2DR

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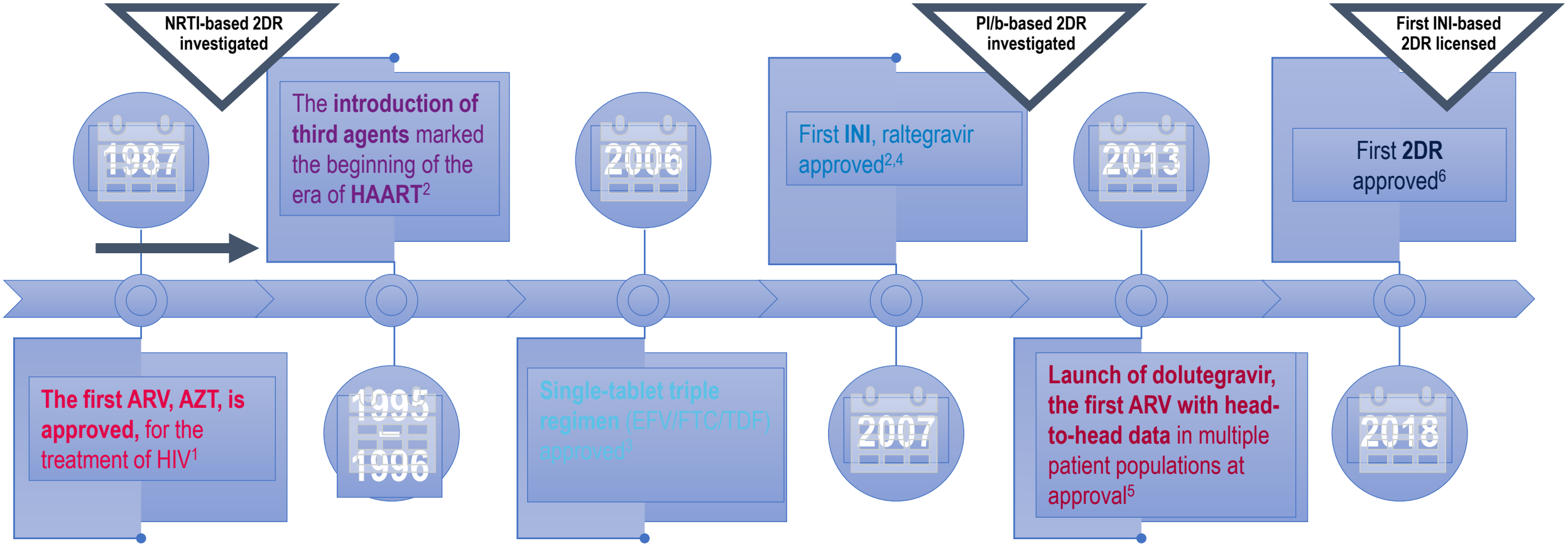
MB had received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, and Teva.

Content

- The past
- The present
- The future

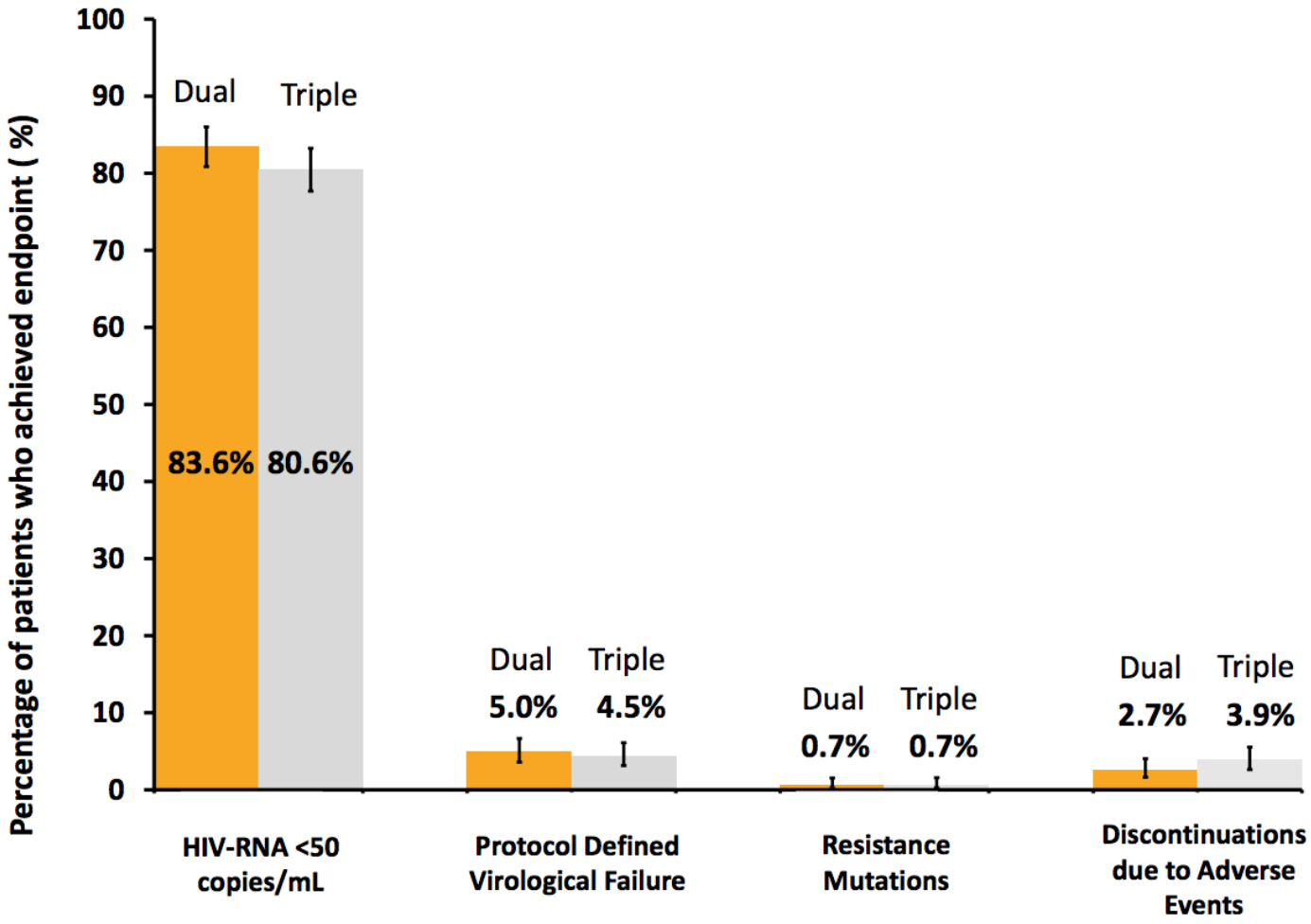
HIV therapy: from saving lives to chronic management



1. Retrovir SmPC Dec 2018; 2. Palmisano L, *et al*. *Ann Ist Super Sanità* 2011;47:44–48; 3. Atripla SmPC Nov 2018; 4. Isentress SmPC Jan 2019; 5. Tivicay SmPC Mar 2019; 6. Juluca SmPC Jan 2019.

Summary efficacy and safety of PI/r +3TC or TDF

N = 1635 patients

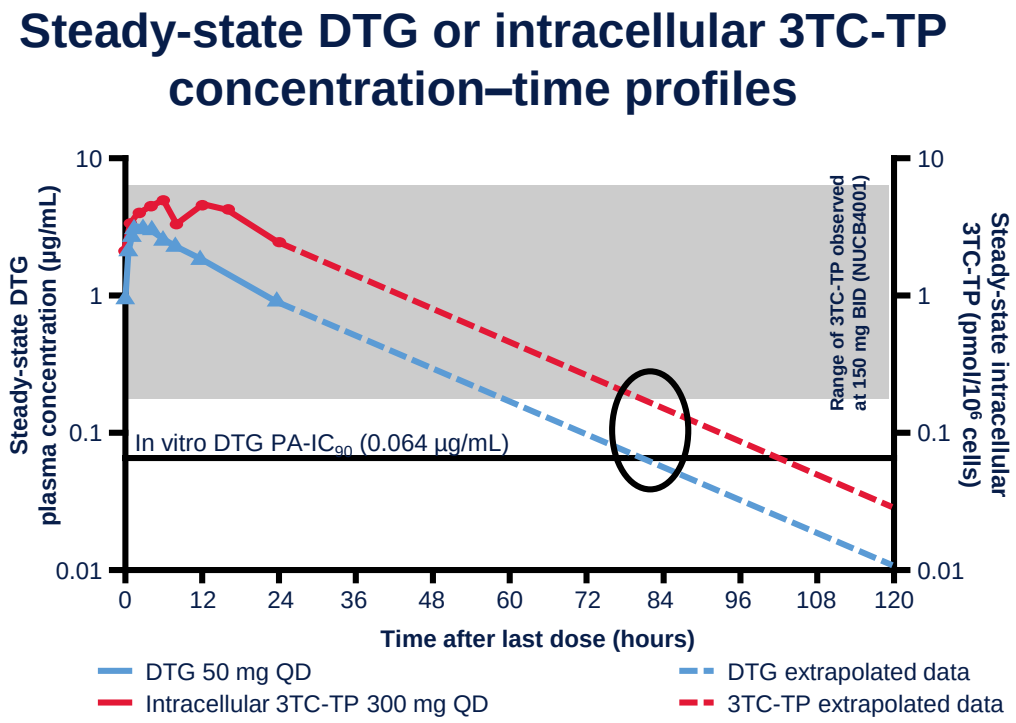


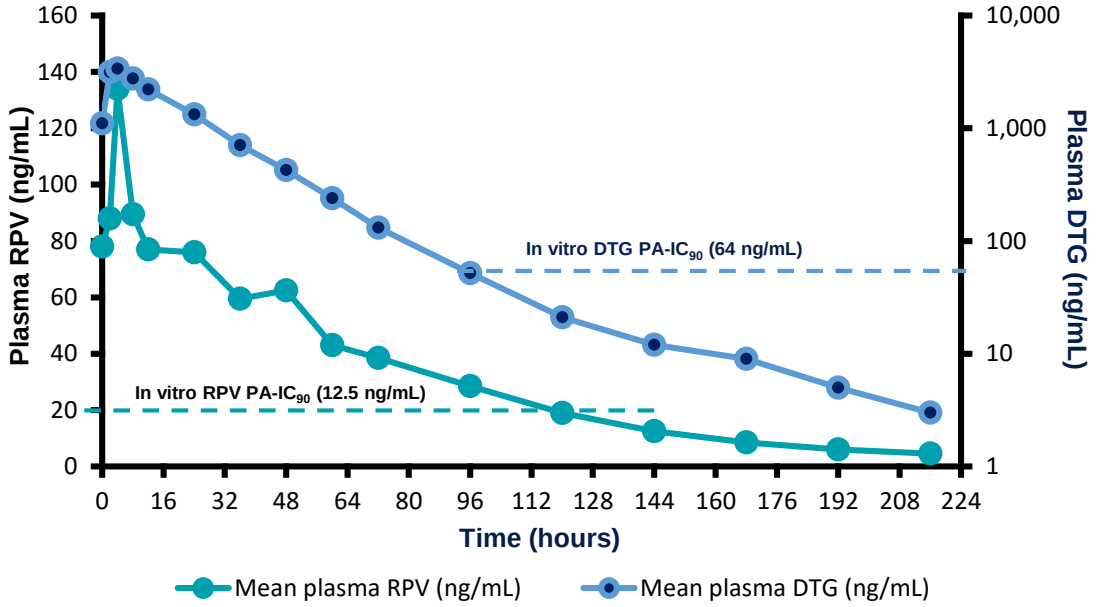
Liew et al. HIVGlasgow 2018, abstract O144

Why DTG – based 2DR?

- Avoid boosting agents (< DDI) when possible
- Demonstrated superior efficacy vs 3 ART classes: NNRTI, PI and INSTI
- DTG – high genetic barrier: high IQ - extremely low rates of resistance development in Phase III clinical trials
- To be combined with other unboosted drugs – ideally to match PK profile to avoid mono-therapy if drug doses are delayed

Matched PK profiles





3TC-TP, lamivudine triphosphate.

Adapted from: : Moore KH, *et al*. *AIDS* 1999;13:2239–2250; Elliot E, *et al*. *J Antimicrob Chemother* 2016;71:1031−1036

Available data

3TC + DTG

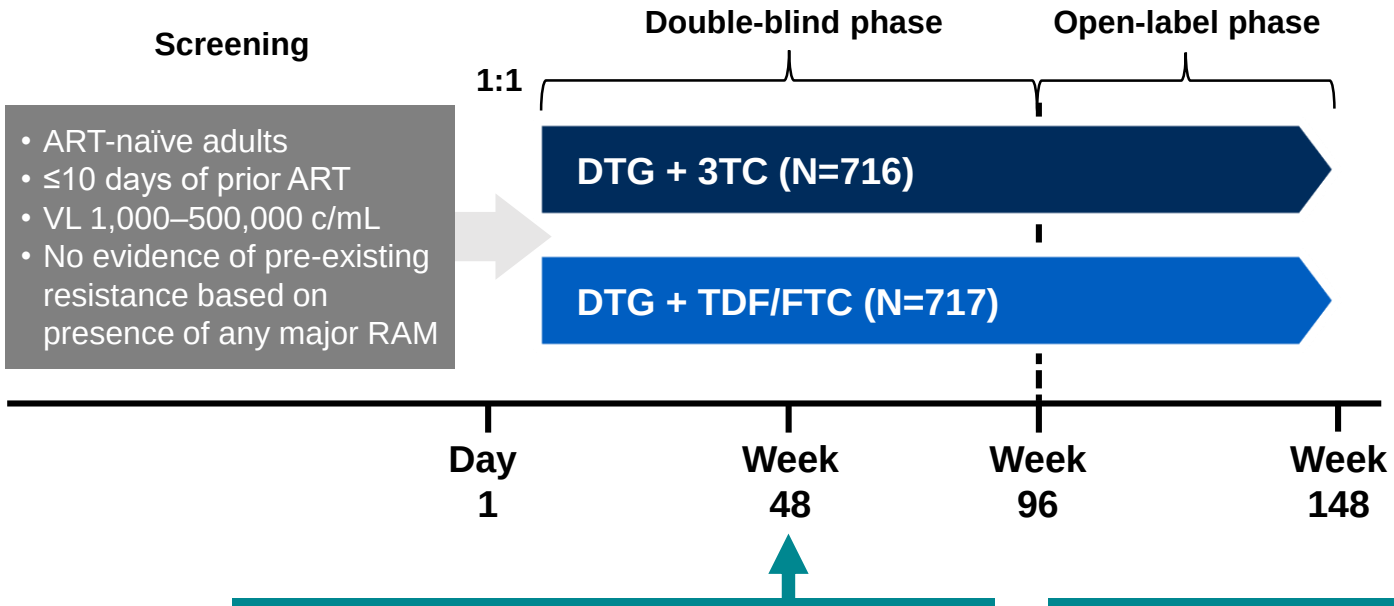
- Naïve
  - Paddle
  - ACTG5353
  - Gemini 1 and 2
- Switch
  - ASPIRE
  - Real world experience/cohorts

RPV + DTG

- Naïve
  - Not indicated
- Switch
  - Sward 1 and 2

GEMINI-1 and -2: Phase III Study Design

Identically designed, randomised, double-blind, parallel-group, multicentre, non-inferiority studies



Countries

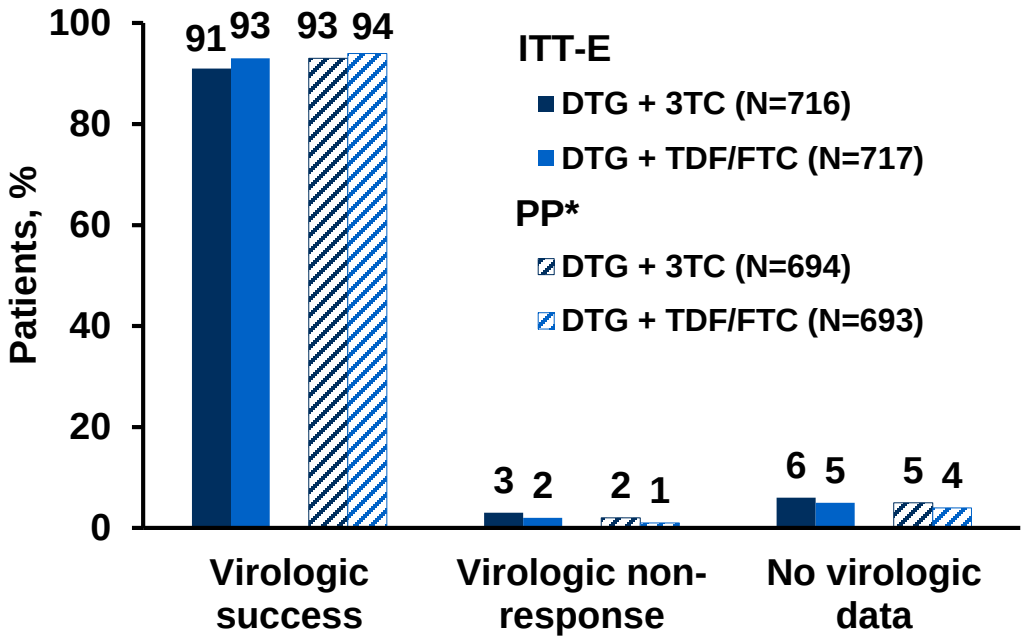
Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

- *−10% non-inferiority margin for individual studies
  Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3)
- Exclusion criteria included severe hepatic impairment or unstable liver disease; evidence of hepatitis B virus infection at screening; anticipated need for hepatitis C virus therapy in the first 48 weeks; creatinine clearance <50 mL/min).

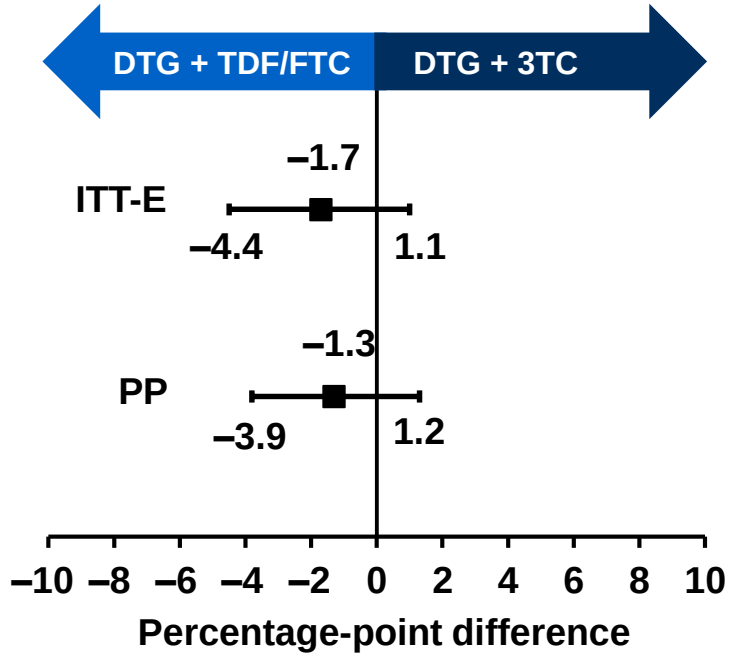
Adapted from: Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix

GEMINI 1 and 2: Pooled Snapshot Outcomes at wk 48

Virologic outcome[1,2]



Adjusted treatment difference (95% CI)[1†]



DTG + 3TC was non-inferior to DTG + TDF/FTC in the proportion of patients with <50 c/mL HIV-1 RNA at Week 48 in pooled Snapshot data using either the ITT-E or PP populations[1]

- Data pooled from both GEMINI-1 and -2 studies

*PP population consisted of subjects in the ITT-E population except those with protocol violations that could affect assessment of antiviral activity; †Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).[1] PP, per protocol

Adapted from: Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix

GEMINI 1 and 2: confirmed virologic withdrawals through wk 48

- Low rates of virologic withdrawals were observed by Week 48

	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW, n (%)	6 (<1)	4 (<1)
Virologic rebound, n (%)	6 (<1)	4 (<1)
Treatment-emergent resistance, n (%)	0	0

No treatment-emergent INI or NRTI mutations were observed among subjects who met CVW criteria

Other results: subpopulations, baseline VL, baseline CD4 (difference at snapshot analysis but not lack of efficacy of 2DR), target not detected, viral load decay rate, no differences in AEs, renal markers, bone markers, lipids…

Adapted from: Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix

What else would we want to know?

Efficacy and safety
- Long-term data?
- Use in broad patient populations?
- Real-world data?
- Direct comparison vs FTC/TAF-based regimens?

Resistance?
- Long term rates of resistance?
- Impact of mutations on virological response?
- Implications for treatment forgiveness?

Data in special populations?
- Pregnancy?
- Hepatitis B?
- T&T?

Impact on viral reservoir and immune activation?
- Sanctuairies

ETC…

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- Sanctuaries

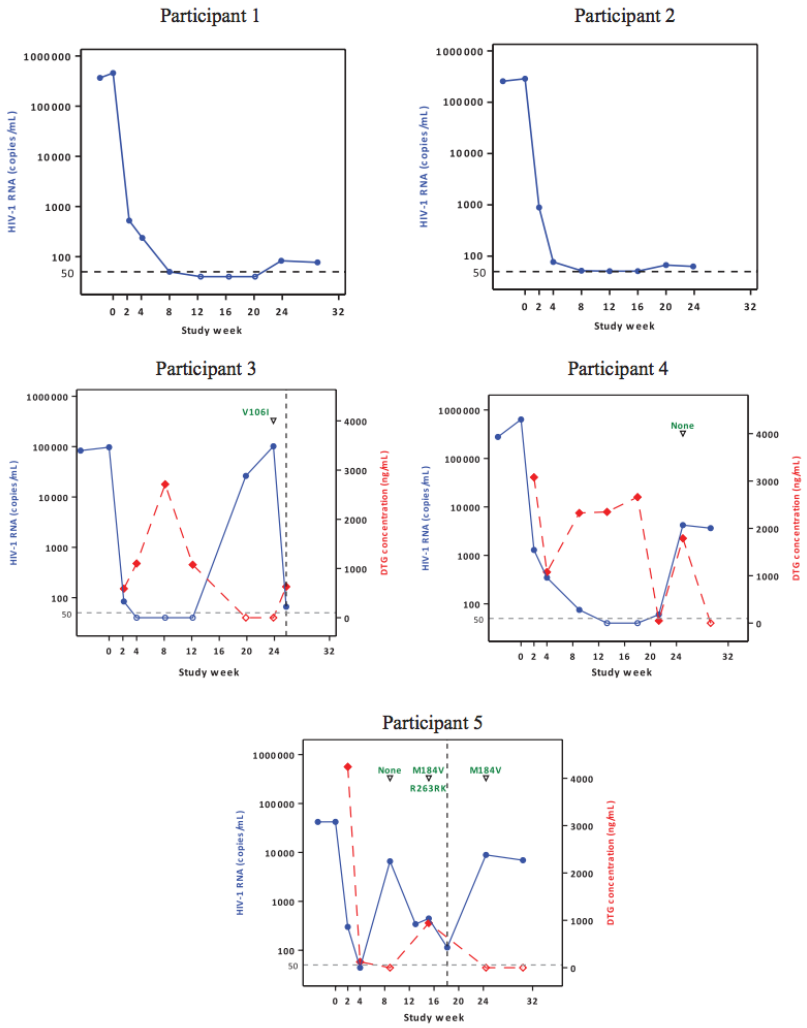
ETC…

ACTG5353

- Phase 2, single-arm, pilot study of DTG OD (50 mg) plus 3TC (300 mg) in treatment-naive participants with HIV-1 RNA ≥1000 and <500 000 copies/mL
- Exclusion criteria included active hepatitis B or major protease, reverse transcriptase, or integrase resistance. The primary efficacy measure was the proportion with HIV-1 RNA <50 copies/mL (FDA Snapshot) at week 24
- Virologic failure (VF) was confirmed HIV-1 RNA >400 copies/mL at week 16/20 or >200 copies/mL at or after week 24
- DTG levels and drug resistance testing were performed at VF

Taiwo et al CID 2018

HIV-1 RNA, DTG plasma concentration, and genotyping results for virologic failures and Snapshot nonsuccesses



- Open circles represent HIV-1 RNA results that are less than the lower limit of quantification
- Open diamonds represent drug level below the in vitro inhibitory concentration for 90% inhibition (IC90) (64 ng/mL)
- Participants 3, 4, and 5 had at least 1 time point with undetectable plasma DTG. Resistance mutations are shown at the time points tested, with “None” representing no mutation detected
- Vertical dashed line represents discontinuation of study treatment
- Horizontal dashed line represents HIV-1 RNA 50 copies/mL

Taiwo et al CID 2018

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Impact on viral reservoir and immune activation?
- **Sanctuaries**

ETC…

DTG/3TC: ACTG5353 & ASPIRE

Parent study	Study week	ART regimen	Last missed doses	Genital HIV RNA (copies/ml)	Plasma HIV RNA* (copies/ml)	CMV DNA (copies/ml)	HSV DNA (copies/ml)	Gonorrhea RNA	Chlamydia RNA
ASPIRE #1	48	RPV/TDF/ FTC	1-2 weeks	42	179	Not detected	Not detected	Not detected	Not detected
ASPIRE #2**	36	DTG+3TC	> 3 months	488	<20	314607	Not detected	Not detected	Not detected
	48	DTG+3TC	Never	79	31	86090	Not detected	Not detected	Not detected
A5353	24	DTG+3TC	Never	48	<40	NA***	NA***	Not detected	Not detected

Legend: RPV: Rilpivirine, TDF: Tenofovir, FTC: emtricitabine, DTG: Dolutegravir, 3TC: Lamivudine. NA = not available. *Plasma HIV RNA at the same rime of genital HIV RNA shedding **ASPIRE participant #2 had detectable HIV RNA at two consecutive time-points, ***not enough semen sample to run these additional tests

3/45 had HIV RNA > 40 in SP

1/20 (5% [95%CI: 0.1%, 25%]) in the ASPIRE threedrug ART arm.
1/18 (5.6% [0.1%, 27%]) in the ASPIRE DTG+3TC arm.
1/13 (7.7% [0.2%, 36%]) in A5353 (DTG+3TC).

No women had detectable genital HIV RNA.

2-20% on suppressive 3DR have detectable genital HIV-RNA

Giannella et al. WAC 2018; Pasquier et al. Basic Clin Androl. 2017

Abstract Number:
THPEB048

22nd International AIDS Conference
July 23 -
Amsterd

Genital HIV-1 Shedding with Dolutegravir (DTG) plus Lamivudine (3TC) Dual Therapy

S. Gianella[1], V.C. Marconi[2], B. Berzins[3], C.A. Benson[1], P. Sax[4], C.J. Fichtenbaum[5], T. Wilkin[6], M. Vargas[1], Q. Deng[1], M.F. Oliveira[1], C. Moser[7], B.O.Taiwo[3].

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Conclusions

- **Genital HIV RNA shedding was comparable between virologically suppressed individuals receiving initial or maintenance DTG+3TC and those on three-drug ART.**
- **These results suggest that DTG+3TC may confer similar transmission prevention benefits as triple therapy.**
- **It is unknown if HIV RNA in genital secretions represent replication competent or transmissible virus.**

- HIV genotyping and urine PCR for gonorrhea and chlamydia were performed if genital HIV RNA was detected.

Acknowledgments

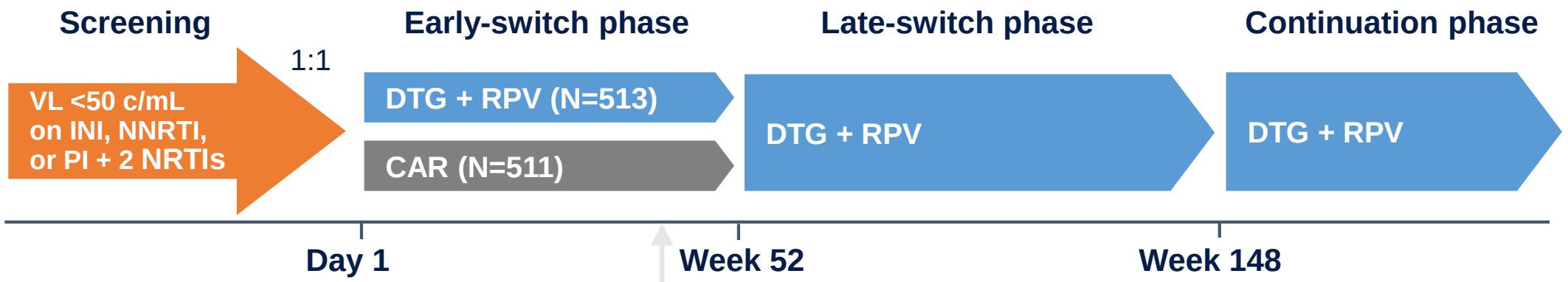
We are grateful to the study participants and the ASPIRE and A5353 clinical research staff at Northwestern University (Sherrie Wolfe), Emory University (Kishna Outlaw), University of Cincinnati (Eva Whitehead), Cornell (Todd Stroberg), University of California at San Diego (Edward Seefried) whose commitment and cooperation made this study possible.

This work was supported by an Investigator Sponsored Study grant "Virologic Activity of DTG +3TC in the Genital Compartment: Substudy of ASPIRE and A5353" from ViiV Healthcare to Northwestern University. ViiV Healthcare/GlaxoSmithKline provided funding and study drugs. Additional support was provided from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636 and UM1 AI106701, the San Diego Center for AIDS Research Translational Virology Core (P30AI036214) as well as the Third Coast Center for AIDS Research (P30AI117943), and Emory Center for AIDS Research (P30AI050409). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or ViiV Healthcare."

Do sanctuary drug concentrations matter?

SWORD 1 and 2: DTG + RPV

Identically designed, randomised, multicentre, open-label, parallel-group, noninferiority studies



Inclusion criteria

- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL for ≥6 months at screening
- HBV negative

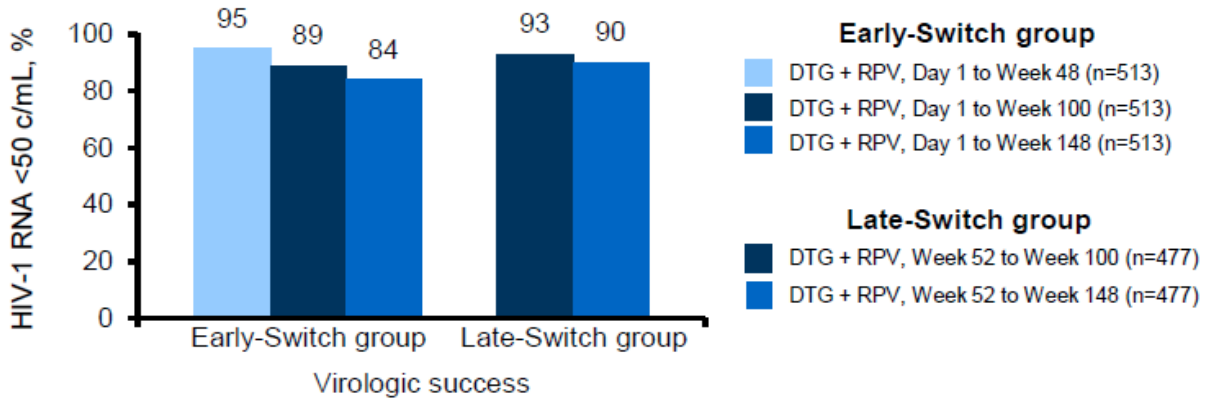
Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)*

*–8% non-inferiority margin for pooled data; –10% non-inferiority margin for individual studies.
CAR, current antiretroviral regimen; VF, virologic failure; VL, viral load.

Adapted from: Aboud, *et al*. *AIDS* 2018. Slides THPEB047; Llibre JM, *et al*. *Lancet* 2018;391:839–849.

SWORD 1 and 2: DTG + RPV was efficacious in the early-switch group through 148 weeks

- Through 148 weeks of treatment, DTG + RPV maintained virological suppression in 84% of patients in the early-switch group
- Virological efficacy in the late-switch group at Week 148 was similar to that of the early-switch group at wk 100

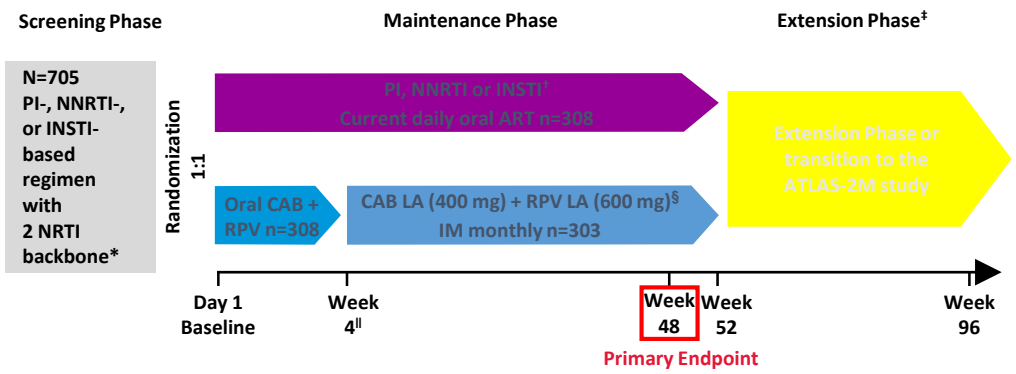


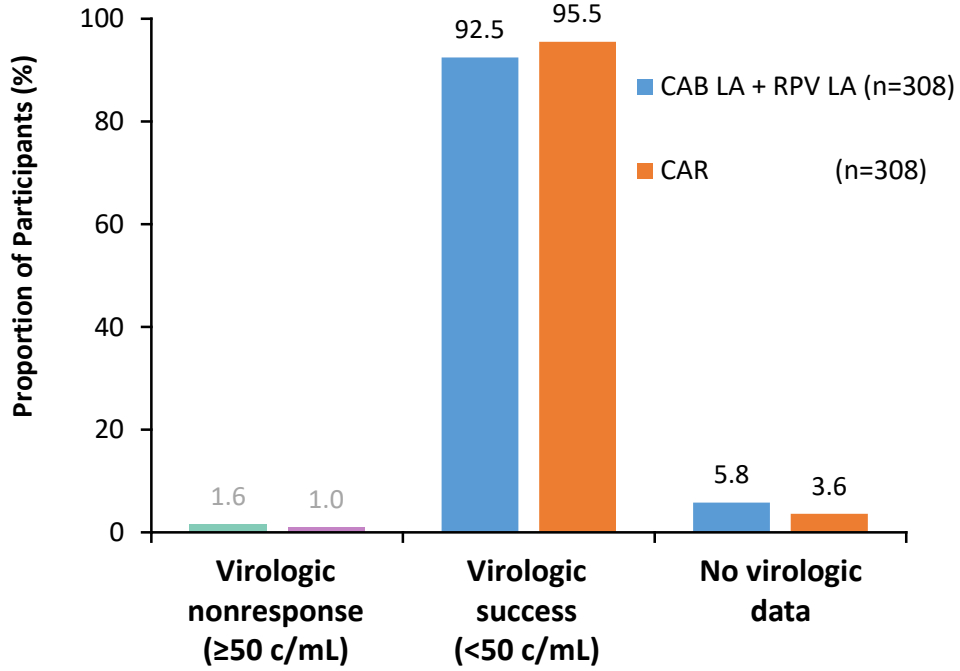
	Early-Switch group			Late-Switch group	
n (%)	DTG + RPV Week 48	DTG + RPV Week 100	DTG + RPV Week 148	DTG + RPV Week 100	DTG + RPV Week 148
Virologic success	486 (95)	456 (89)	432 (84)	445 (93)	428 (90)
Virologic non-response	3 (<1)	13 (3)	14 (3)	8 (2)	11 (2)
Data in window, not <50 c/mL	0	5 (<1)	1 (<1)	3 (<1)	4 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	12 (2)	3 (<1)	4 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	1 (<1)	0	0
Change in ART	0	0	0	2 (<1)	3 (<1)
No virologic data	24 (5)	44 (9)	67 (13)	24 (5)	38 (8)
Discontinued because of AE or death	17 (3)	27 (5)	40 (8)	11 (2)	17 (4)
Discontinued for other reasons	7 (1)	17 (3)	25 (5)	10 (2)	19 (4)
Missing data during window but on study	0	0	2 (<1)	3 (<1)	2 (<1)

Adapted from van Wyk J, *et al*. *BHIVA* 2019. Poster P008.

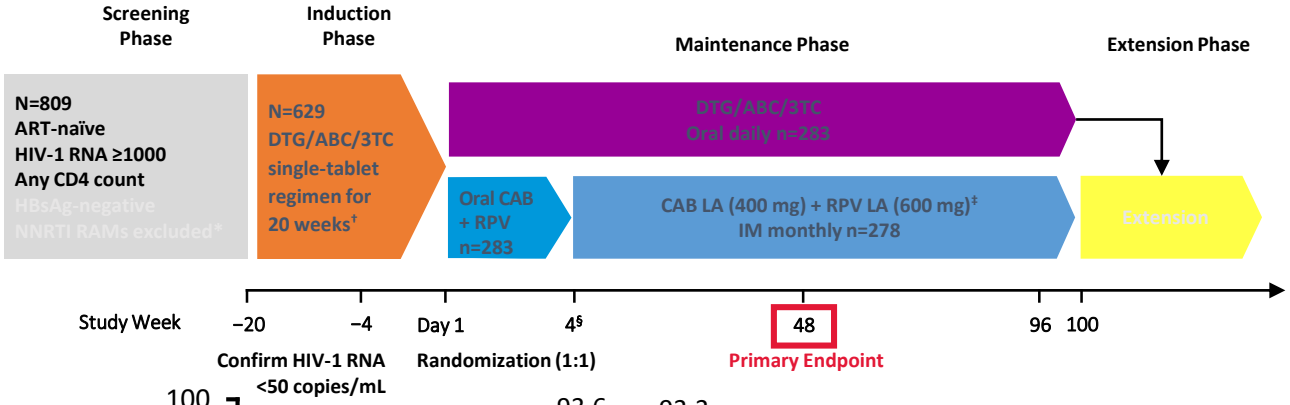
Injectable CAB/RPV – Phase III results

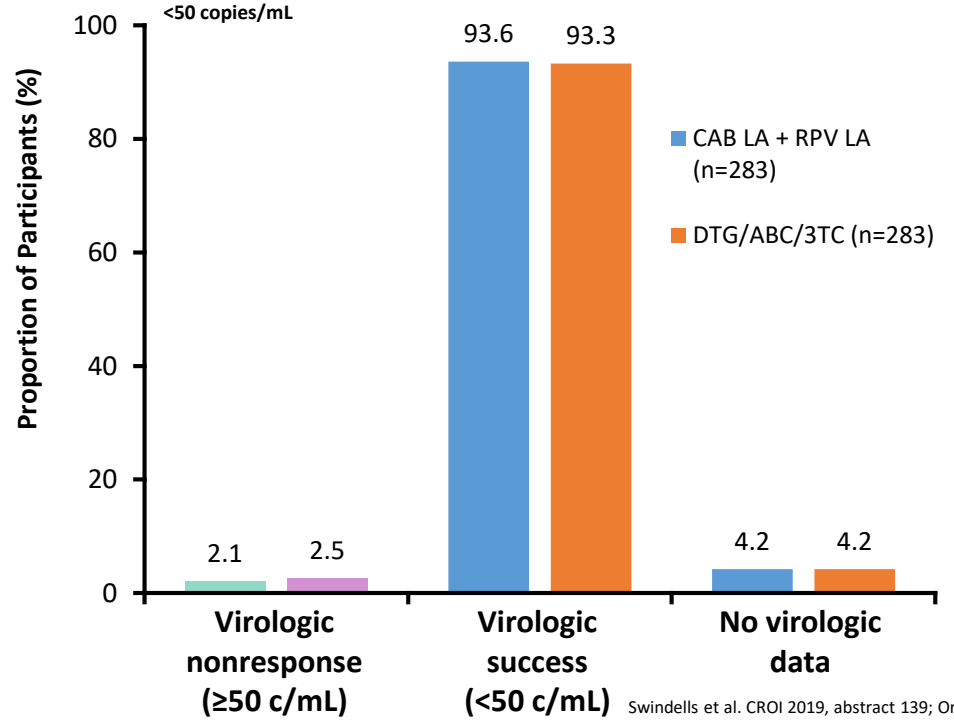
ATLAS





FLAIR





Swindells et al. CROI 2019, abstract 139; Orkin et al. CROI 2019, abstract 140LB

ATLAS and FLAIR confirmed virologic failures: CAB LA + RPV LA

Sex, Country, HIV-1 Subtype	Previous CAR	SVF Timepoint	Viral Load at SVF/CVF (c/mL)	SVF Timepoint RAMs (HIV-1 RNA)		Drug Sensitivity at SVF† (Fold Change)	Baseline RAMs (PBMC/HIV-1 DNA; Day 1)	
				RT	INSTI*		RT	INSTI*
F, Russia, A/A1	3TC, AZT, LPV/r	Week 8	79,166 / 25,745	E138A	L74I	**RPV (2.4)** CAB (0.8) DTG (0.9)	E138E/A	L74I
F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	Week 12	695 / 258	V108I E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)	V108V/I E138K	None
M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	Week 20	544 / 1841	E138E/K	N155H L74I	**RPV (6.5)** **CAB (2.7)** DTG (1.2)	None	L74I

Sex, Country, HIV-1 Subtype, Virologic Load (Baseline)	Baseline RAMs (HIV-1 RNA)		SVF Timepoint	Viral Load at SVF/CVF (c/mL)	SVF Timepoint RAMs (HIV-1 RNA)		Drug Sensitivity at SVF† (Fold Change)
	NNRTI	INSTI*			NNRTI	INSTI*	
F, Russia, A1, 54K	None	L74I	Week 20	373 / 456	E138E/A/K/T	L74I, Q148R	**RPV (7.1)** **CAB (5.2)** DTG (1.0)
M, Russia, A1, 23K	None	L74I	Week 28	287 / 299	K101E	L74I, G140R	**RPV (2.6)** **CAB (6.7)** DTG (2.2)
F, Russia, A1, 20K	None	L74I	Week 48	488 / 440	E138K	L74I, Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

Swindells et al. CROI 2019, abstract 139; Orkin et al. CROI 2019, abstract 140LB

MK-8591 + doravirine and 3TC in participants infected with HIV: DRIVE2Simplify

- Participants will be treated OD with MK-8591, 100 mg DOR, 300 mg 3TC, and placebo to MK- 1439A for a minimum of 24 weeks

- Between week 24 through week 52, 3TC and placebo to MK-1439A may be discontinued

- Around Week 60, participants may be switched to a selected open label dose of MK-8591 and DOR 100 mg OD and continue treatment until Week 120

Matthews et al. Open Forum Infectious Diseases, Volume 5, Issue suppl_1, November 2018, Page S203

New combinations/drugs: candidates for 2DR?

- DOR + DTG
- GS-CA1 + ?
- Other LA ARVs

Conclusions

- Extensive experience and data on 3DR but 2DR might be the future
- Drug characteristics (genetic barrier, IQ, PK forgiveness, etc.)
- Long acting, injectables, implants etc. in development – cost will matter…
- No drug is magic…

THANK YOU