/mL - Week 25	78% (7/9)	28% (5/18)	40% (2/5)	38% (3/8)
<200 copies/mL - Week 25	78% (7/9)	39% (7/18)	60% (3/5)	38% (3/8)

Safety up to Week 96

- IBA plus OBR was well tolerated
- **No new safety concerns emerging between Week 25 and 96**
- 22 of 27 patients completed treatment up to 96 weeks
- Reasons for early discontinuations (**none related to IBA**)
  - 2 Consent withdrawals
  - 1 Physician decision
  - 2 Deaths (Advanced cardiovascular disease, Progression of CMV disease)

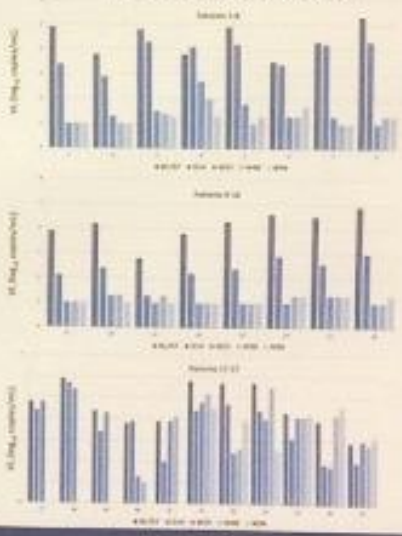
CD4 Changes up to Week 96

- Median CD4 Cell Count increase:
  - Week 25: 42 cell/µL (N=27)
  - Week 96: 45 cell/µL (N=22)

Efficacy up to Week 96

- **Patients virally suppressed at Week 25 maintained suppression at Week 96**
  - Week 25: 15 of 27 patients
  - Week 96: 15 of 27 patients (including 5 early discontinuations)
- Median VL decrease (N=27):
  - Week 25: 2.5 $\log_{10}$
  - Week 96: 2.8 $\log_{10}$

Viral Load - BL/D7 to Week 96



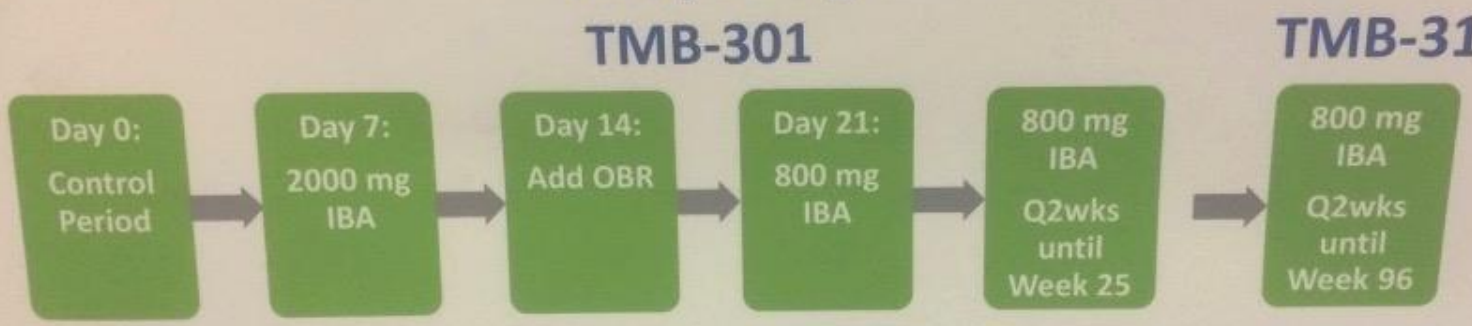
Conclusion

In MDR HIV-1 patients, IBA was effective in combination with DTG and/or DRV. Patients with DTG and/or DRV resistance had a low DSS score reflecting overall high-level baseline drug resistance. Because of limited options, a significant proportion of these patients had these drugs added to their OBR. Baseline resistance to these two drugs did not appear to have a negative impact on efficacy outcomes.

In addition, safety and efficacy of IBA observed at Week 25 were maintained through

Eligible patients, i.e. patients who completed the 25-week *TMB-301 study* and enrolled in US and Puerto Rico, continued to receive IBA at *800 mg every 2 weeks* under study TMB-311 for up to 96 weeks.

Study Design



Baseline Characteristics

TMB-301

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- Median viral load of 35,350 c/mL
  - 18% with viral load ≥ 100,000 c/mL
- Median CD4⁺ cell count of 73 cells/µL
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    - 12 patients with < 10 cells/µL
  - 10 patients with 50-200 cells/µL
  - 13 patients with > 200 cells/µL
- Median OSS of 2
- 17 patients required investigational agent (fostemsavir) in OBR

TMB-311

Patients who rolled over from TMB-301

- N = 27
- Median viral load of 21,700 c/mL
  - 19% with viral load ≥ 100,000 c/mL
- Median CD4⁺ cell count of 102 cells/µL
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    - 5 patients with < 10 cells/µL
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  - 9 patients with > 200 cells/µL
- Median OSS of 2
- 13 patients required investigational agent (fostemsavir) in OBR

Response in DTG Resistance/Susceptible Patients

- 18 patients with DTG resistance
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- 26 patients incorporated DTG in OBR (16 in susceptible; 10 in resistant group)
- 4 of 9 patients who discontinued early were from DTG resistant group

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	DTG no OBR	DTG in OBR	DTG no OBR	DTG in OBR
Median OSS	1.0	1.0	2.0	2.0
>0.5 log_{10} VL reduction – Day 14	88% (7/8)	70% (7/10)	100% (6/6)	82% (13/16)
Median VL reduction - Day 14	1.1 log_{10}	1.0 log_{10}	1.1 log_{10}	1.1 log_{10}
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Median VL reduction - Week 25	0.6 log_{10}	0.0 log_{10}	1.2 log_{10}	2.9 log_{10}
<50 copies/mL - Week 25	38% (3/8)	10% (1/10)	33% (2/6)	69% (11/16)
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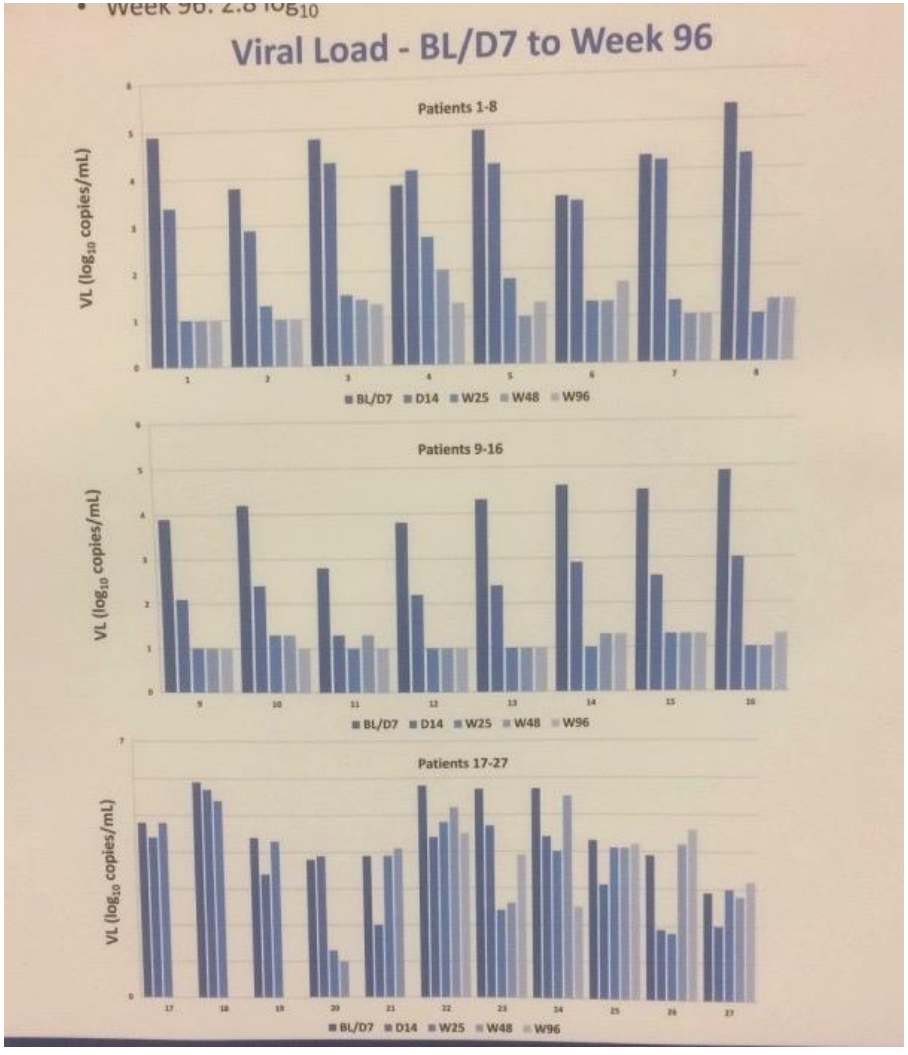
Response in DRV Resistance/Susceptible Patients

- 27 patients with DRV resistance
  - 20 of 27 had major DRV resistant mutations (V32/I47/I50/I54/L76)
- 18 of 27 incorporated DRV(r) in OBR and 15 had daily dose = 600 mg
- 5 of 9 patients who discontinued early were from DRV resistant group

	DRV Resistant		DRV Susceptible	
	DRV no OBR	DRV in OBR	DRV no OBR	DRV in OBR
Median OSS	2.0	1.0	2.0	2.5
>0.5 log_{10} VL reduction – Day 14	78% (7/9)	83% (15/18)	80% (4/5)	88% (7/8)
Median VL reduction - Day 14	0.9 log_{10}	1.4 log_{10}	0.9 log_{10}	1.0 log_{10}
>0.5 log_{10} VL reduction - Week 25	78% (7/9)	61% (11/18)	60% (3/5)	88% (7/8)
Median VL reduction - Week 25	2.8 log_{10}	0.8 log_{10}	0.7 log_{10}	2.4 log_{10}
<50 copies/mL - Week 25	78% (7/9)	28% (5/18)	40% (2/5)	38% (3/8)
<200 copies/mL - Week 25	78% (7/9)	39% (7/18)	60% (3/5)	38% (3/8)

- Week 96: 2.8 log_{10}



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In Silico Simulation Of Long-Acting Tenofovir Alafenamide Subcutaneous Implant

Rajith KR Rajoli[1], Zach Demkovich[2], Ariane van der Straten[2], Charles Flexner[3], Andrew Owen[1], Marco Siccardi[1]

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3- Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, MD, USA

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Introduction

- Tenofovir alafenamide (TAF) is a prodrug of tenofovir with high potency supporting long-acting (LA) administration, providing the delivery challenges can be met.
- Tenofovir (TFV) prodrugs are used first-line for both pre-exposure prophylaxis and therapy, meaning that an LA option would have widespread applicability.
- The aim of this work was to use physiologically-based pharmacokinetic (PBPK) modelling to simulate critical dose and release rate parameters for a subcutaneous implant providing therapeutic TAF exposure for > 6-months.

Methods

- A subcutaneous compartment with a mechanistic modelling approach was integrated to a previously published whole-body PBPK model[1] using Simbiology (MATLAB 2018a) and the drug specific parameters are shown in Table 1.
- TAF subcutaneous implants were simulated in five hundred virtual healthy women with a BMI in the range of 29.2 ± 12.51 kg/m^2.
- PBPK models were initially qualified against available data of TAF oral formulation[2] (GS-US-320-1382) considering international guidelines for PBPK modelling.[3]
- A range of release rates varying from 0.5 mg/day to 0.8 mg/day were simulated and the pharmacokinetic (PK) parameters of TAF and TFV in plasma and concentration of TFV-diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs) were predicted.
- TFV:TAF ratio of 1.39 ± 0.026 and TFV-DP:TFV ratio of 83.6 ± 54.2 were derived from various multiple dose clinical studies.[3,4]
- TFV-DP cervical and rectal tissue concentrations were simulated considering plasma to tissue ratio of 0.031 and 0.02, respectively, as described in various clinical studies.[5,6]

Table 1 Drug specific parameters used in the PBPK model

	Tenofovir alafenamide
Log P	1.6
pKa	3.96
Blood-to-plasma ratio	1.5
Protein binding	80%
Absorption rate	[2]6.24 h^{-1}
Apparent clearance	[2]149 L/h
Oral bioavailability	[2]0.55

Results

- The PBPK model was qualified against available PK data in humans with observed vs. simulated AUC$_{last}$ (ng.h/ml) - 158 vs. 239 (50.7%), C$_{max}$ (ng/ml) - 239 vs. 172 (-28%) and T$_{max}$ (h) - 0.5 vs. 0.6 (20%).
- TAF PK was simulated for 28-days post administration.
- Simulated PK for implants with release rate of 0.6 mg/day and higher resulted in a mean intracellular concentration over TFV-DP target concentrations of 48 fmol/10^6 cells.[9]

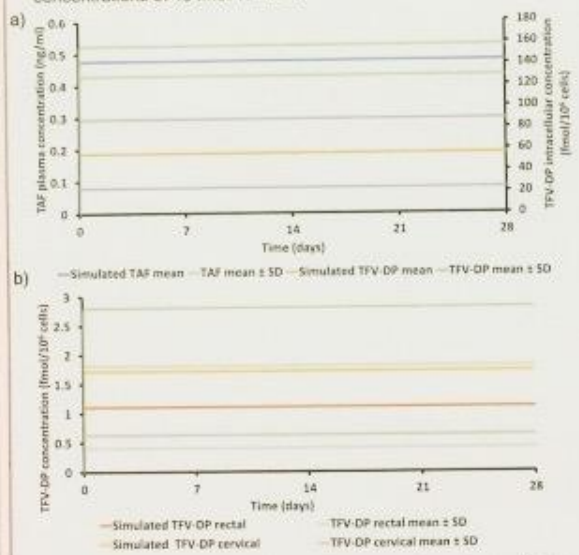

Figure 1 a) TAF, TFV and TFV-DP subcutaneous implant pharmacokinetics; (b) TAF cervical and rectal tissue concentrations at 0.6 mg/day

- The TFV-DP cervical and rectal concentrations ranged between 1.47 - 2.44 fmol/10^6 cells and 0.95 - 1.57 fmol/10^6 cells, respectively, between the release rates of 0.5 - 0.8 mg/day.

Table 2 Simulated pharmacokinetics following subcutaneous implant at various zero-order release rates of TAF

		Simulated	
Release rate	Compound	AUC (ng.h/ml)	C$_{avg}$ (ng/ml)
0.8 mg/day	TAF, plasma	430 ± 41.9	0.64 ± 0.06
	TFV, plasma	598 ± 58.2	0.89 ± 0.09
	TFV-DP, PBMCs[1]	-	79.7 ± 46.1
0.7 mg/day	TAF, plasma	374 ± 37.5	0.56 ± 0.06
	TFV, plasma	520 ± 52.1	0.78 ± 0.08
	TFV-DP, PBMCs[1]	-	70.5 ± 41.1
0.6 mg/day	TAF, plasma	321 ± 32.1	0.48 ± 0.05
	TFV, plasma	446 ± 44.6	0.67 ± 0.07
	TFV-DP, PBMCs[1]	-	58.3 ± 32.6
0.5 mg/day	TAF, plasma	269 ± 27.2	0.40 ± 0.04
	TFV, plasma	374 ± 37.8	0.56 ± 0.06
	TFV-DP, PBMCs[1]	-	47.6 ± 27.2

Values are presented as mean ± standard deviation. AUC is measured for 28 days (672 hours) subsequent to implant administration. [1] Intracellular concentrations represented in fmol/10^6 cells. TAF - tenofovir alafenamide, TFV - tenofovir, TFV-DP - tenofovir diphosphate, PBMCs - peripheral blood mononuclear cells

Table 3 TFV-DP simulated cervical and rectal pharmacokinetics after subcutaneous implant at different zero-order release rates of TAF

	Simulated		
Release rate	TFV-DP PBMCs	TFV-DP cervical	TFV-DP rectal
0.8 mg/day	79.7 ± 46.1	2.44 ± 1.41	1.57 ± 0.91
0.7 mg/day	70.5 ± 41.1	1.92 ± 1.12	1.24 ± 0.72
0.6 mg/day	58.3 ± 32.6	1.72 ± 1.09	1.11 ± 0.70
0.5 mg/day	47.6 ± 27.2	1.47 ± 0.83	0.95 ± 0.53

Values are presented as mean ± standard deviation. TFV-DP concentrations are represented in fmol/10^6 cells. An average ratio of 0.031 and 0.02 for TFV-DP cervical/TFV-DP PBMC and TFV-DP rectal/TFV-DP PBMC was used for the simulation of TFV-DP concentrations in cervical and rectal tissues respectively.

Conclusions

- PBPK model qualification was successfully performed against observed data for oral TAF.[2]
- The presented strategy focused on amount of drug required per day and total dose was assumed to be infinite. Recent efforts have already achieved implants containing up to 190 mg[10] TAF but implant depletion is likely to change shape of the represented PK profile over time.
- These simulations suggest at least 0.6 mg/day is needed to provide average TFV-DP concentrations above the target concentration in PBMCs.
- The predicted lower exposure in cervical and rectal tissues warrants future clinical investigation.

References

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3. EMA PBPK guidelines. 2018.
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9. Gunawardana M et al. AAC. 2015; 59(7):3913-9.
10. Erica B S et al. CROI 2016, abstract #879.

Sous-type CRF 02

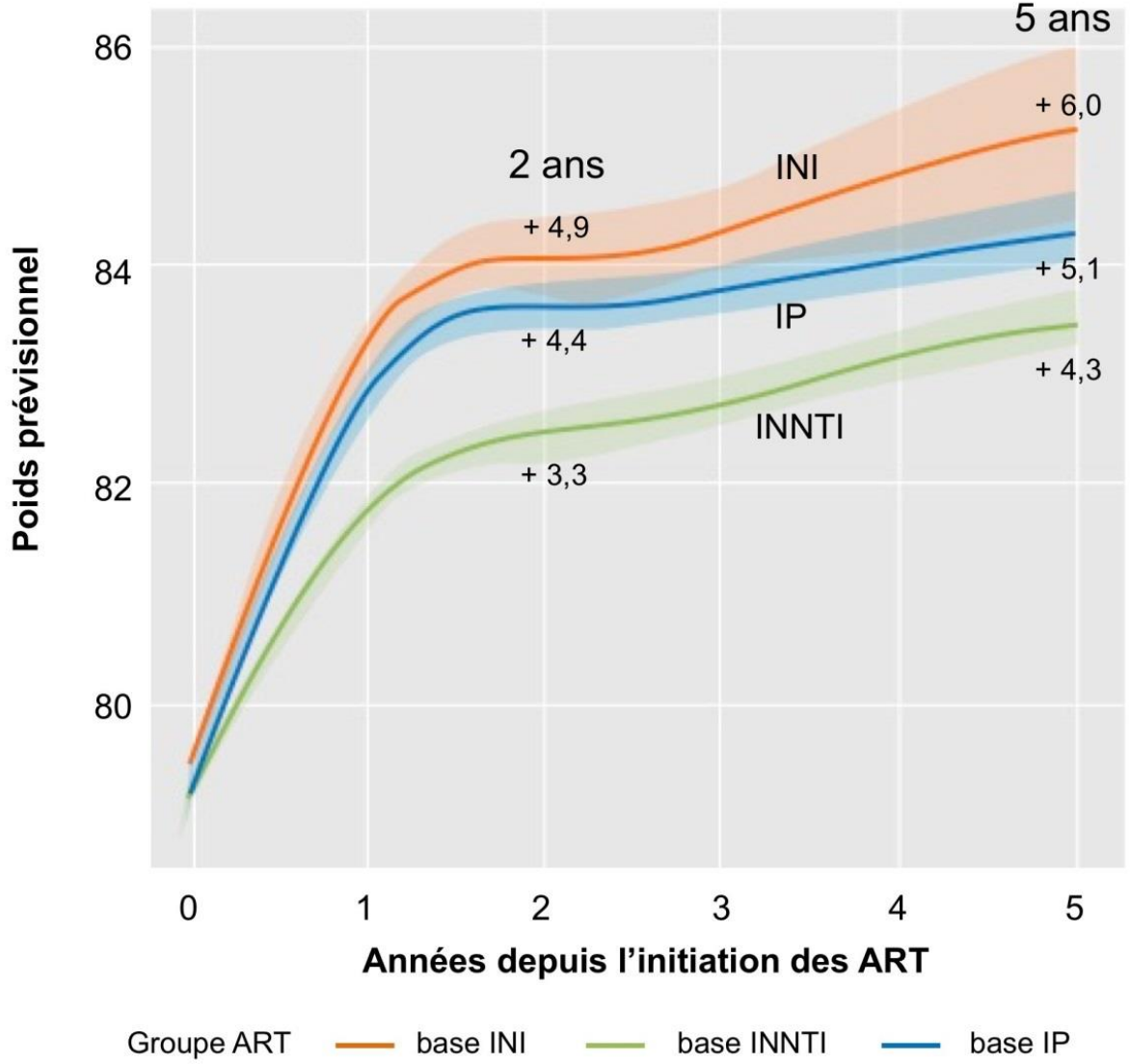
Données démographiques et immunovirologiques en fonction du sous-type viral

	Total	Sous-type B	CRF02_AG	URFs	Autres sous-types	p
n (%)	1 121 (100)	628 (56)	222 (20)	64 (6)	207 (18)	
Âge (années) – médiane (IQR)	36 (28-45)	36 (28-44)	37 (30-48)	35 (28-44)	36 (28-47)	0,105
Hommes, n (%)	1 009 (90)	604 (96)	182 (82)	54 (84)	169 (82)	< 0,001
Pays de naissance, n (%)						< 0,001
France	790 (70)	472 (75)	148 (67)	46 (72)	124 (60)	
Autres pays européens	37 (3)	21 (3)	5 (2)	4 (6)	7 (3)	
Afrique sub-saharienne	74 (7)	8 (1)	32 (14)	3 (5)	31 (15)	
Autre/inconnu	220 (20)	127 (20)	37 (17)	11 (17)	45 (22)	
Voie de transmission, n (%)						< 0,001
HSH	788 (70)	492 (78)	130 (59)	46 (72)	120 (58)	
HTS	199 (18)	55 (9)	65 (29)	12 (19)	67 (32)	
IDU	5 (0)	3 (0)	1 (0)	1 (2)	0 (0)	
Autre/inconnu	129 (12)	78 (12)	26 (12)	5 (8)	20 (10)	
Région du diagnostic, n (%)						< 0,001
Région parisienne	476 (42)	242 (39)	105 (47)	41 (64)	88 (43)	
Autres régions	645 (58)	386 (61)	117 (53)	23 (36)	119 (57)	
Année du diagnostic, n (%)						0,164
2014	355 (100)	221 (62)	62 (17)	18 (5)	54 (15)	
2015	381 (100)	204 (54)	75 (20)	24 (6)	78 (20)	
2016	385 (100)	203 (53)	85 (22)	22 (6)	75 (19)	
CV (log_{10} copies/ml), médiane (IQR)	5,51 (4,71-6,46)	5,40 (4,66-6,26)	5,83 (4,96-6,60)	5,45 (4,68-6,73)	5,65 (4,76-6,56)	0,004
CD4 (cellules/mm^3), moyenne (IC_{95})	478 (329-636)	495 (340-650)	437 (294-591)	491 (307-590)	459 (334-650)	0,040

CROI 2019 - D'après Visseaux B et al., abstr. 867, actualisé

Anti-intégrases et prise de poids

Poids par groupe d'antirétroviraux



CROI 2019 - D'après Bourgi K et al., P670, actualisé

Gain de poids - patients naïfs

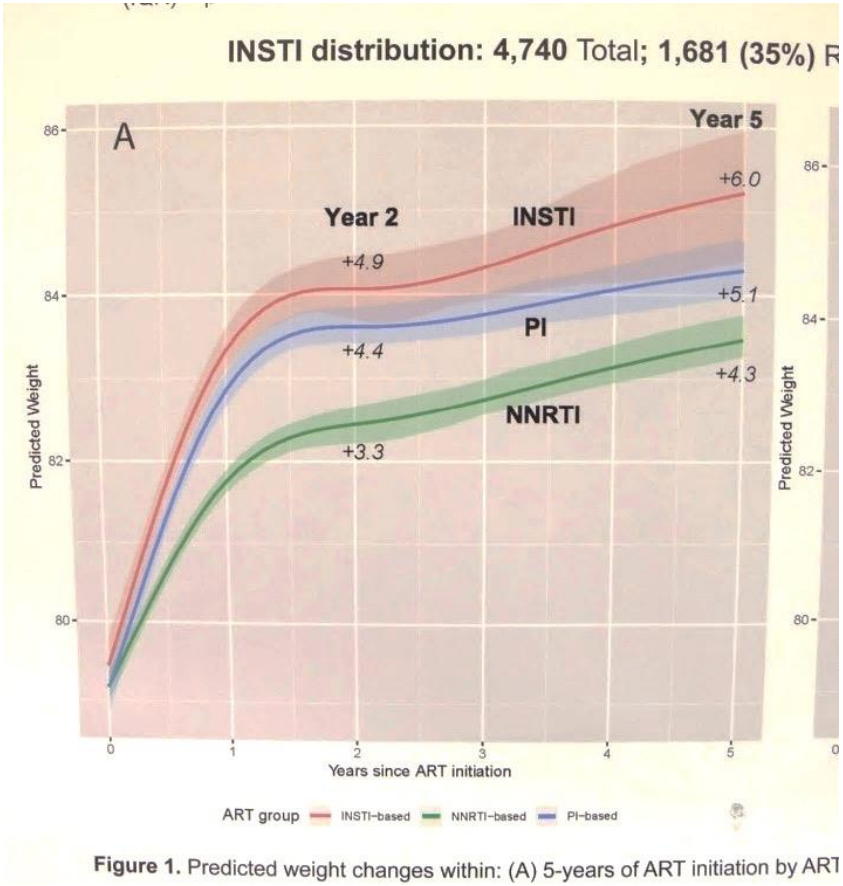
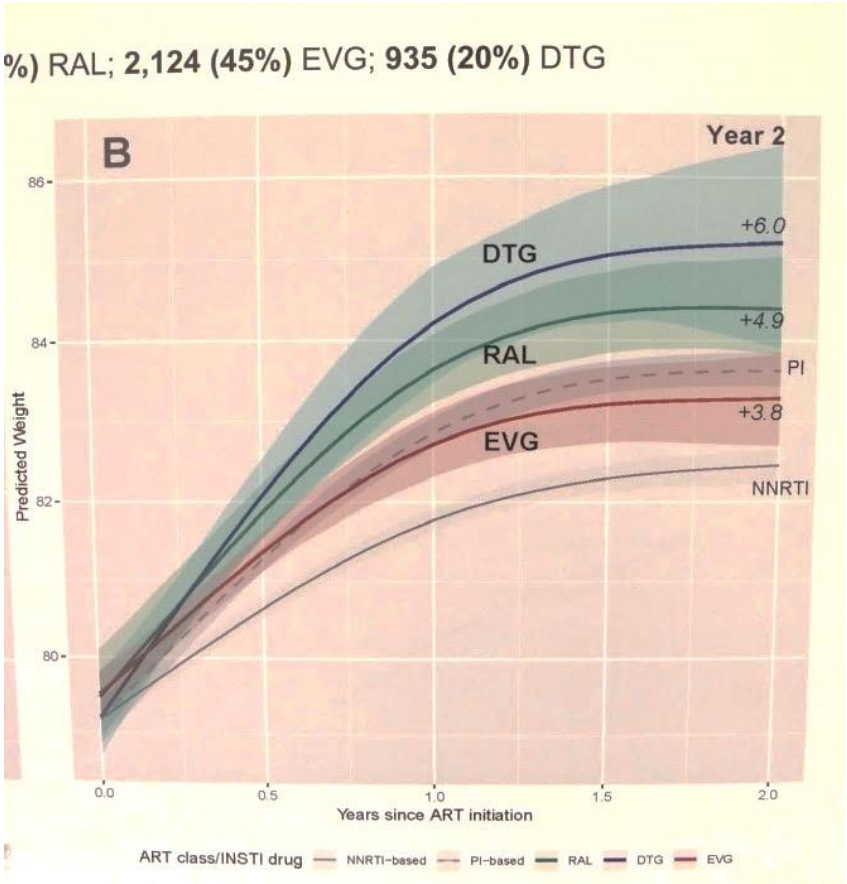


Figure 1. Predicted weight changes within: (A) 5-years of ART initiation by ART



Gain de poids - patients naïfs

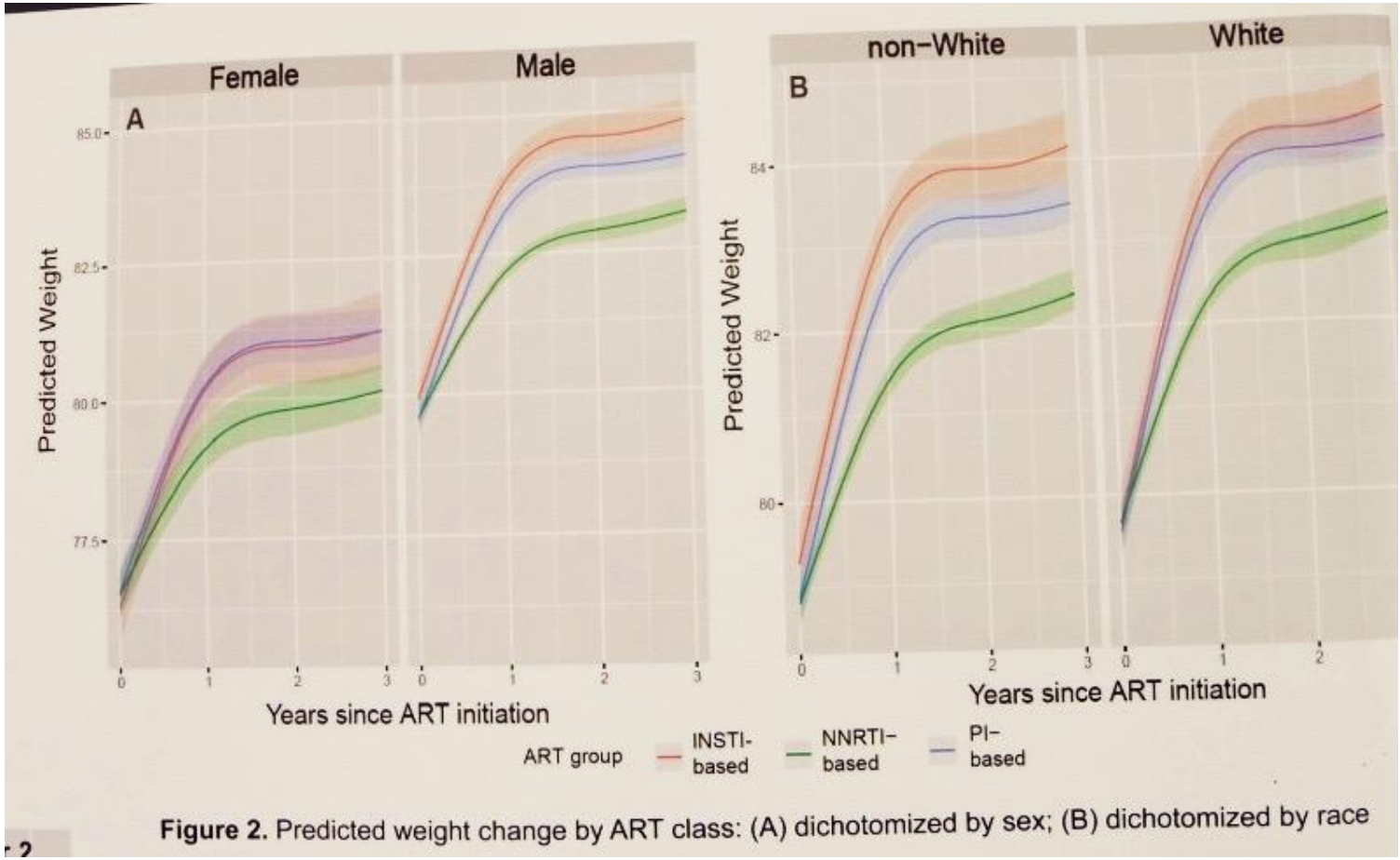


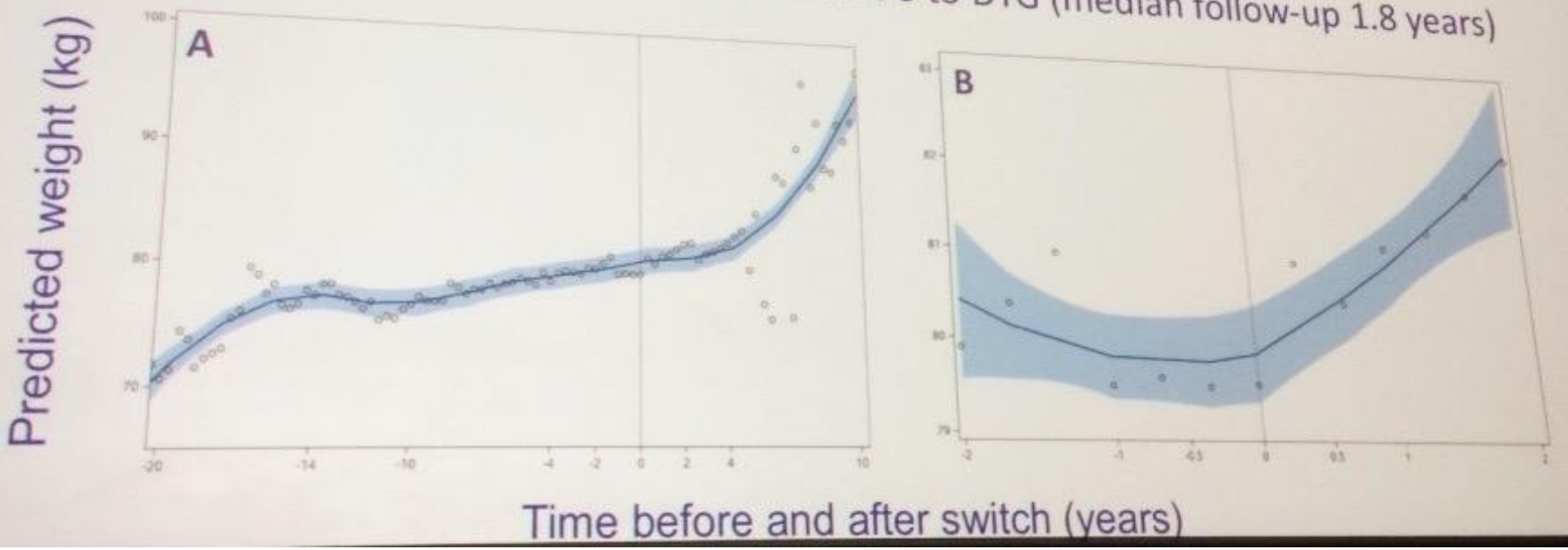
Figure 2. Predicted weight change by ART class: (A) dichotomized by sex; (B) dichotomized by race

Switch InSTIs: prise de poids

Results I

972 adults switched to INSTI at median 7.8 years after parent trial entry. 691 had suppressed HIV-1 RNA at time of switch:

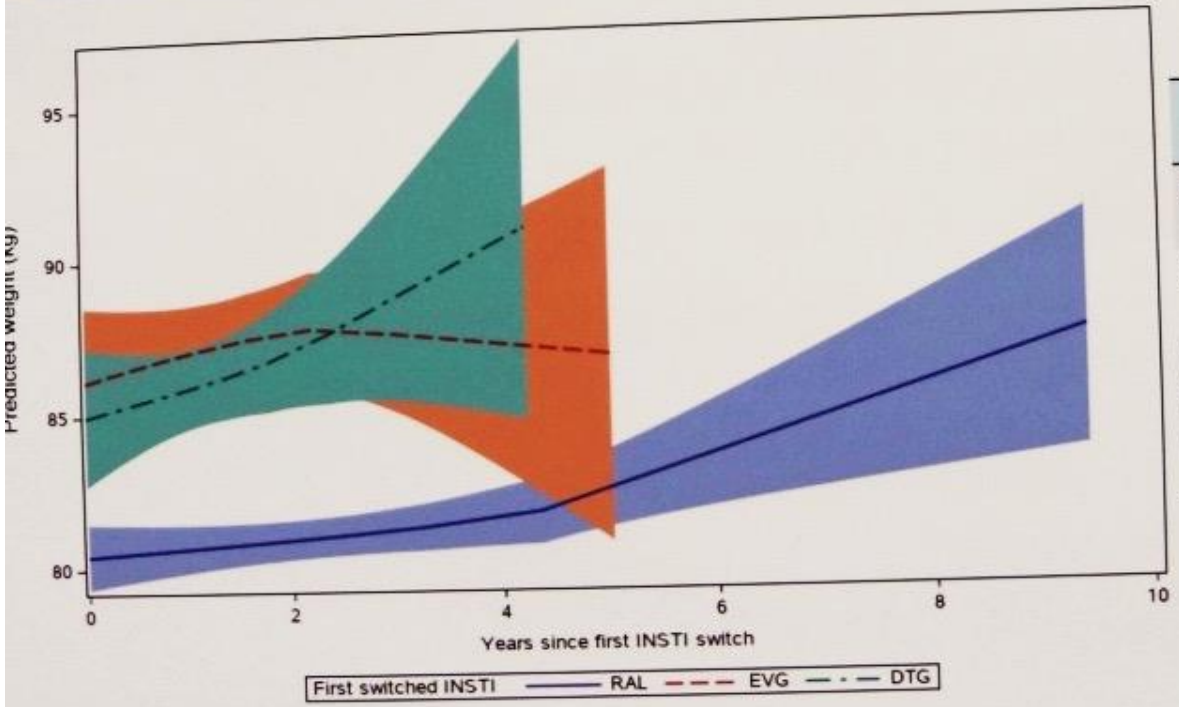
- -82% male, 45% non-white
- -Median age 51 years, $CD4^+$ T cell count 610 cells/µL, and BMI 26 kg/m^2
- -63% switched from PI, 35% from NNRTI
- -289 switched to RAL, 204 to EVG and 198 to DTG (median follow-up 1.8 years)



.669

Switch InSTIs: prise de poids

Figure 2: Weight gain pre-/post-switch to INSTI by agent

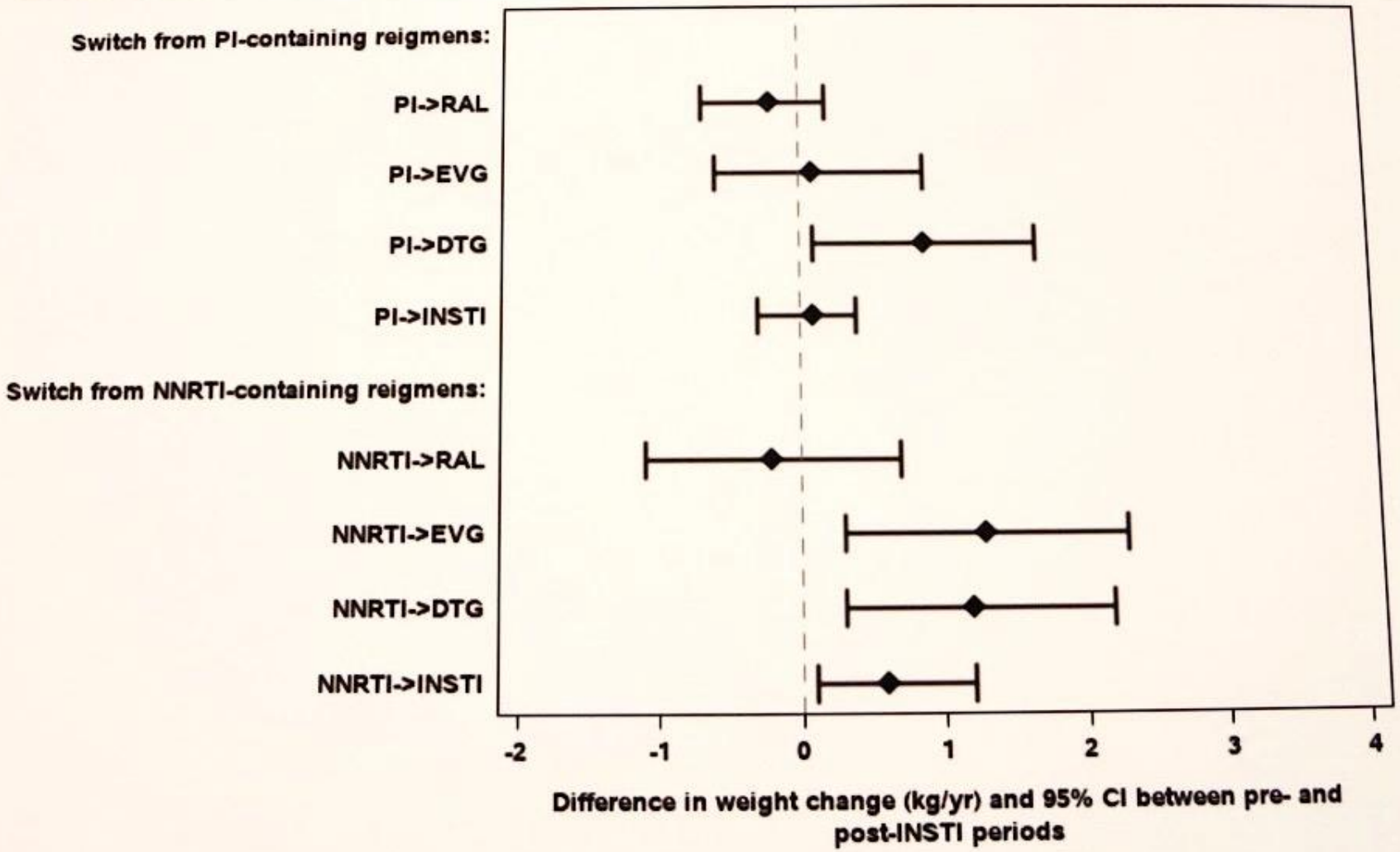


	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2 (0.11)	0.5 (0.008)	0.5 (<0.0001)
Post-INSTI	1.3 (<0.0001)	0.9 (<0.0001)	0.3 (0.045)
Pre-post difference	1.0 (0.0009)	0.5 (0.11)	-0.2 (0.37)

kg/year (p value)
DTG=dolutegravir, EVG=elvitegravir, RAL=raltegravir

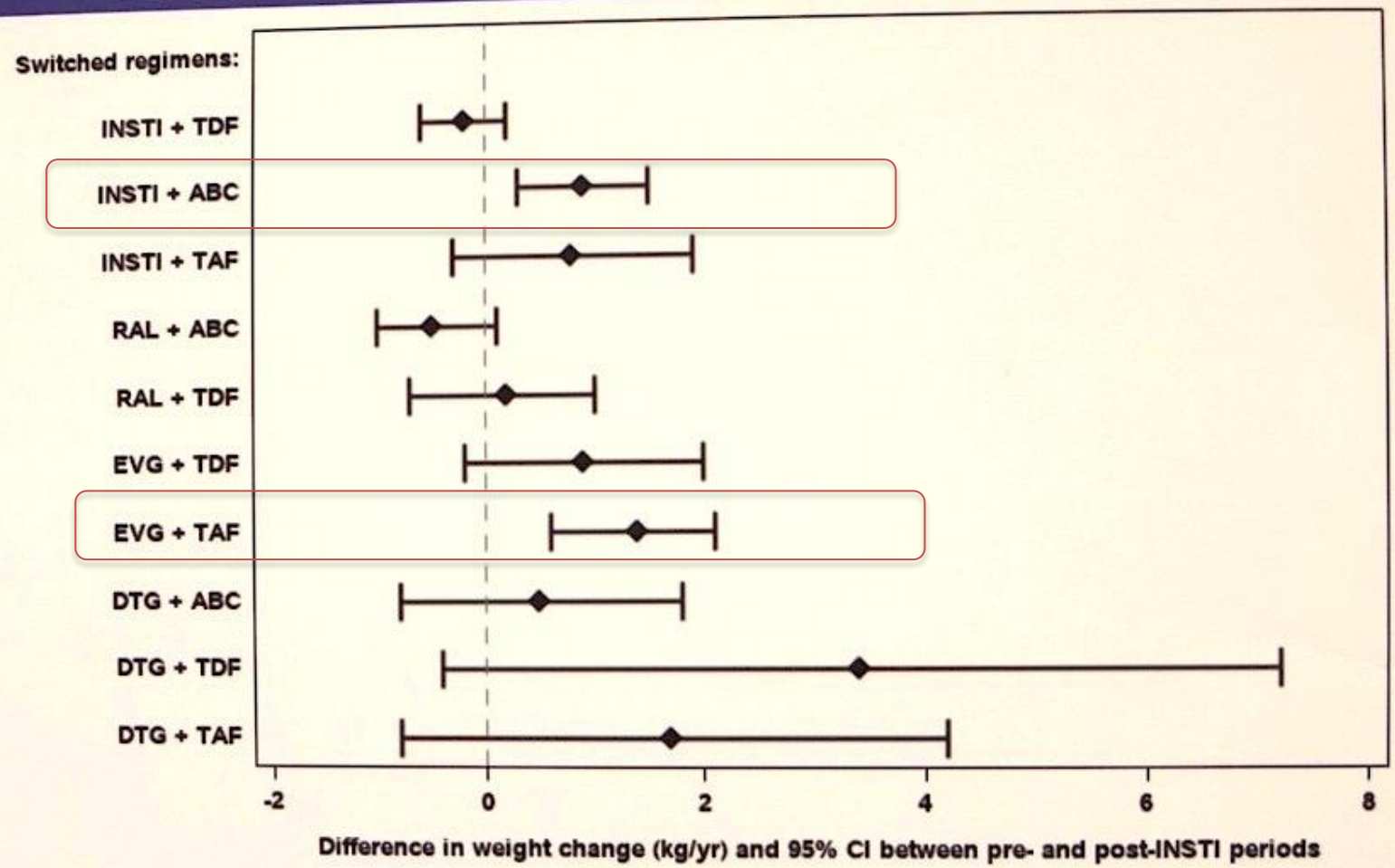
,669

Figure 3: Annual weight gain by pre-switch ART class



- Switch to DTG from PI or NNRTI, and switch to EVG from NNRTI statistically significant ($p<0.05$), though subset analyses limited by sample size.

Figure 4: Annual weight gain by NRTI backbone at switch



Switch to any INSTI with ABC and switch to EVG with TAF statistically significant ($p<0.05$), though subset analyses limited by sample size.

61% of ABC, 87% TDF, 4% of TAF use at switch to INSTI had same NRTI backbone pre-switch

Switch / gain de poids

Figure 1. Multivariable linear mixed model (MVLMM)-estimated BMI by ART regimen type among participants who switched ART regimen (N = 653).

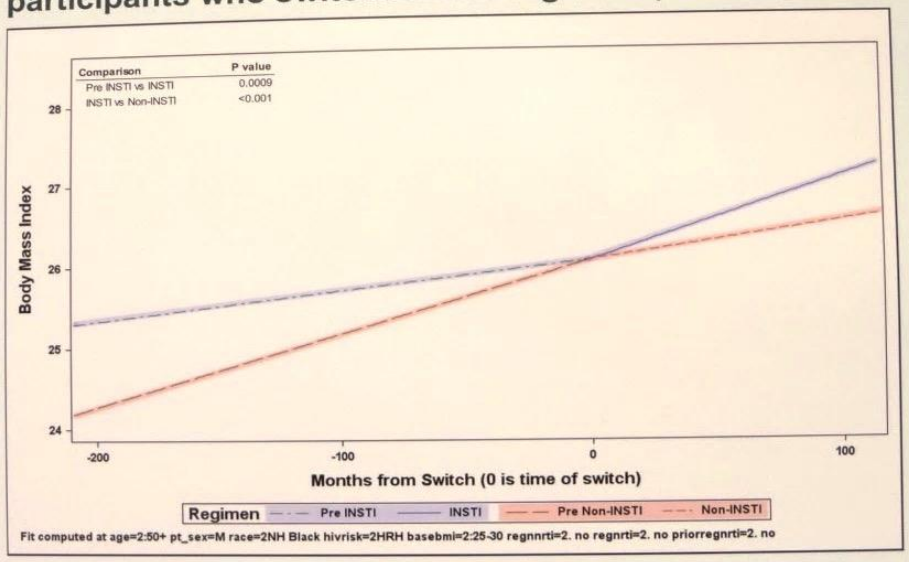
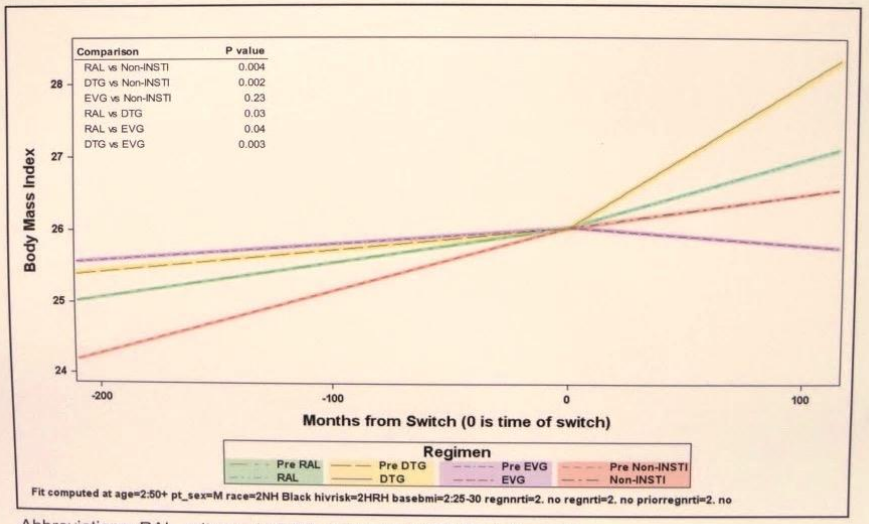


Figure 2. Multivariable linear mixed model (MVLMM)-estimated BMI by INSTI regimen type among participants who switched ART regimen (N=653).

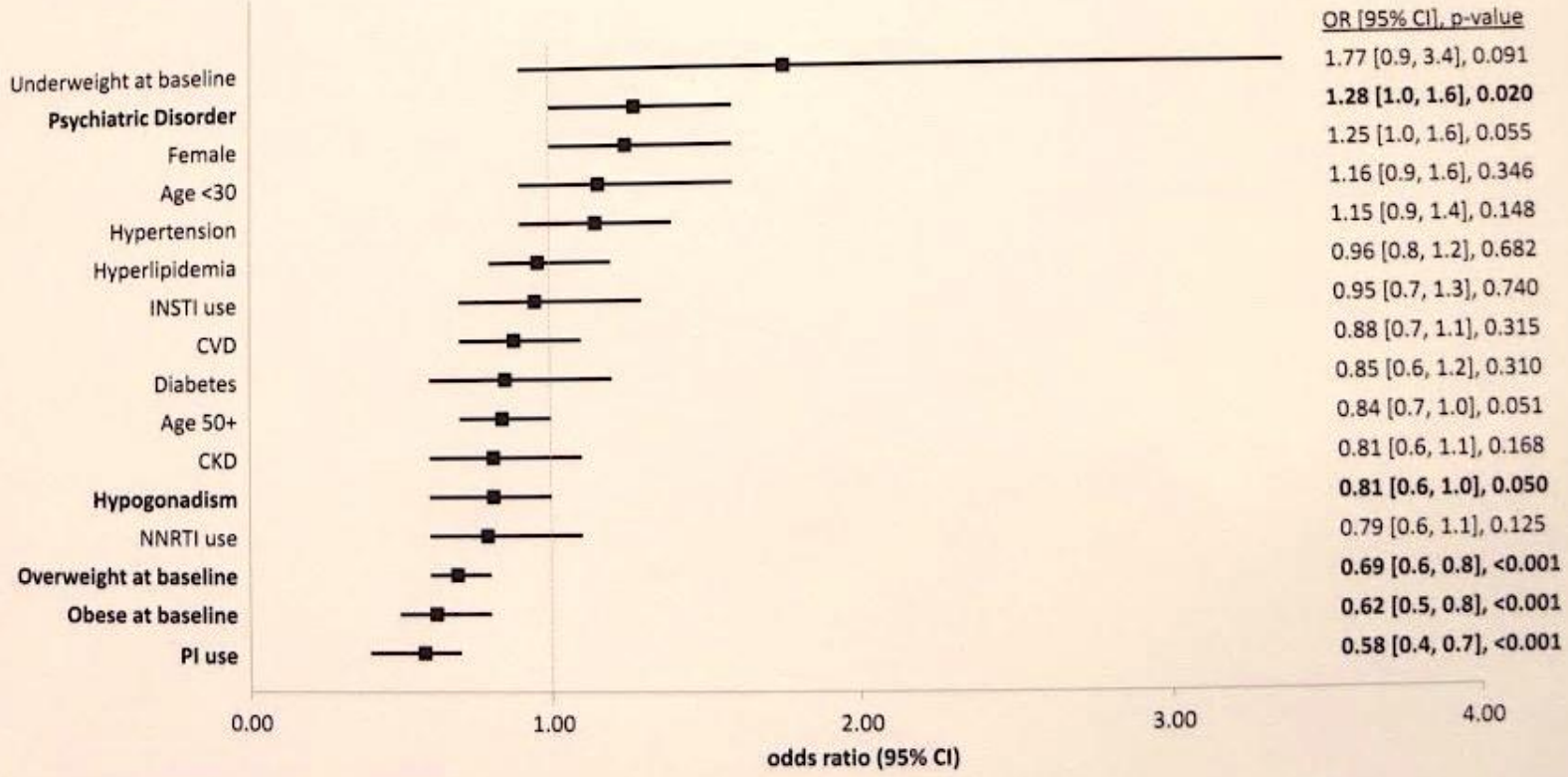


Abbreviations: RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir.

F Palella Jr, 674

7. MULTIVARIATE ANALYSIS OF WEIGHT GAIN ≥3%

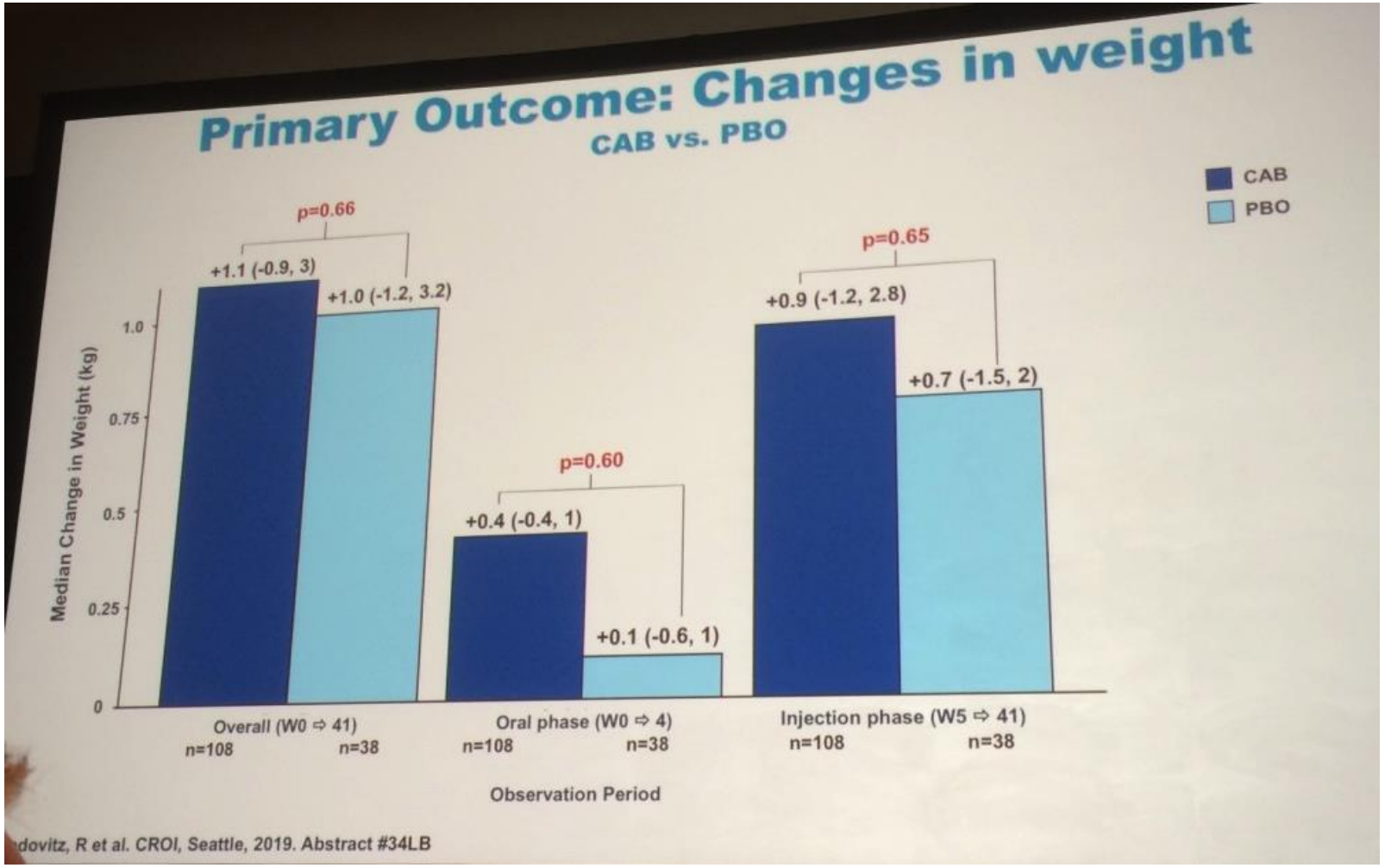
Factors identified as negatively associated with weight gain ≥3% via logistic regression* were overweight or obese at baseline, hypogonadism, and use of PI-containing therapies. Psychiatric disorders were positively associated with weight gain via logistic regression. INSTI-containing ART was not significantly associated with weight gain ≥3% in the logistic regression. Significant variables are shown in bold.



*Binary multivariable logistic Regression with "Weight Gain ≥3%" as the dependent variable.
OR=odds ratio; CI=confidence interval. Significant variables in bold. Reference category for age was 30-50. Reference category for baseline BMI was normal.

G Mc Comsey, 671

CAB vs Pbo chez sujet sain



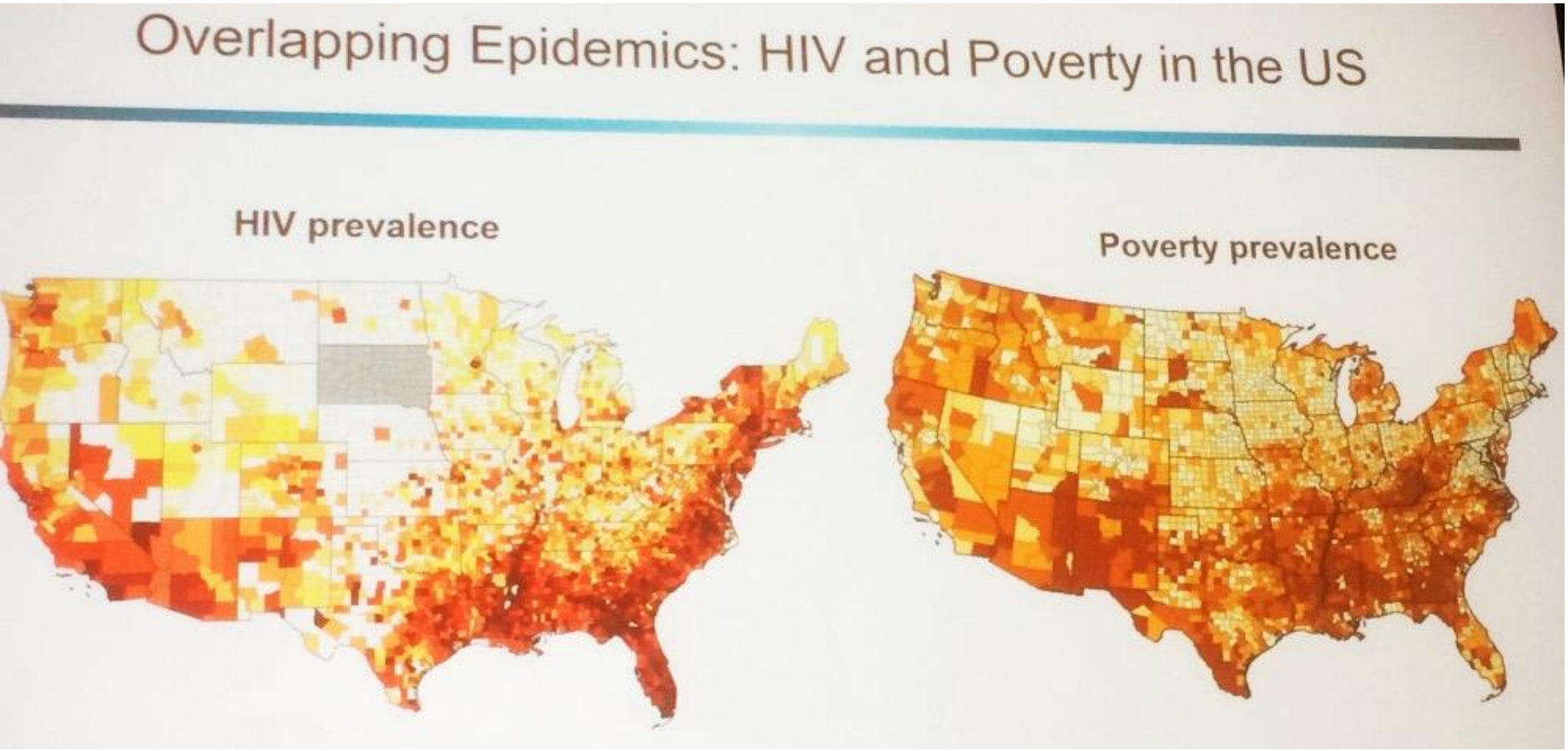
Landovitz, 34LB

Overlapping Epidemics: HIV and Obesity in the US

HIV prevalence

Obesity prevalence

Overlapping Epidemics: HIV and Poverty in the US



Contributors to Body Weight: HIV, ART, and Environment

Antiretrovirals & HIV
- Inflammation
- Microbial translocation
- Energy absorption
- Lipid trafficking
- Adipose tissue distribution

Diet
- Food preferences
- Food insecurity
- Access to healthy foods (food deserts)

Activity
- Regular exercise
- Opportunities for physical activity
- Safety, walkability

Environment
Sociocultural knowledge, Economic resources
Attitudes, beliefs, & practices regarding diet, nutrition, exercise
Conceptions of 'health'

Host
- Race/ethnicity
- Gender
- Family history
- Comorbidities
- Other medications

Habits
- Smoking
- Alcohol
- Drugs

Mental Health
- Depression
- Stress
- Stigma

ACTG 5257: Greater Weight and Waist Circumference Gains with RAL vs. DRV/r or ATV/r

1,809 ART-naïve randomized to TDF/FTC with ATV/r, DRV/r, or RAL

Average weight +3.8 kg over 96 weeks

21% severe (>10%) weight gain, higher odds with RAL

Average waist circumference +3.4cm over 96 weeks, higher odds with RAL

Greater WC increases on RAL in female and black patients

Factors associated with severe (>10%) weight gain over 96 weeks

Factor	Adjusted Odds Ratio	95% CI	p-value
ATV/r vs RAL	0.72	(0.53 to 0.99)	p=0.04
DRV/r vs. RAL	0.73	(0.53 to 0.99)	p=0.04
Black (non-Hispanic)	1.55	(1.10 to 2.20)	p=0.01
Baseline log10 HIV-RNA	2.52	(2.00 to 3.16)	p<0.0001
Baseline CD4 count (100 cells/ul)	0.78	(1.18 to 1.39)	p<0.0001

Bhagwat P, et al. CROI 2017; Oral #695. Bhagwat P, et al. OFID 2018

SCOLTA Cohort (Italy): Weight Gain - A Possible Side Effect of All Antiretrovirals?

BMI increases in all participants switching to new regimens (primarily due to PI failure)

Higher age, lower BMI, and lower CD4 were associated with greater weight gain

Weight gain on INSTIs was not significantly different from darunavir or rilpivirine

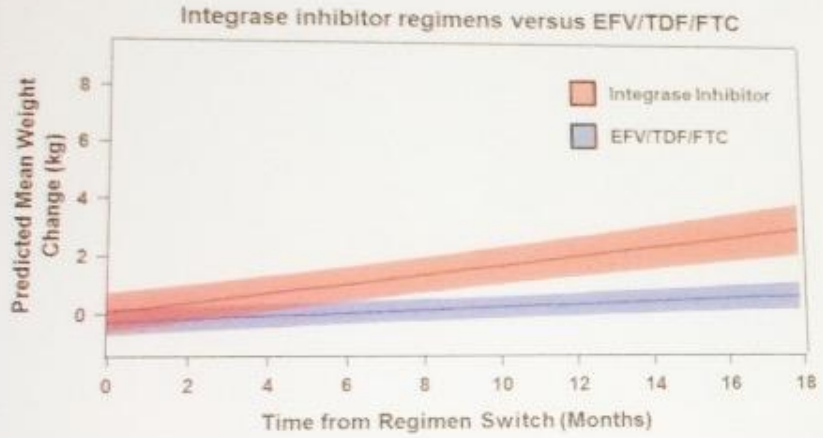
BMI change in 1118 Patients Switched to INSTI vs. Darunavir or Rilpivirine

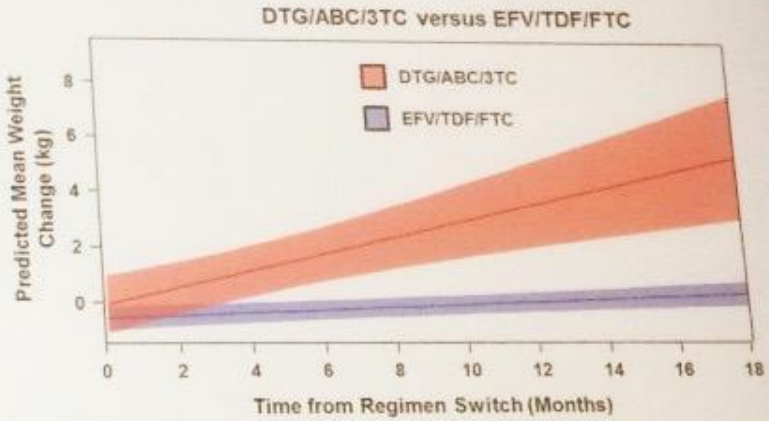
Time from Switch	Switch to INSTI			Switch to non-INSTI	
	Dolutegravir N=225	Raltegravir N=382	Elvitegravir N=148	Darunavir N=145	Rilpivirine N=218
6 months	0.28 ± 0.10	0.26 ± 0.08	0.42 ± 0.11	0.35 ± 0.11	0.30 ± 0.11
	p=0.006	p=0.001	p<0.001	p=0.001	p=0.005
12 months	0.37 ± 0.13	0.36 ± 0.10	0.42 ± 0.15	0.48 ± 0.14	0.30 ± 0.14
	p=0.004	p<0.001	p=0.004	p<0.001	p=0.03

- Cohort characteristics: median age 46 years, 72% male, 19% with CD4 <200 cells/ul
- Adjusted for sex, age, CD4+, detectable viral load, CDC stage, duration of ART, lipodystrophy, and BMI at entry

Taramasso L. *et al. Open Forum Inf. Dis*, 2017

Southeastern US: Weight Gain in PLWH Switched from Efavirenz to INSTI-based Regimens





Retrospective, single-site study (n=495)

Adults on EFV/TDF/FTC with viral suppression for 2 years switched to an INSTI vs. continued on EFV/TDF/FTC

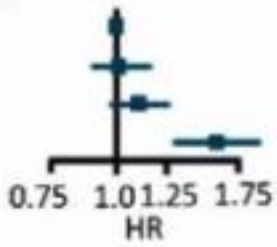
Weight gain highest among those switching to Doultegravir with ABC/3TC

Norwood J. *et al. JAIDS*. 2017

Increased SCD Risk With HIV Associated With Low CD4+ Cell Counts and High HIV-1 RNA Levels

Adjusted Risk of SCD by HIV status and Time-Updated CD4+ Cell Count

Group	Person-Yrs	SCD Events	HR (95% CI)
HIV-Uninfected	808, 587	2259	1.00
HIV+, CD4: 500+	139, 200	306	1.03 (0.90-1.18)
HIV+, CD4: (200, 500)	127, 817	318	1.11 (0.97-1.28)
HIV+, CD4: < 200	44, 389	153	1.57 (1.29-1.92)



Adjusted Risk of SCD by HIV status and Time-Updated Viral Load

Group	Person-Yrs	SCD Events	HR (95% CI)
HIV-Uninfected	808, 587	2259	1.00
HIV+, VL: < 500	219, 893	480	0.98 (0.87-1.09)
HIV+, VL: 500+	91, 513	297	1.70 (1.46-1.98)

SCD Risk Factor Among Veterans With HIV	HR (95% CI)
Age, 10 yrs	1.38 (1.27-1.50)
Male sex	2.04 (1.08-3.84)
Prevalent CVD	1.88 (1.58-2.23)
Controlled HTN	1.45 (1.20-1.76)
Current vs never-smoker	1.62 (1.28-2.06)
HCV infection	1.40 (1.19-1.66)
BMI, 5 kg/m^2	1.10 (1.02-1.20)
Anemia (Hb 12-13.9 vs 14 g/dL)	1.35 (1.14-1.59)
Alcohol misuse or dependence	1.43 (1.17-1.74)
COPD	1.24 (1.02-1.50)

Freiberg. CROI 2018. Abs 32.

HIV Post Mortem Sudden Cardiac Death in San Francisco County

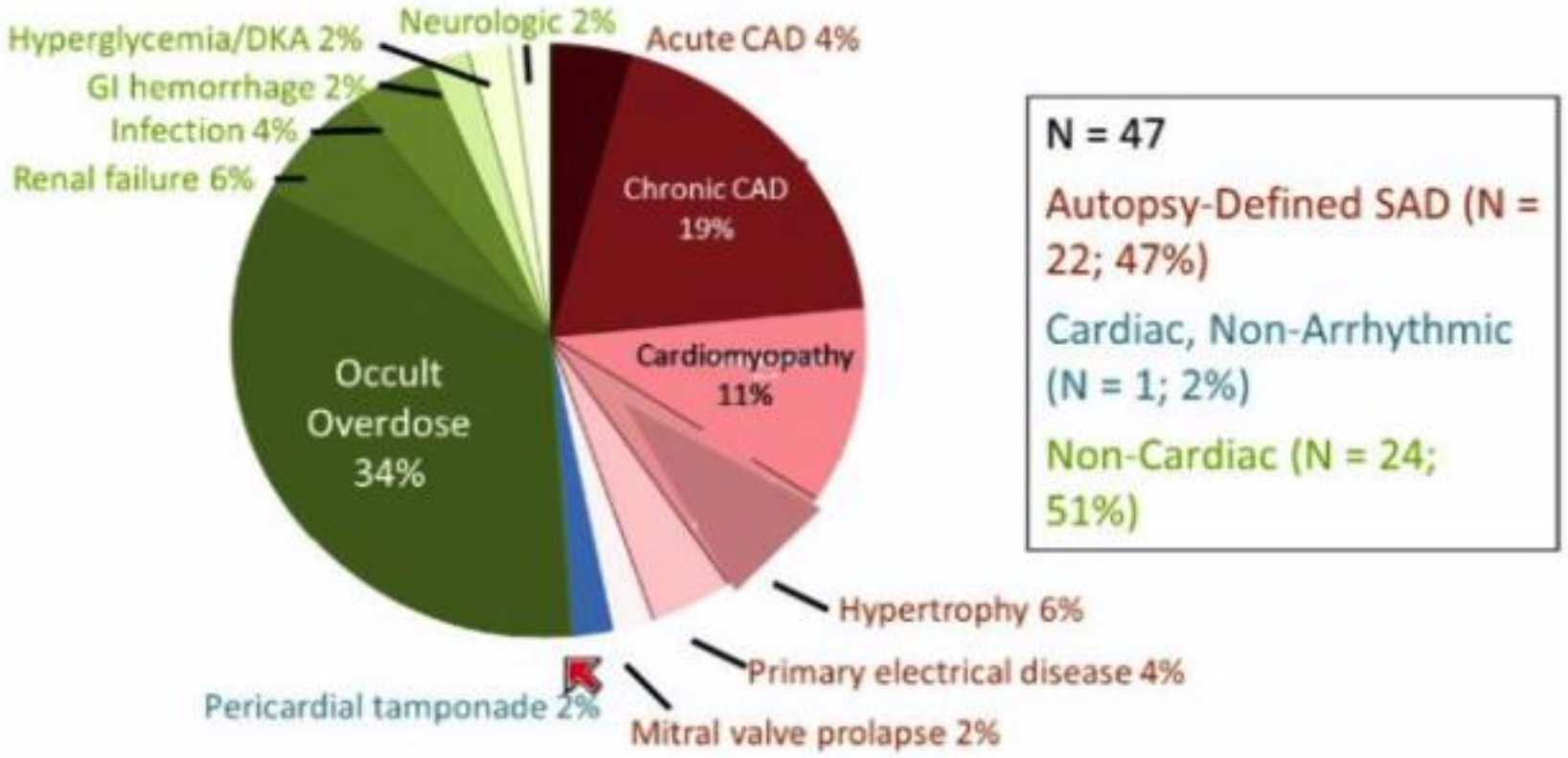
- Countywide prospective medical examiner surveillance of out-of-hospital cardiac arrest deaths 2/1/2011 to 9/21/2016
  - Each adjudicated for WHO-defined (presumed) SCD (past medical history, medications, EMS runsheets and rhythms, witness/family interviews)
  - Each presumed SCD adjudicated for sudden arrhythmic death (SAD, by autopsy, chemistries, toxicology, histology)
  - HIV out-of-hospital cardiac arrest deaths presumed SCD: N = 47; non-HIV SCDs: N = 505

Outcome	Total	Male	Female	Black	Hispanic	White
Presumed SCD IRR for HIV+ vs HIV- (95% CI)	1.86 (1.39-2.50) P < .0005	1.38 (1.02-1.88) P = .04	2.31 (0.74-7.21) P = .15	1.05 (0.53-2.09) P = .89	0.81 (0.20-3.33) P = .77	2.00 (1.42-2.82) P < .0005
SAD IRR for HIV+ vs HIV- (95% CI)	1.58 (1.02-2.43) P = .039	1.16 (0.75-1.79) P = .51	N/A	1.01 (0.36-2.83) P = .76	N/A	1.75 (1.08-2.85) P = .023

One Third of Apparent SCDs Among Persons Living With HIV the Result of Occult Overdose

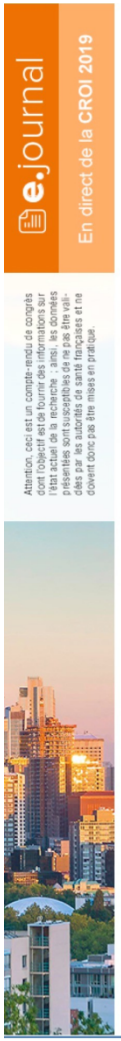
- Occult overdose rate 34% among HIV+ SCD cases vs 13% among HIV- SCD cases ($P < .0001$)

Adjudicated Etiologies of Autopsied HIV+ Presumed SCD

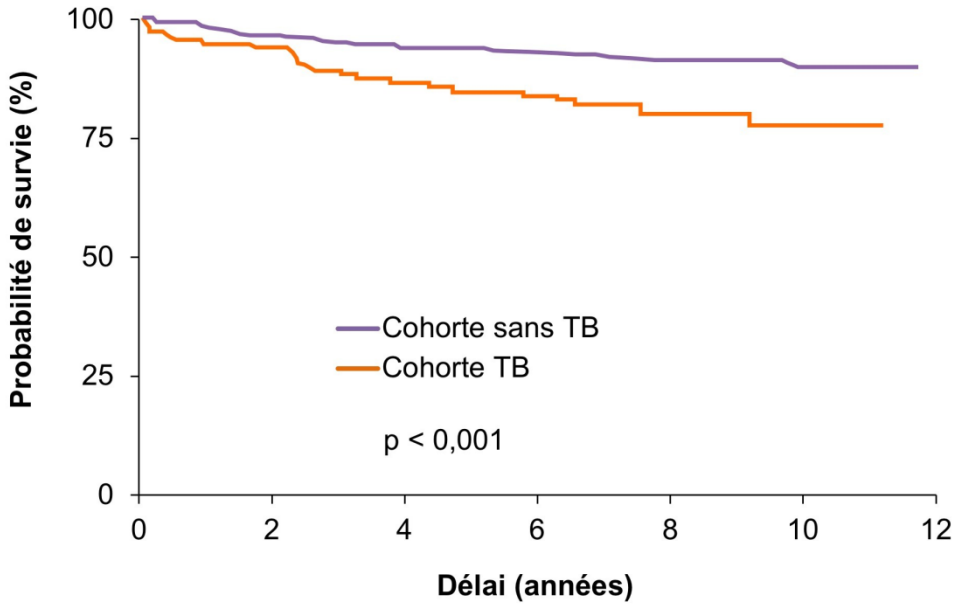


Tseng, CROI 2019, Abstr 33.

VIH-TB: Devenir après Tt TB



Résultats – Analyse de survie



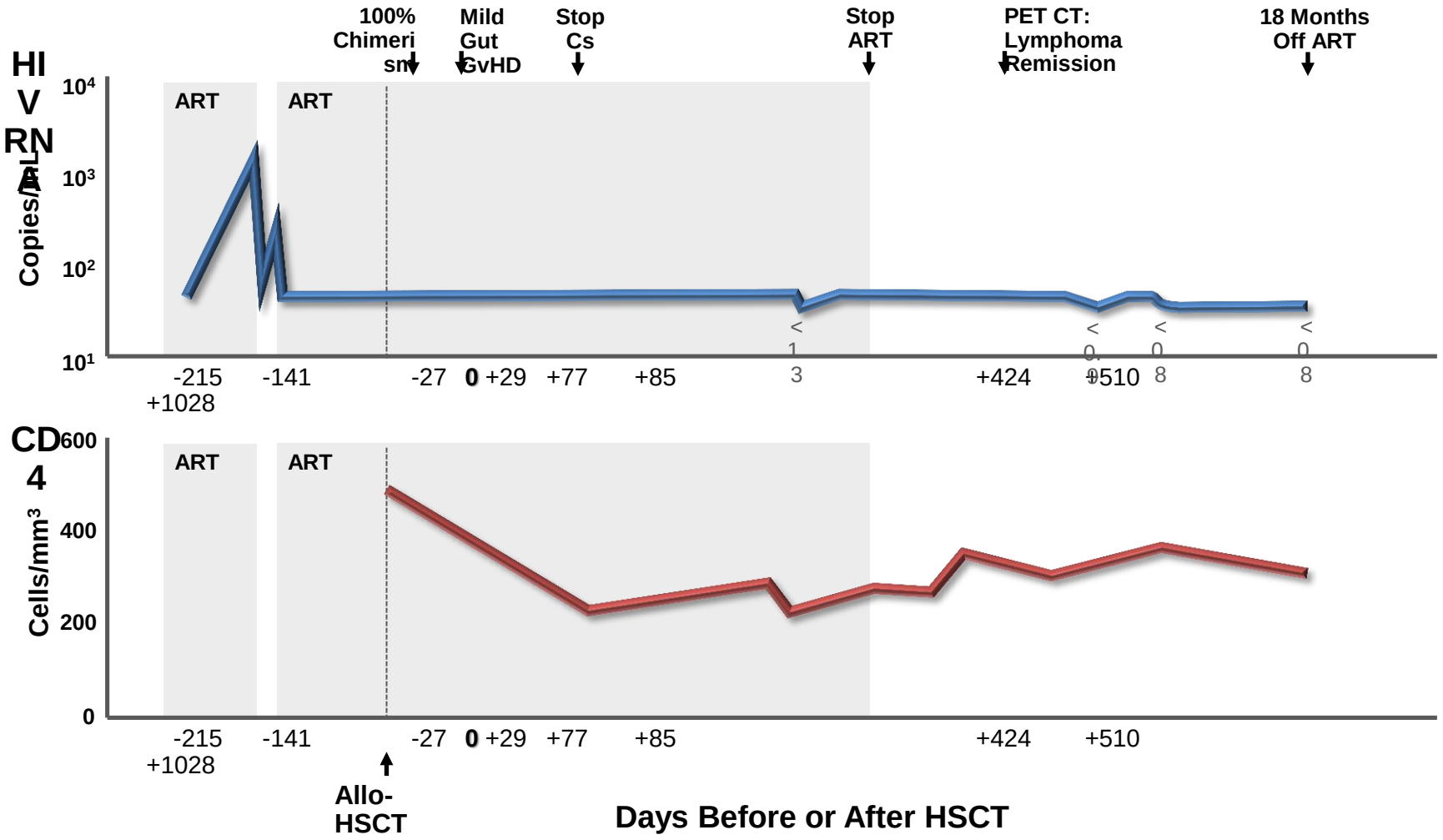
Patients à risque							
Cohorte sans TB	574	511	465	420	373	185	0
Cohorte TB	134	116	94	79	51	24	0

Note : délai "0 est 8 mois après le diagnostic de TB (cohorte TB) et 8 mois après l'inclusion (cohorte sans TB)

CROI 2019 - D'après Joseph Y et al., abstr. 83, actualisé

Latence/cure

Sustained HIV Remission Following Homozygous CCR5 Delta32 Allogeneic HSCT

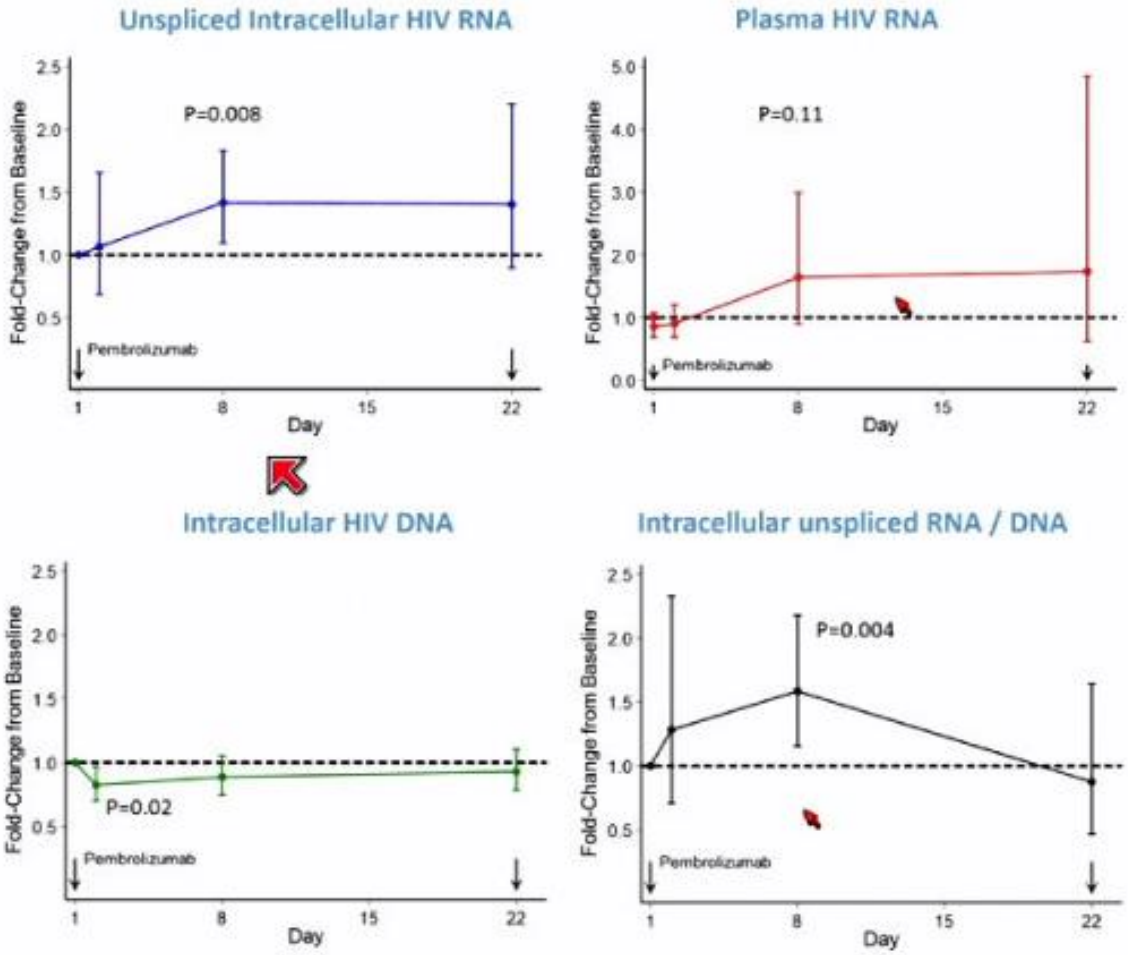


HvGD: host versus graft disease; Cs: cyclosporine

Gupta RK, et al. *Nature*. 2019;Mar 5. [Epub ahead of print]; Gupta RK, et al. 26th CROI. Seattle, 2019. Abstract 29LB.

Pembrolizumab – Anti-PD-1 mAb Reverses HIV Latency

- 32 patients with advanced cancer
- 11 AIDS-defining and 25 non-AIDS defining cancers
- Not on chemotherapy
- 28/32 with VL<20
- Evaluations on Days 1, 2, 8, and 22



Uldrick TS, et al. CROI 2019. Abs. 27.

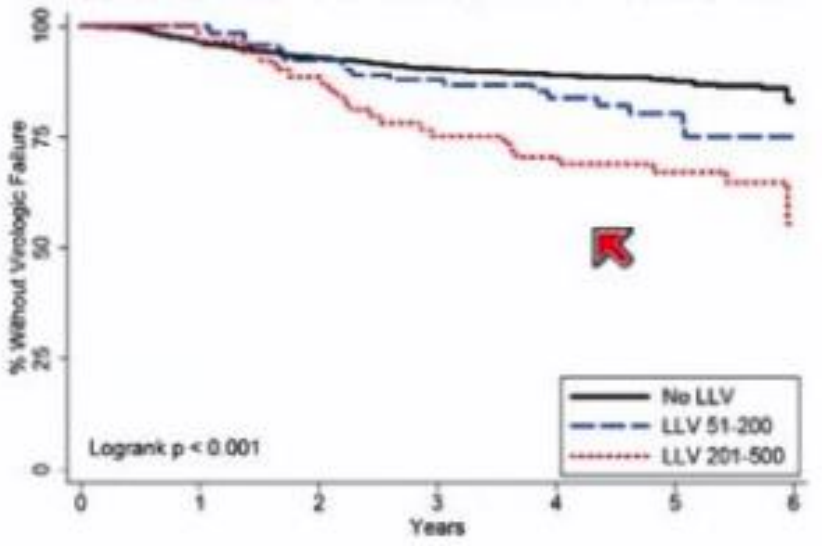
Low Level Viremia and the Latent Reservoir

Clonal populations of T cells contribute to low level viremia[1]

- 10 patients with persistent low level viremia evaluated by single genome sequencing of HIV RNA, cell associated DNA, and viral outgrowth assays. Clonality assessed by phylogenetics and integration site analysis
- 9/10 had multiple single genome HIV RNA sequences that didn't change over time
- 6/9 had matched proviral sequences

- Relationship between blips and low level viremia and virologic failure evaluated in HIV Research Network
- Data from 2795 patients included from 14 sites, 2005-2015

Rates of Virologic Failure by Low Level Viremia[2]



1. Halvas EK, et al. CROI 2019. Abs. 23. 2. Fleming J, et al. CROI 2019. Abs. 497.

Activité antivirale élevée d’une nouvelle race d’anticorps neutralisants à large spectre

D'après Pegu A et al., abstr. 28LB, actualisé

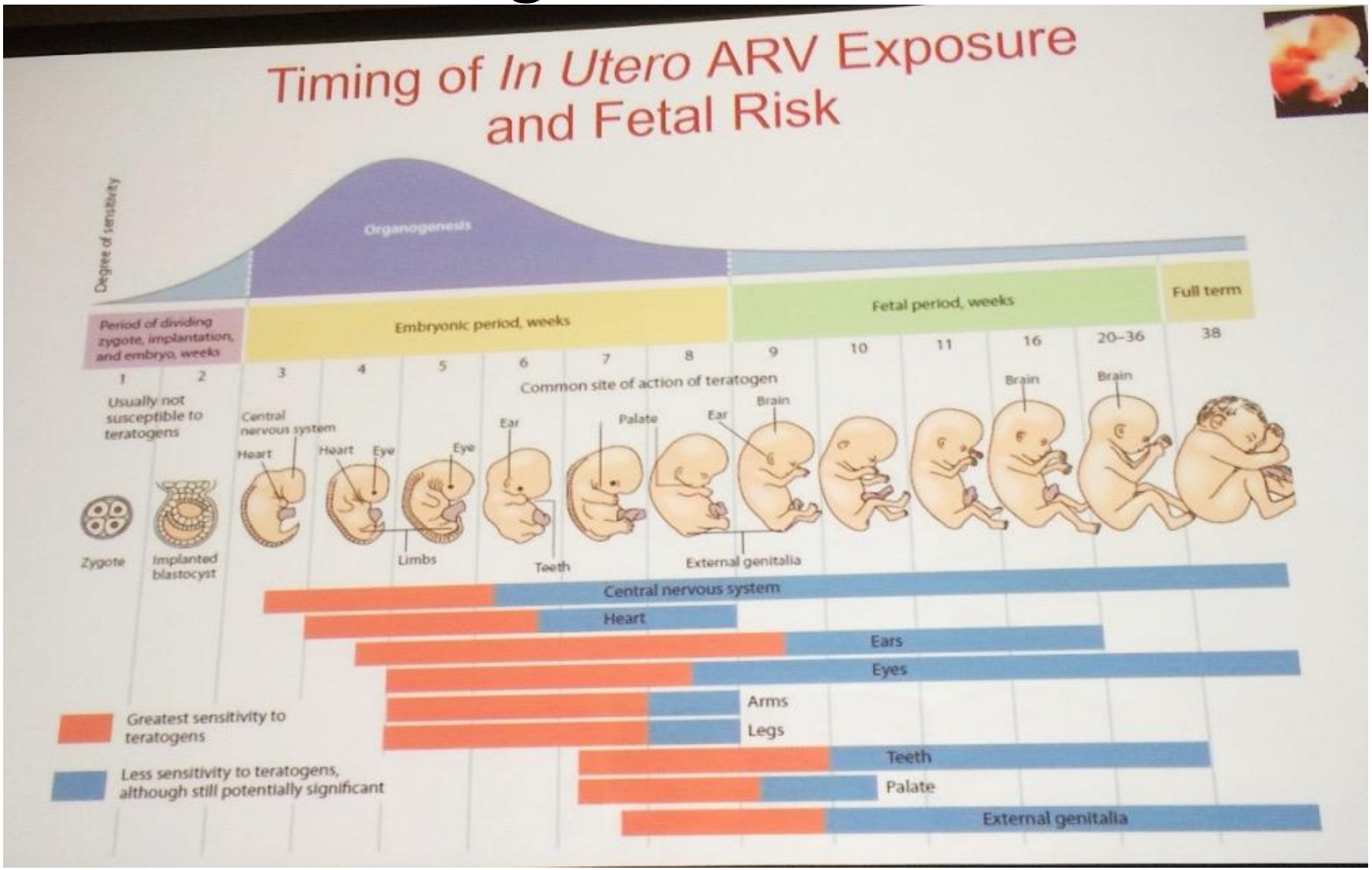
Les **anticorps neutralisants à large spectre** (bnAbs)ont démontré une activité importante et complémentaire des antirétroviraux. Mais, en raison de leur nature monospécifique, l’utilisation d’un seul bnAb conduit à une sélection rapide de résistance chez la plupart des patients infectés par le VIH-1.

Il est donc recommandé d’utiliser une combinaison de 2 ou plus de bnAbs pour maintenir une inhibition durable de la réplication virale. Pour pallier ce défaut, les anticorps trispécifiques (Abs) permettent à une seule molécule d'interagir avec trois déterminants indépendants de l'enveloppe du VIH-1 :

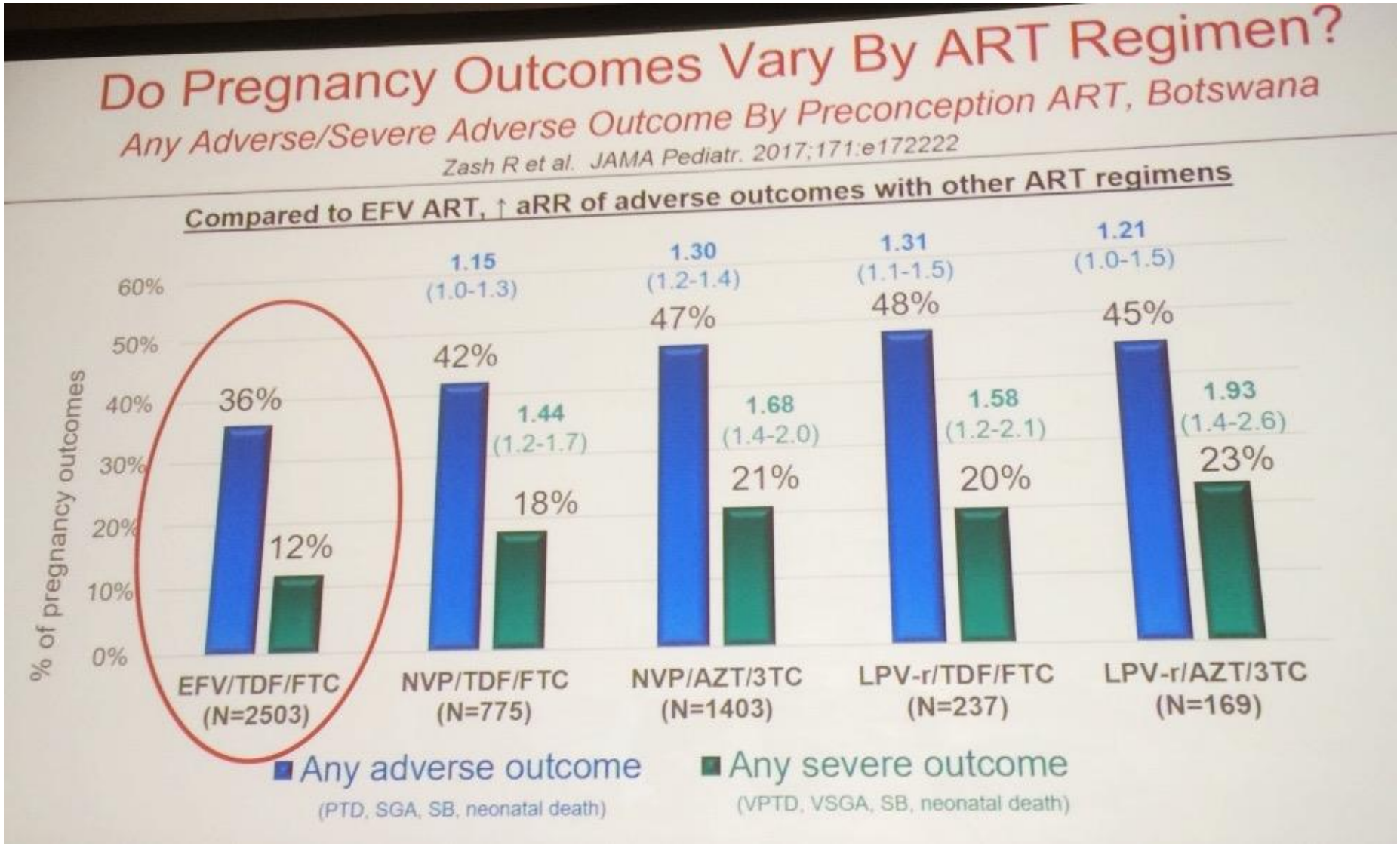
- le site de liaison au CD4,
- la région externe proximale de la membrane (MPER),
- le site glycan V1V2

ARV / Grossesse

Risque tératogène au cours de la grossesse

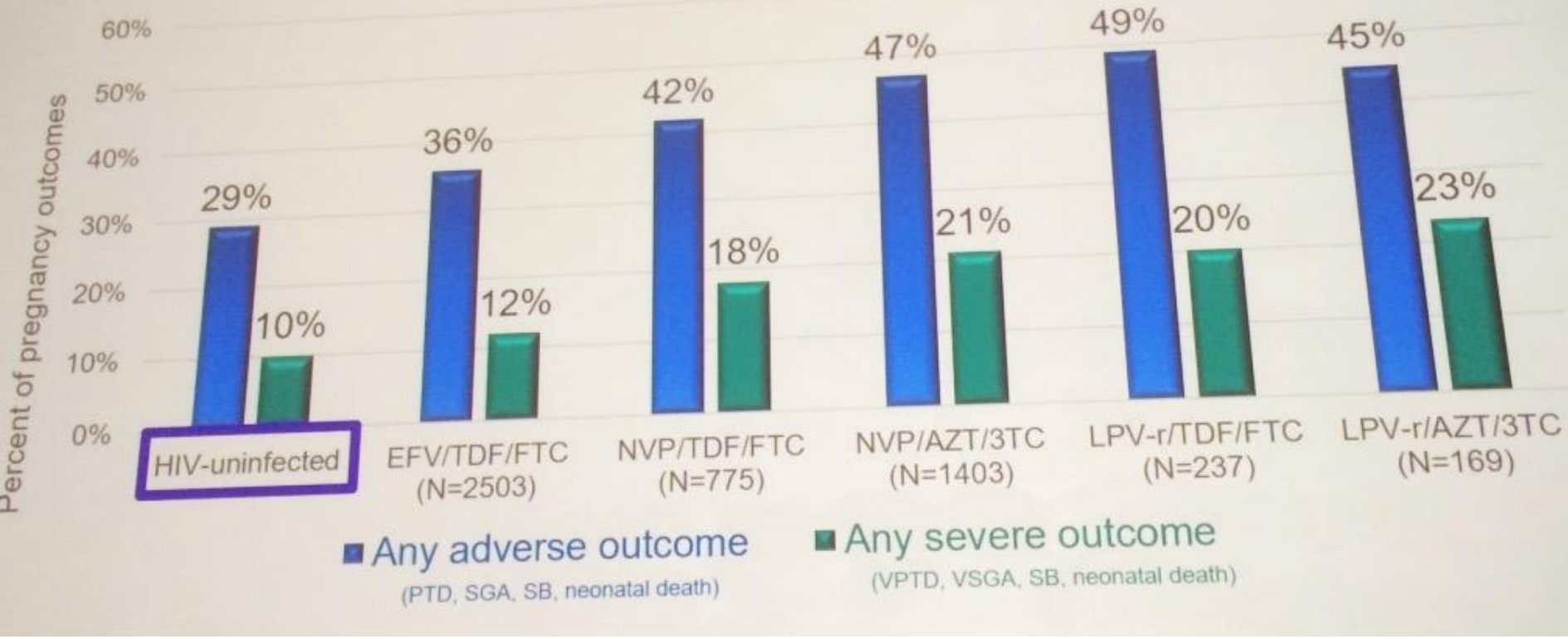


Pregnancy outcome , Botswana



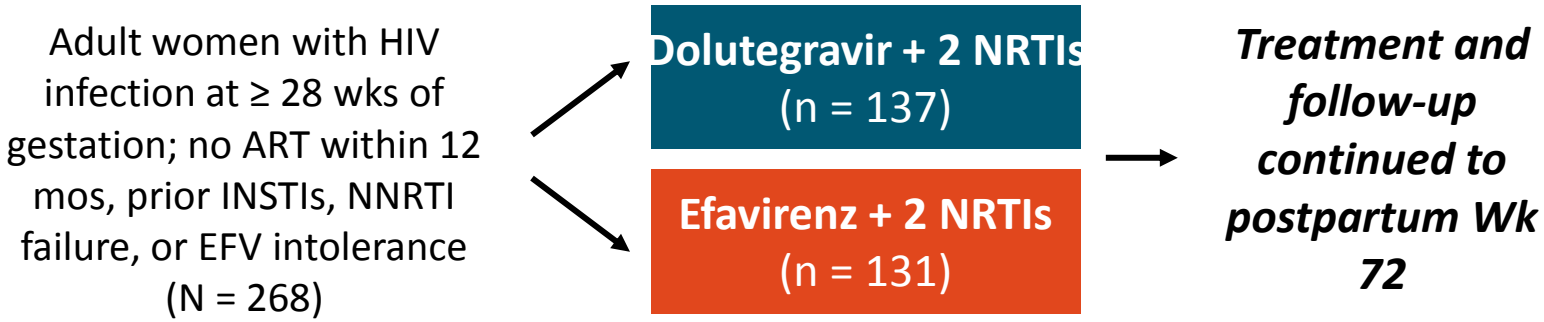
Regardless of ART Regimen, Pregnancy Outcomes Were Worse in HIV+ Women On ART than HIV-Uninfected Women

Zash R et al. JAMA Pediatr. 2017;171:e172222aa



DolPHIN-2: Study Design

- Randomized, open-label, active-controlled phase III trial



- Primary endpoint: HIV-1 RNA < 50 copies/mL at delivery
- Secondary endpoints: HIV-1 RNA < 1000 copies/mL at delivery, MTCT, maternal and infant safety

Kintu. CROI 2019. Abstr 40LB. NCT03249181.

Slide credit: clinicaloptions.com

DolPHIN-2: Baseline Characteristics

Characteristic in ITT Population	DTG-Based ART (n = 126)	EFV-Based ART (n = 123)	Overall (N = 249)
Median age, yrs (IQR)	28 (24-32)	27 (24-30)	28 (24-31)
Median estimated gestation, wks (IQR)	31 (29-34)	31 (29-33)	31 (29-34)
Median gravidity, n (IQR)	3 (2-4)	3 (2-4)	3 (2-4)
Median previous live births, n (range)	2 (0-9)	2 (0-6)	2 (0-9)
Primigravida, n (%)	16 (12.7)	14 (11.4)	30 (12.0)
Previous stillbirth, n (%)	2 (1.6)	2 (1.6)	4 (1.6)
Other medications, n (%)			
▪ Herbal/traditional medicine	41 (32.5)	45 (36.6)	86 (34.5)
▪ Supplements and vitamins	48 (38.1)	46 (37.4)	94 (37.8)
▪ Other comedications	32 (25.4)	36 (29.3)	68 (27.3)
Median CD4+ cell count, cells/mm^3 (IQR)	463 (327-660)	414 (268-575)	446 (295-633)
Median HIV-1 RNA, log$_{10}$ (IQR)	4.4 (3.6-4.7)	4.4 (3.9-4.8)	4.5 (3.8-4.8)

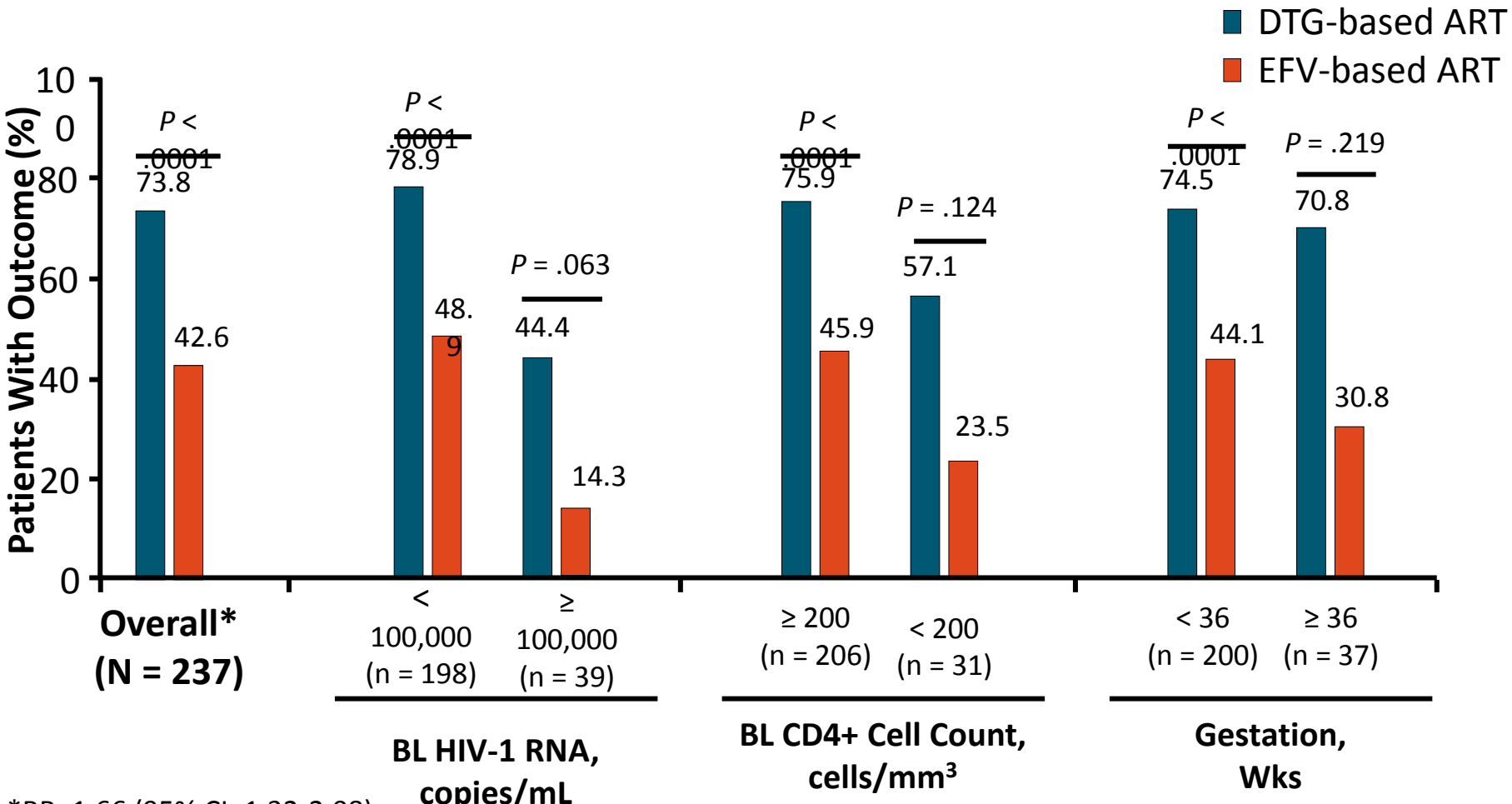
No significant differences in alcohol use (19.7%), maternal smoking (5.6%), psychiatric disorders (4.5%), or maternal weight (70 kg) between arms.

Kintu. CROI 2019. Abstr 40LB.

Slide credit: clinicaloptions.com

DolPHIN-2: Virologic Suppression

HIV-1 RNA < 50 Copies/mL at Delivery in Evaluable ITT Patients



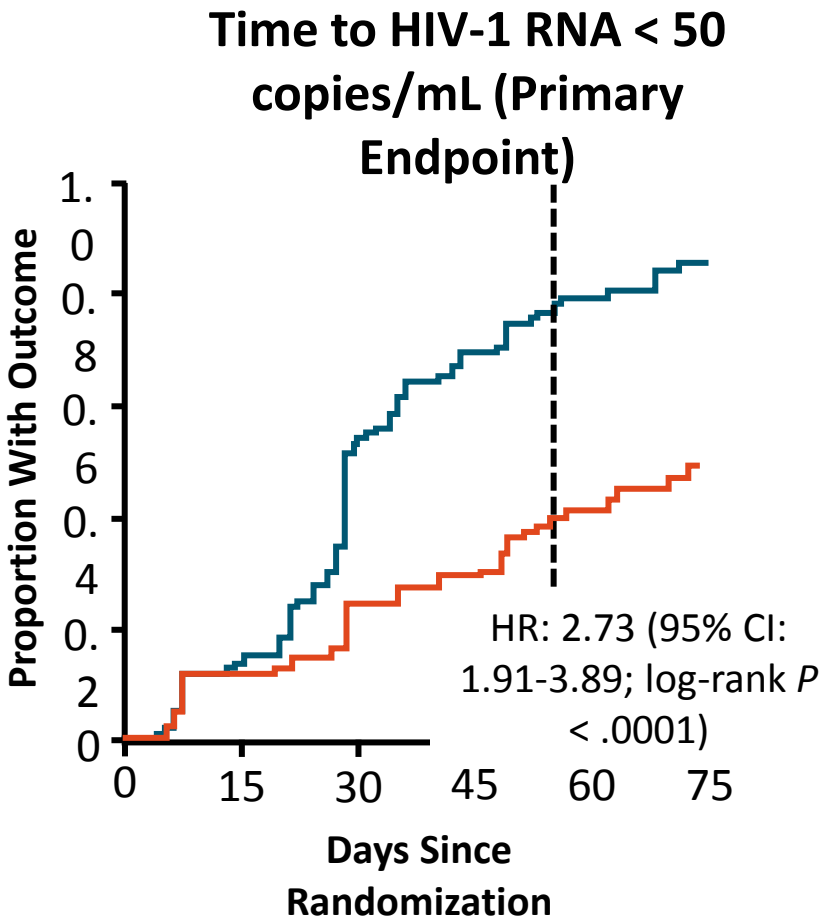
*RR: 1.66 (95% CI: 1.32-2.08).

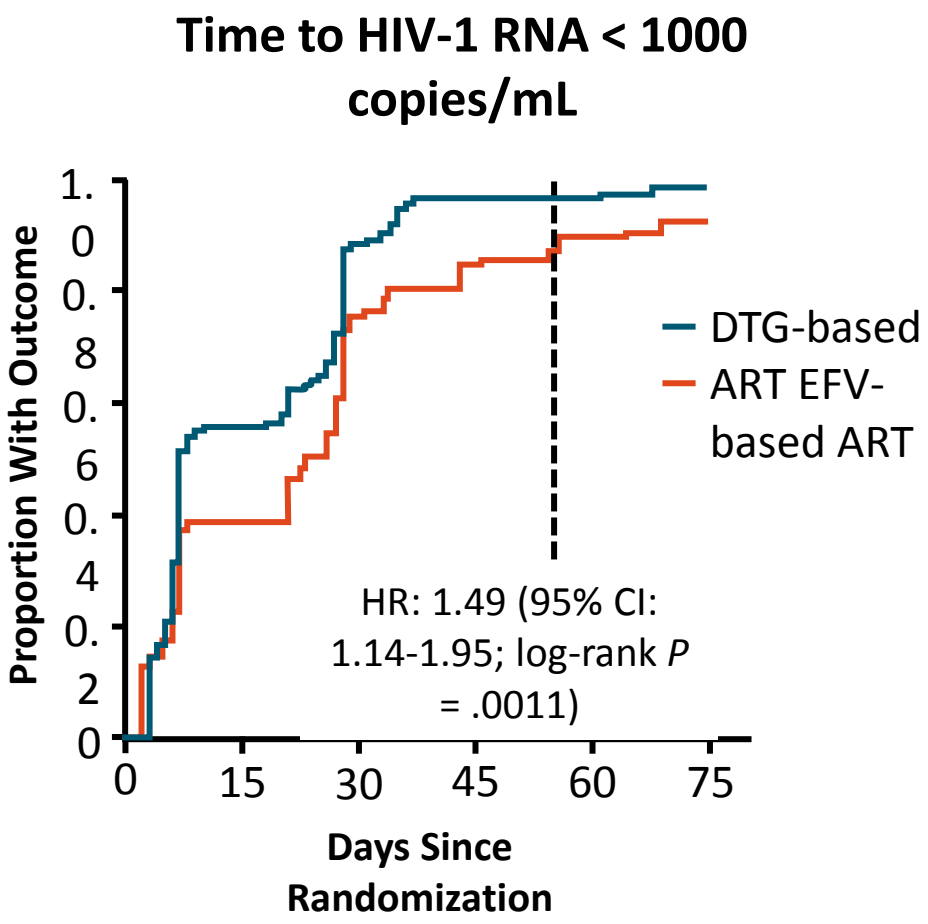
Results unaffected by BL HIV-1 RNA or CD4+ cell count, gestation at entry, maternal age, or country in multivariate analysis.

Kintu. CROI 2019. Abstr 40LB. Reproduced with permission.

Slide credit: clinicaloptions.com

DolPHIN-2: Kinetics of Virologic Suppression





HIV-1 RNA < 1000 copies/mL at delivery: 92.6% in DTG arm vs 82.6% in EFV arm (RR: 1.11; 95% CI: 1.00-1.23; *P* = .05).

Median time on ART at delivery: 55 days (IQR: 33-77).

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Slide credit: clinicaloptions.com

DolPHIN-2: Mother-to-Child Transmission

- Infant transmissions: 3 in DTG arm vs 0 in EFV arm

Characteristic of Transmission Event in DTG Arm	MTCT #1	MTCT #2	MTCT #3
Gestation at enrollment, wks	32	32	30
ART exposure before delivery, days	35	32	24
Time from delivery to first PCR positivity for infant, days	5	3	11
Maternal HIV-1 RNA, copies/mL			
▪ Baseline	48,969	32,844	31,354
▪ Day 7	5211	210	258
▪ Day 28	53	100	--
▪ Delivery	29	20	200

Kintu. CROI 2019. Abstr 40LB.

Slide credit: clinicaloptions.com

DolPHIN-2: Infant Safety

Safety Outcome in Evaluable Live Births	DTG-Based ART (n = 123)	EFV-Based ART (n = 119)	Overall (N = 242)
Median gestation at delivery, wks (IQR)	39.9 (37.6-41.9)	39.9 (38.3-41.4)	39.9 (37.9-41.6)
▪ Preterm at < 37 wks, n (%)	21 (17.1)	18 (15.1)	39 (16.1)
▪ Preterm at < 34 wks, n (%)	6 (4.9)	6 (5.0)	12 (5.0)
≥ 1 serious AE, n (%)	65 (52.8)	55 (46.2)	120 (49.6)
Infant deaths,* n (%)	5 (4.1)	3 (2.5)	8 (3.3)
Disorder by system organ class, n (%)			
▪ Infections and infestations	14 (11.4)	11 (9.2)	25 (10.3)
▪ Respiratory, thoracic, mediastinal	8 (6.5)	3 (2.5)	11 (4.5)
▪ Pregnancy, puerperium, perinatal	2 (1.6)	7 (5.9)	9 (3.7)
▪ Metabolism and nutrition	2 (1.6)	1 (0.8)	3 (1.2)
▪ Nervous system	2 (1.6)	1 (0.8)	3 (1.2)
▪ General	1 (0.8)	1 (0.8)	2 (0.8)
▪ Hepatobiliary	1 (0.8)	0	1 (0.4)
▪ Injury, poisoning and procedures	1 (0.8)	0	1 (0.4)
▪ Social circumstances	1 (0.8)	0	1 (0.4)

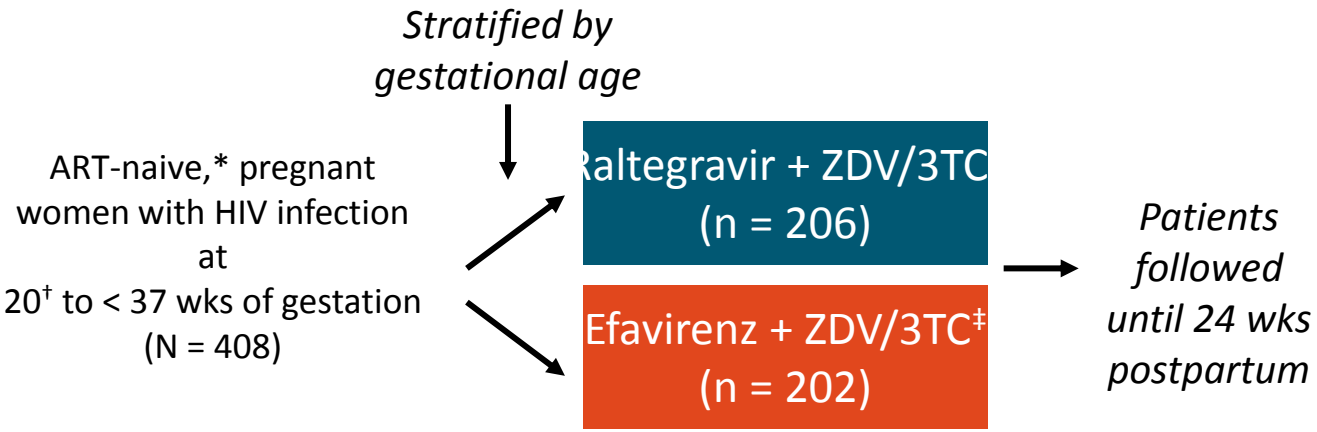
*All unrelated/not likely related to ART or IRIS.

Slide credit: clinicaloptions.com

Kintu. CROI 2019. Abstr 40LB.

NICHD P1081: Study Design

- Multicenter, randomized, open-label phase IV trial



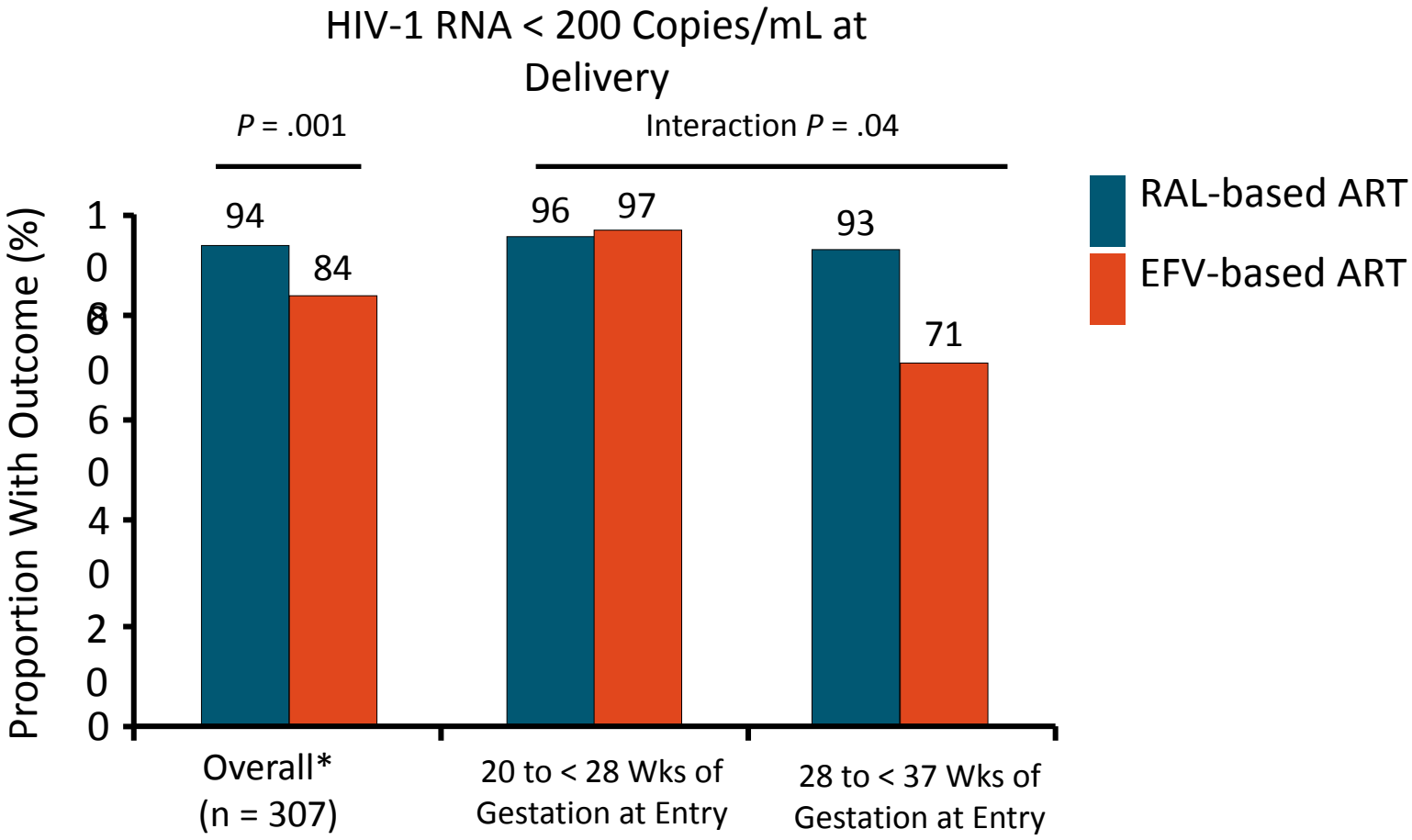
*Short-course ZDV (≤ 8 wks) for prevention of MTCT in previous pregnancies allowed. †Minimum gestational age reduced from 28 to 20 wks after 22% of study population enrolled. ‡Alternative NRTI backbone permitted if clinically indicated.

- Primary endpoints: HIV-1 RNA < 200 copies/mL at delivery, discontinuation of RAL or EFV prior to delivery, grade ≥ 3 AEs (mother and infant)
- Secondary endpoints: rapid/sustained HIV-1 RNA decline with continued use of study ARV until delivery, stillbirth, preterm birth, infant HIV infection

Mirochnick. CROI 2019. Abstr 39LB. NCT01618305.

Slide credit: clinicaloptions.com

NICHD P1081: Efficacy



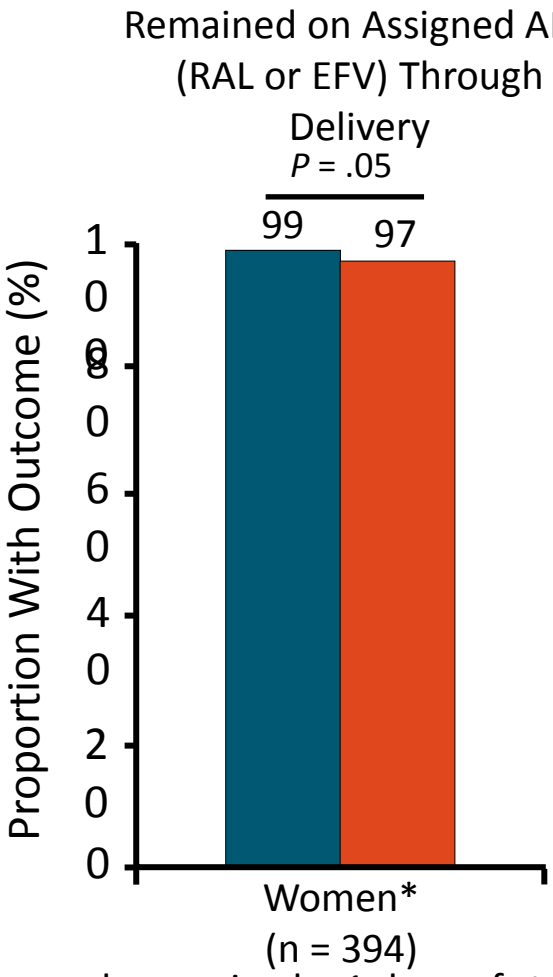
*Primary efficacy population: women with HIV-1 RNA ≥ 200 copies/mL and no genotypic resistance to any study ARV at entry.

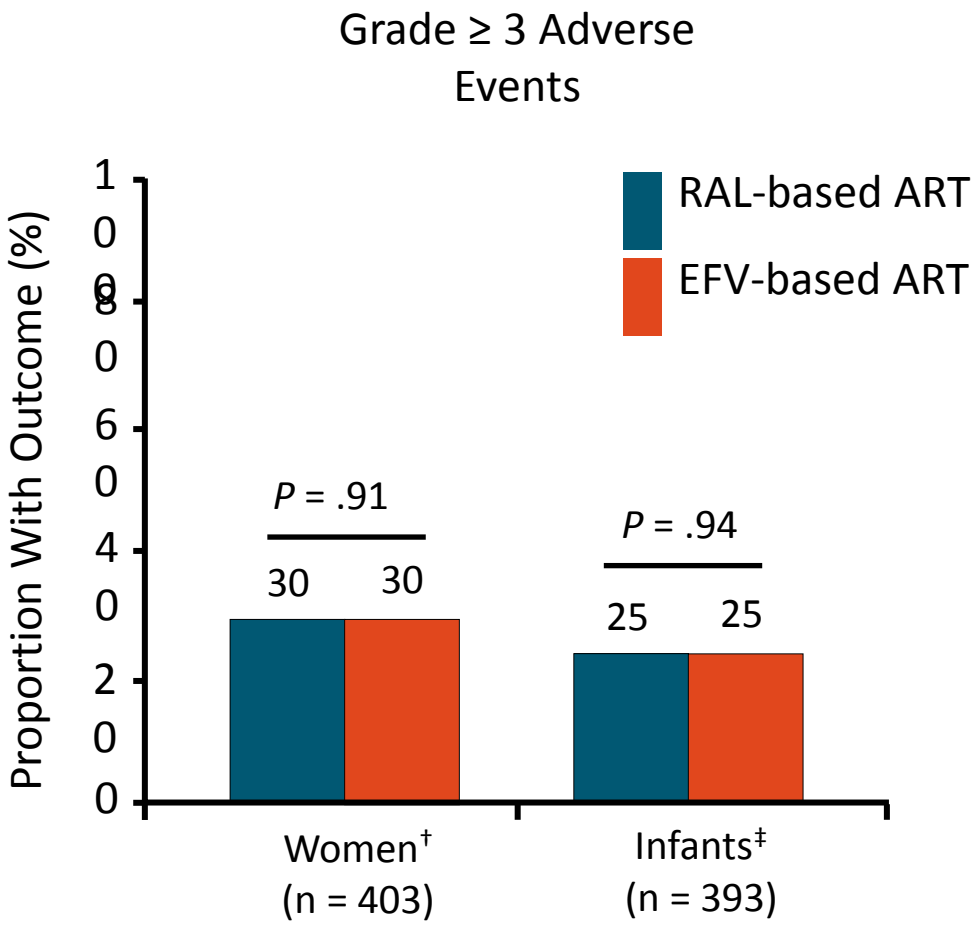
Similar trends observed in sensitivity analyses when restrictions on HIV-1 RNA and resistance lifted.

Mirochnick. CROI 2019. Abstr 39LB. Reproduced with permission.

Slide credit: clinicaloptions.com

NICHD P1081: Tolerability and Safety





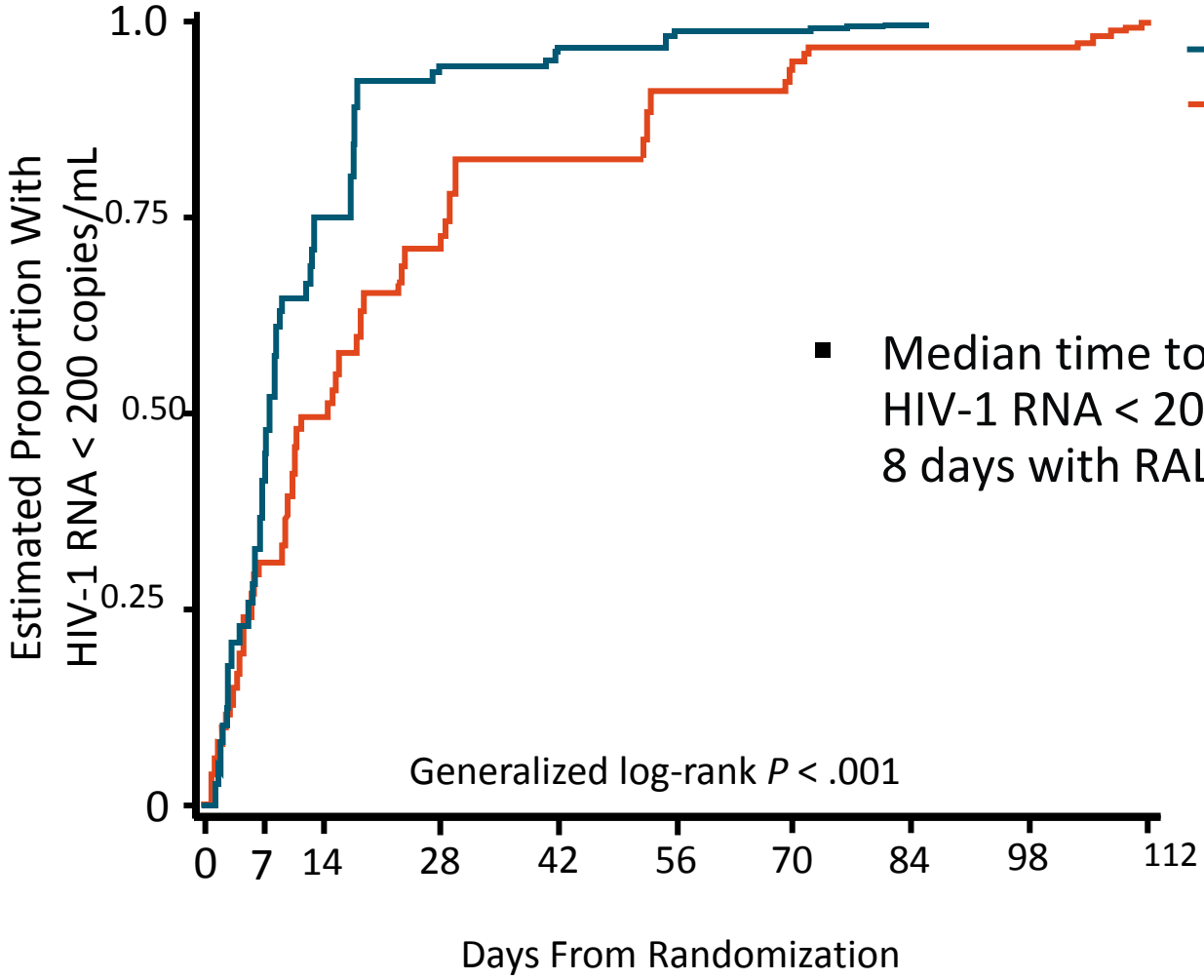
*Women who received ≥ 1 dose of study ARV and delivered on-study. †Women who received ≥ 1 dose of study ARV.

‡Live-born infants whose mother received ≥ 1 dose of study ARV and delivered on-study.

Mirochnick. CROI 2019. Abstr 39LB. Reproduced with permission.

Slide credit: clinicaloptions.com

NICHD P1081: Kinetics of Virologic Suppression



- Median time to HIV-1 RNA < 200 copies/mL: 8 days with RAL vs 15 days with EFV

Mirochnick. CROI 2019. Abstr 39LB. Reproduced with permission.

Slide credit: clinicaloptions.com

NICHD P1081: Secondary Safety Endpoints

Outcome, n/N (%)	RAL-Based ART	EFV-Based ART	*P* Value*
Stillbirth	3/200 (2)	1/194 (1)	.62
Preterm delivery (< 37 wks of gestation)	24/195 (12)	20/190 (11)	.63
Infant HIV infection	1/190 (1)	6/184 (3)	.06

*Fisher's exact test.

Slide credit: clinicaloptions.com

Mirochnick. CROI 2019. Abstr 39LB.

Traitement INH et grossesse

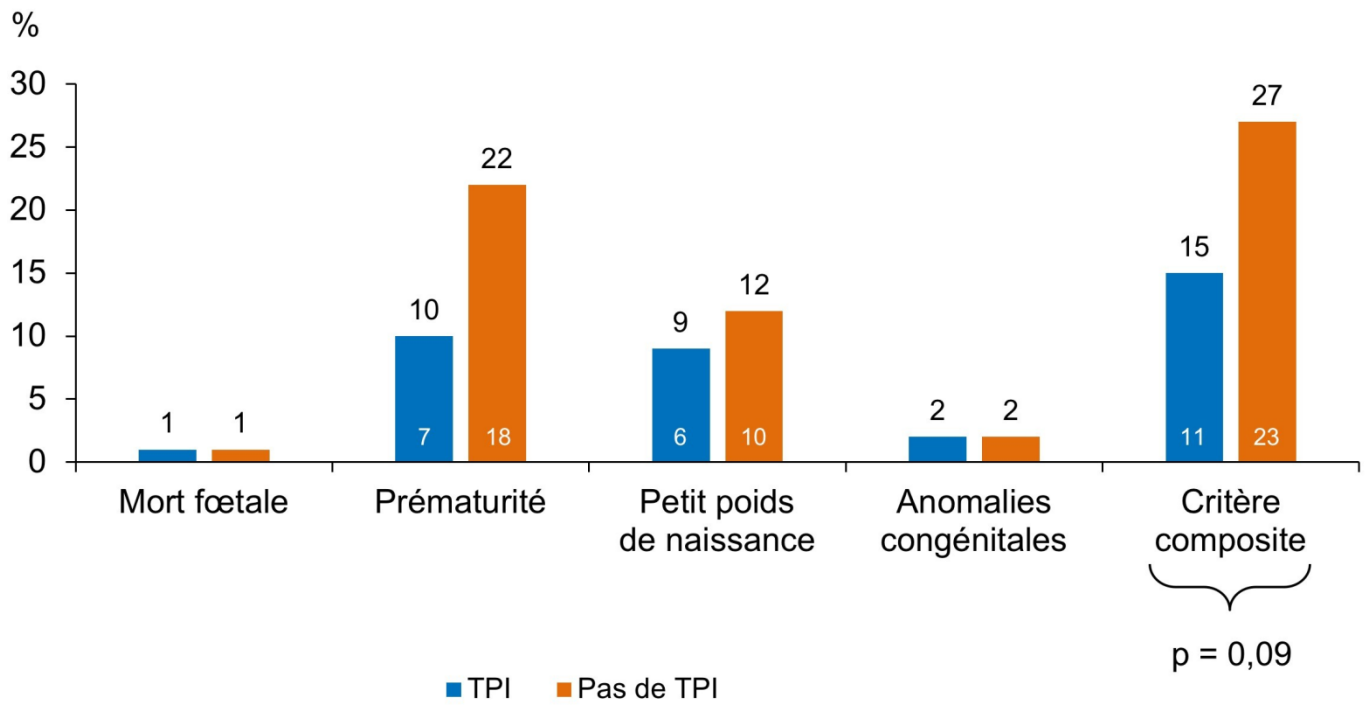
Devenir des mères et des enfants

	TPI (n = 69)	Pas de TPI (n = 82)	p
Avortement spontané ou mort né (%)	1 (1)	1 (1)	1,00
Âge gestationnel médian à la naissance (semaines)	39 (38-40)	39 (37-40)	0,82
Prématurité (%) 34-36 semaines 28-35 semaines < 28 semaines	7 (10) 5 2 0	18 (22) 17 1 0	0,06 0,18
Faible poids de naissance (< 2,5 kg) [%]	6 (9)	10 (12)	0,60
Petit âge gestationnel (< 10e percentile) [%]	8 (12)	14 (17)	0,49
Anomalie congénitales (%)	1 (2)	2 (2)	1,00
Décès maternelle (< 42 jours) [%]	0 (0)	1 (1)	1,00
Décès infantile (%)	1 (2)	0 (0)	0,45
TB maternelle (%)	0 (0)	1 (1)	1,0
TB infantile (%)	0 (0)	0 (0)	–
Hospitalisation maternelle (%)	10 (15)	12 (15)	0,98
Hospitalisation infantile (%)	10 (15)	8 (10)	0,36
Issues défavorables de la grossesse (%)	11 (16)	23 (28)	0,09
Décès fœtus/enfant/mère ou tuberculose (%)	2 (3)	3 (4)	1,00

TPI : traitement préventif par isoniazide

CROI 2019 - D'après Salazar-Austin N et al., abstr. 77, actualisé

Issues défavorables des grossesses dans le groupe TPI



CROI 2019 - D'après Salazar-Austin N et al., abstr. 77, actualisé

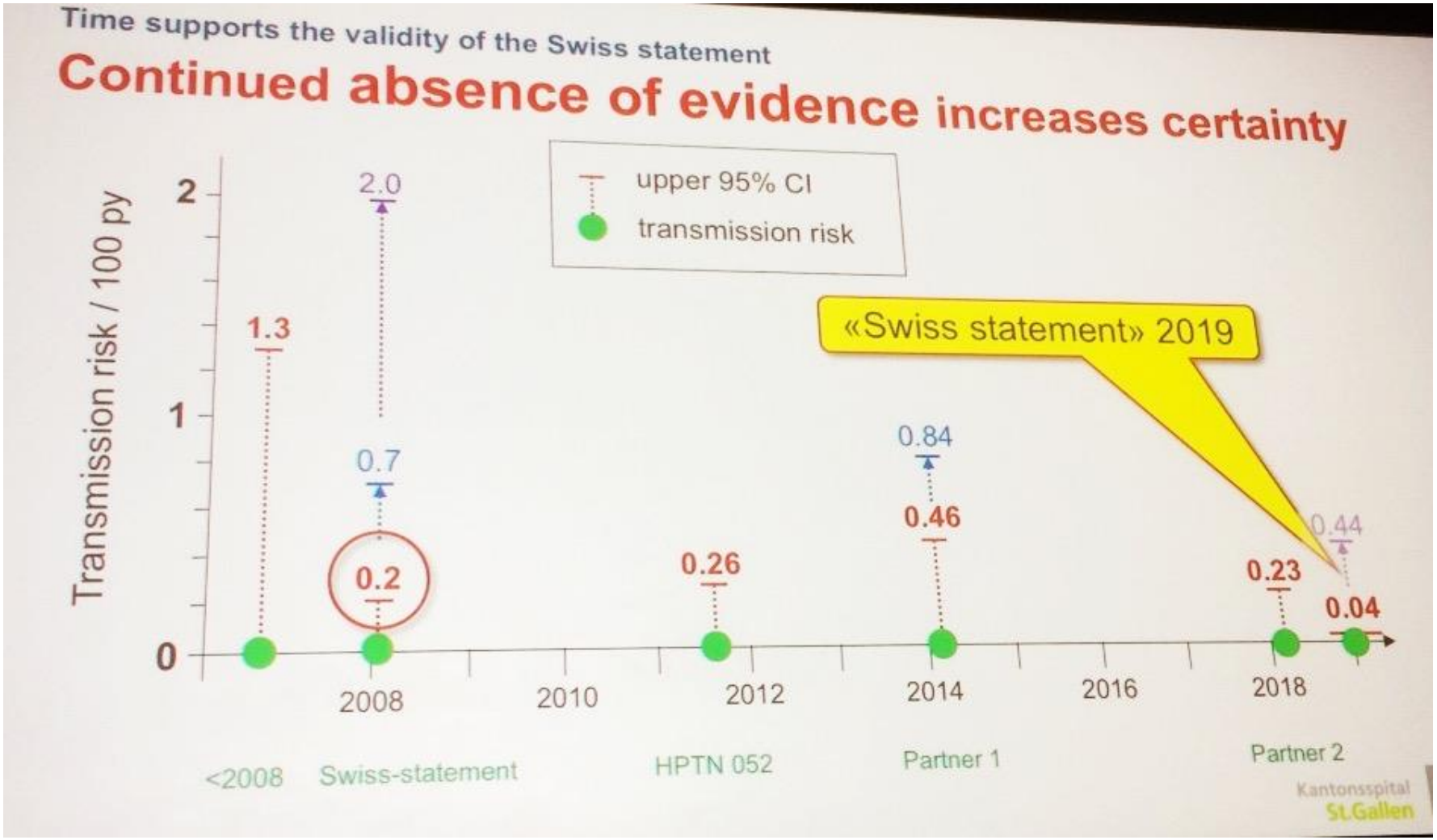
Prévention

PrEP Surveillance Study: Resistance Mutations, Acute HIV Infection

- Identification of FTC, but not TDF, resistance associated mutations common among previous PrEP users
- Diagnosis in acute stage more common in previous PrEP users vs never-users
- In New York, NAAT required prior to PrEP initiation if symptoms of acute HIV infection present or if individual reports condomless sex in previous 4 wks
  - Only 25% of PrEP users had evidence of negative NAAT before starting PrEP, and only 5% had negative NAAT within 0-2 days before PrEP initiation

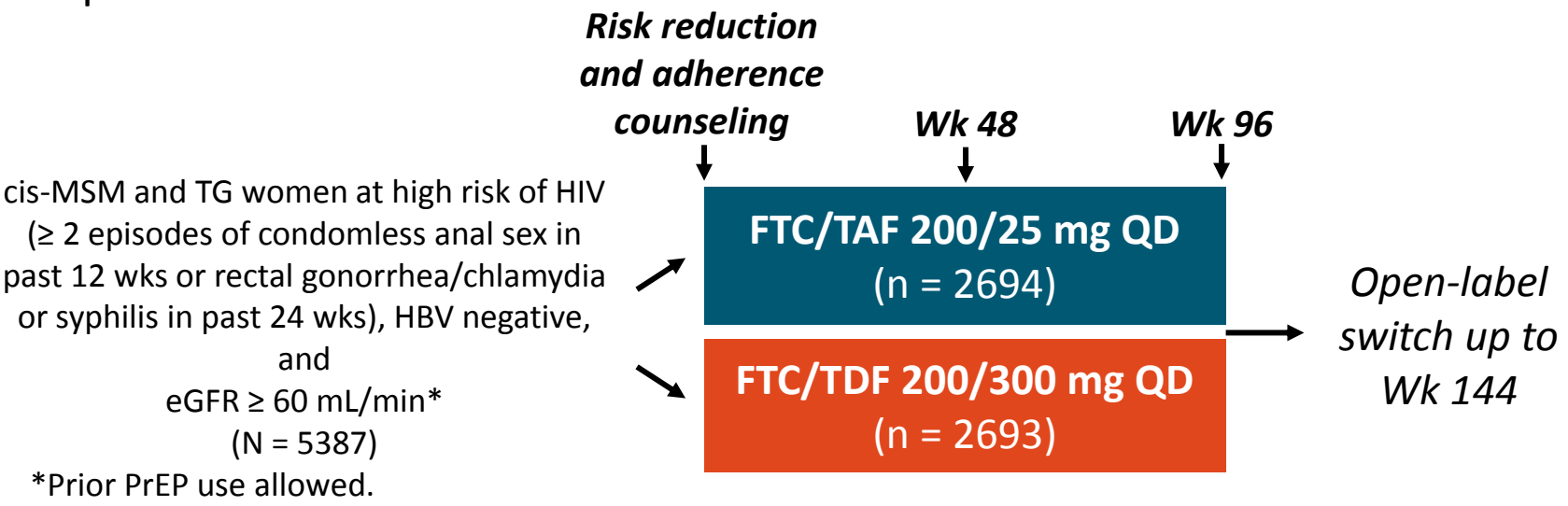
Outcome, %	PrEP Users (n = 91)	Never Users (n = 3594)
Genotype data available	75	63
Resistance mutations ▪ M184I/V/IV/MV ▪ K65R	 29 0	 2 < 1
Acute HIV infection	33	9

U = U


Time supports the validity of the Swiss statement
Continued absence of evidence increases certainty
Transmission risk / 100 py
2
1
0
upper 95% CI
transmission risk
«Swiss statement» 2019
1.3
2.0
0.7
0.2
0.26
0.84
0.46
0.44
0.23
0.04
2008
2010
2012
2014
2016
2018
<2008
Swiss-statement
HPTN 052
Partner 1
Partner 2
Kantonsspital St.Gallen

DISCOVER: Study Design

- Randomized, double-blind, active-controlled, international, multicenter phase III trial



- Primary endpoint: HIV incidence/100 PY
  - Noninferiority upper bound of 95% CI for incidence rate ratio of FTC/TAF vs FTC/TDF: < 1.62
  - Expected incidence 1.44/100 PY based on prior studies
- Secondary endpoints: adherence, resistance, safety, including renal biomarkers and BMD substudy

Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.

DISCOVER: Baseline Characteristics

Characteristic	FTC/TAF (n = 2694)	FTC/TDF (n = 2693)
Median age, yrs (range)	34 (18-76)	34 (18-72)
Race, n (%)		
▪ White	2264 (84)	2247 (84)
▪ Black	240 (9)	234 (9)
▪ Asian	113 (4)	120 (5)
Hispanic/Latino ethnicity, n (%)	635 (24)	2683 (5)
Transgender woman, n (%)	45 (2)	29 (1)
HIV risk factors, %		
▪ ≥ 2 episodes condomless anal sex (receptive) in past 12 wks	60	58
▪ Rectal gonorrhea in past 24 wks	10	10
▪ Rectal chlamydia in past 24 wks	13	12
▪ Syphilis in past 24 wks	9	10
▪ Recreational drug use in past 12 wks	67	67
▪ Binge drinking (≥ 6 drinks on ≥ 1 occasion; at least monthly)	23	22
Taking FTC/TDF for PrEP at baseline, %	17	16

Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.com

DISCOVER: HIV Incidence

- Primary analysis conducted when 100% of individuals completed 48 wks of PrEP and 50% of individuals completed 96 wks of PrEP
- 22 HIV infections observed during 8756 PY of follow-up
- Noninferiority of FTC/TAF vs FTC/TDF for HIV prevention established
  - Upper bound of 95% CI of incidence rate ratio < 1.62

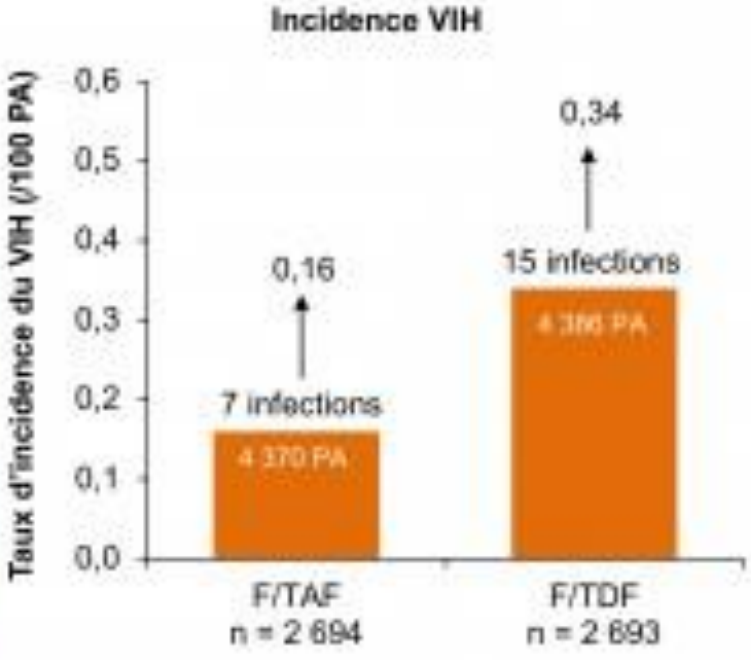
HIV Incidence	FTC/TAF (n = 2694)	FTC/TDF (n = 2693)
HIV infections, n	7	15
PY of follow-up	4370	4386
Rate of HIV incidence/100 PY	0.16	0.34
Incidence rate ratio for FTC/TAF vs FTC/TDF (95% CI)	0.47 (0.19-1.15)	

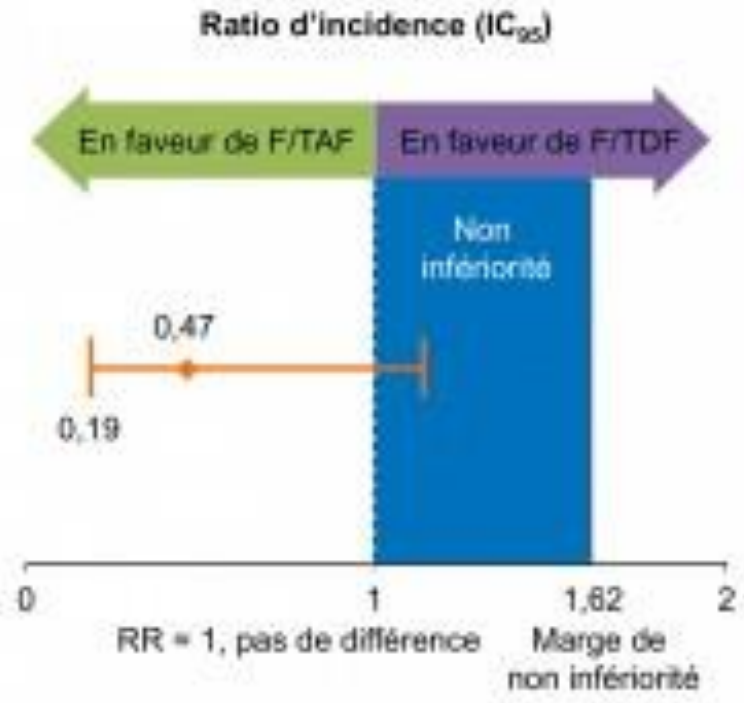
Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.com

DISCOVER
critère primaire de jugement : incidence du VIH

22 infections VIH chez 8 756 personnes/année (PA) de suivi

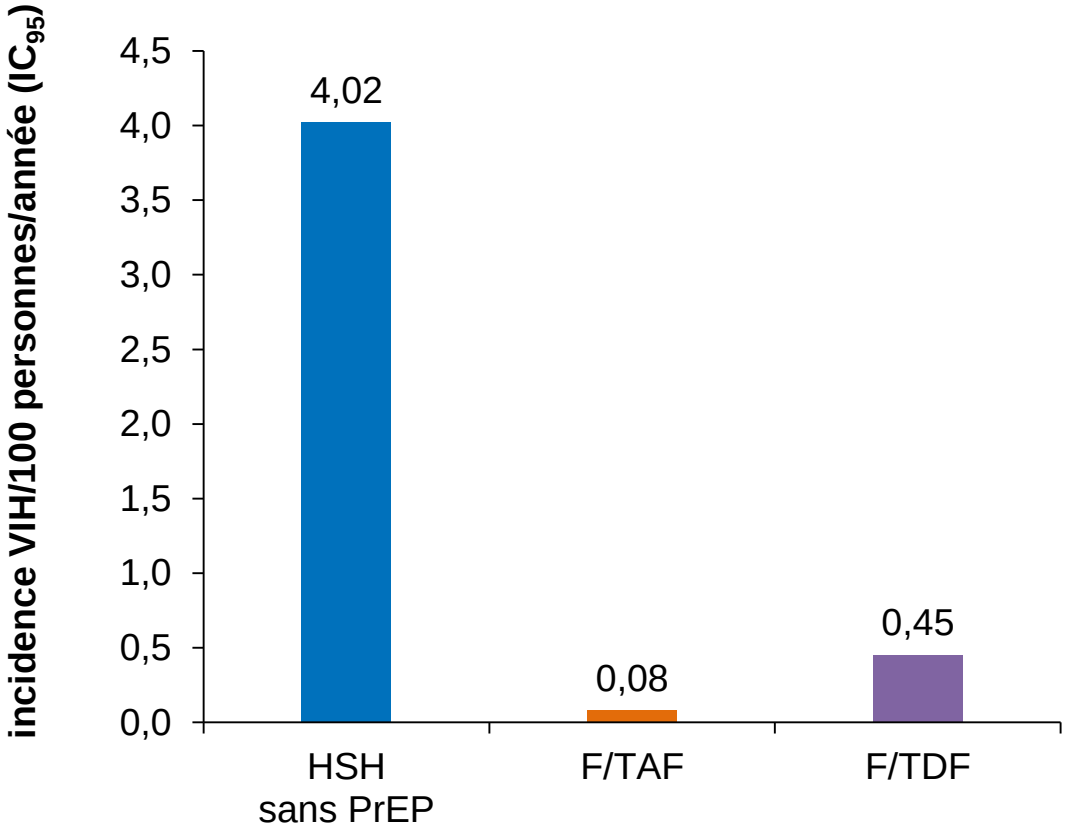




→ **F/TAF est non inférieur à F/TDF pour la PrEP**

CROI 2019 - D'après Charles B. Hare et al., abstr. 104LB, actualisé

DISCOVER
Comparaison des résultats en termes de taux d'infection VIH par rapport aux HSH à risque mais sans PrEP



CROI 2019 - D'après Charles B. Hare et al., abstr. 104LB, actualisé

DISCOVER: Common AEs

AEs Occurring in ≥ 10% in Either Arm, %	FTC/TAF (n = 2694)	FTC/TDF (n = 2693)
Rectal chlamydia	29	29
Oropharyngeal gonorrhea	28	27
Rectal gonorrhea	26	25
Exposure to communicable disease	17	16
Diarrhea	16	16
Nasopharyngitis	13	13
Upper respiratory tract infection	13	12
Syphilis	13	12
Urethral chlamydia	10	10

- Incidence of gonorrhea, chlamydia, or syphilis through Wk 96 of study
  - FTC/TAF: 145.1/100 PY; FTC/TDF: 138.8/100 PY

Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.com

DISCOVER: Bone Safety at Wk 48

- Bone safety substudy conducted in 383 individuals demonstrated more favorable BMD outcomes with FTC/TAF vs FTC/TDF

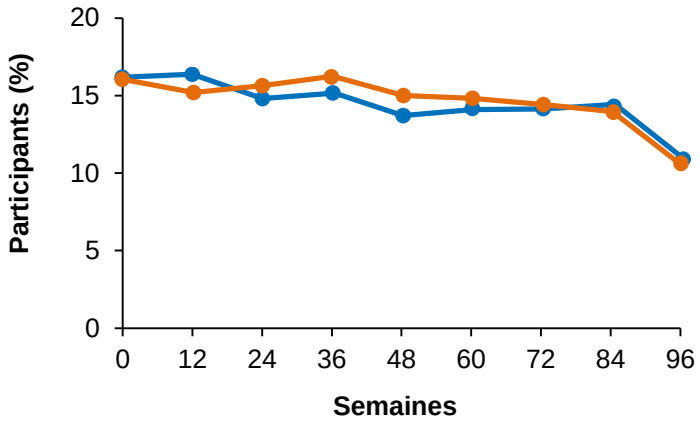
BMD Outcome	FTC/TAF	FTC/TDF	*P* Value
Spine BMD	(n = 159)	(n = 160)	
▪ Mean % change from BL	+0.50	-1.12	< .001
▪ ≥ 3% increase, %	17	9	.052
▪ ≥ 3% decrease, %	10	27	< .001
Hip BMD	(n = 158)	(n = 158)	
▪ Mean % change from BL	+0.18	-0.99	< .001
▪ ≥ 3% increase, %	9	6	.5
▪ ≥ 3% decrease, %	4	18	< .001

Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.com

DISCOVER
Infections sexuellement transmissibles à S96

Résultats de laboratoire pour gonocoque/chamydia



	n (taux : n/100 PA)	
	F/TAF	F/TDF
Gonocoque (toute localisation)	1 053 (47,1)	1 059 (45,3)
Rectal	651 (21,6)	662 (20,5)
Chlamydia (toute localisation)	1 049 (41,9)	1 071 (41,6)
Rectale	810 (27,5)	835 (28,2)
Syphilis	365 (10,3)	370 (9,5)

- Incidence des gonocoques, chlamydia ou syphilis pendant l'étude
  - F/TAF = 145,1/100 personne/année (PA)
  - F/TDF : 138,8/100 personne/année

CROI 2019 - D'après Charles B. Hare et al., abstr. 104LB, actualisé

DISCOVER: Renal Safety Through Wk 48

- Renal safety outcomes more favorable with FTC/TAF vs FTC/TDF
  - Including median changes in ratios of proximal tubular proteins (retinol-binding protein, β_2-microglobulin) to creatinine (data not shown)

Renal Outcome	FTC/TAF (n = 2694)	FTC/TDF (n = 2693)	*P* Value
Median change from baseline in $eGFR_{CG}$, mL/min	+1.8	-2.3	< .001
Discontinuation due to renal events, n	2	6	NR
Fanconi syndrome, n	0	1	NR

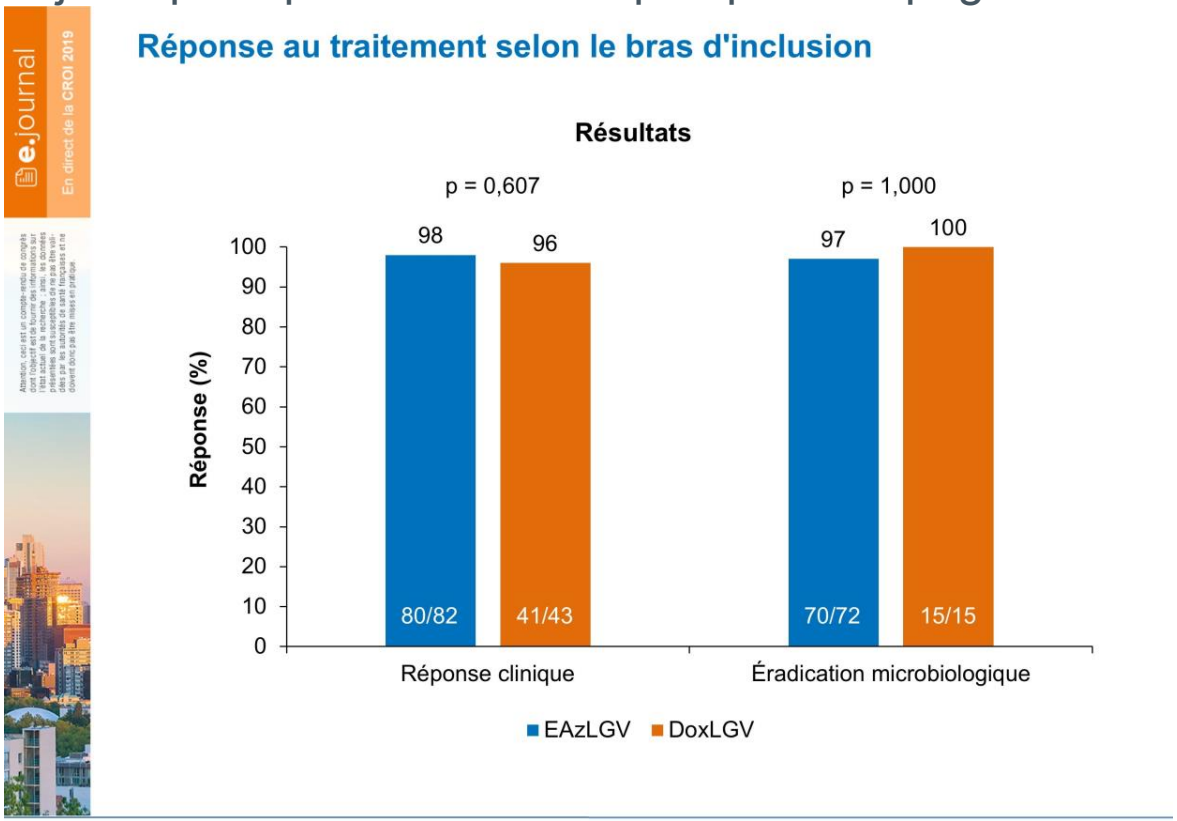
Hare. CROI 2019. Abstr 104LB.

Slide credit: clinicaloptions.com

Traitement efficace de la lymphogranulomatose vénérienne (LGV) rectale avec un traitement prolongé par azithromycine

D'après Blanco J et al., P1011, actualisé

Le traitement de référence est la doxycycline (doxLGV) à 200 mg/j pour au moins 21 j. Une alternative moins validée serait l'azithromycine (AZIT) 1 g par semaine pendant 3 semaines (EAzLGV) et c'est l'analyse de ce schéma thérapeutique qui représente l'objectif principal de ce travail prospectif espagnol.



CROI 2019 - D'après Blanco J et al., P1011, actualisé