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BHIVA ‘Best of CROI’ Feedback Meetings

London | *Edinburgh*

Wakefield | *Cardiff*

Birmingham | *Haydock*

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ART, new drugs and strategies, resistance

Plan

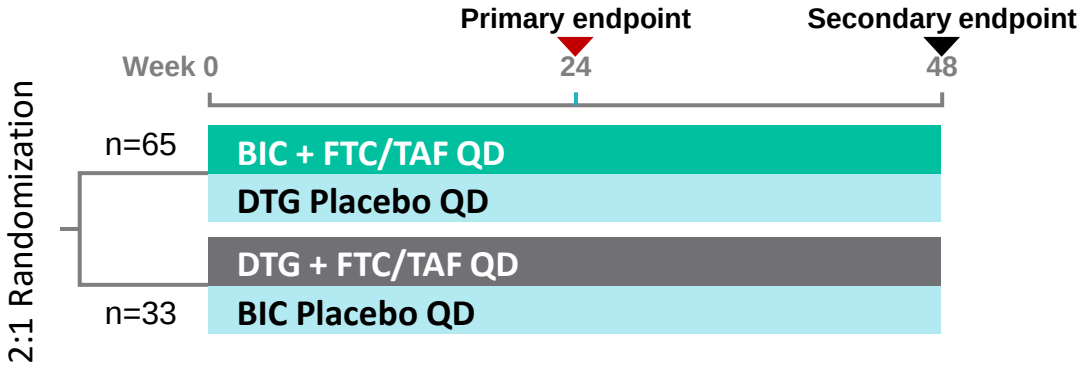
- Naïve
- Switch
- Resistance
- Strategies
- PK
- Novel Agents

Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy
Sax P

- Bictegravir (BIC; GS-9883) is a novel, once-daily, INSTI
  - Potent in vitro activity against wild-type and most INSTI-resistant variants with low potential for drug-drug interactions
  - BIC plasma half-life approximately 18 hours
  - Among INSTIs, BIC has the longest dissociation constant ($t_{½}$) from wild-type HIV-1 integrase-DNA complexes
  - A 10 day study of BIC monotherapy in HIV-1 infected patients demonstrated rapid decline in HIV-1 RNA >2 $\log_{10}$ copies/mL
  - BIC is currently in clinical development co-formulated with tenofovir alafenamide (TAF) and emtricitabine (FTC) for the treatment of HIV-1 infection

Study Design

- Treatment-naïve
- HIV-1 RNA ≥1,000 c/mL
- HBV and HCV negative
- CD4 ≥200/µL



- Randomized, double-blind, active-controlled study (125 screened, 98 randomized)
- Primary Endpoint: proportion with HIV-1 RNA <50 copies/mL at Week 24
- After Week 48, all patients who completed the double-blind phase entered an extension phase and received open label BIC/FTC/TAF

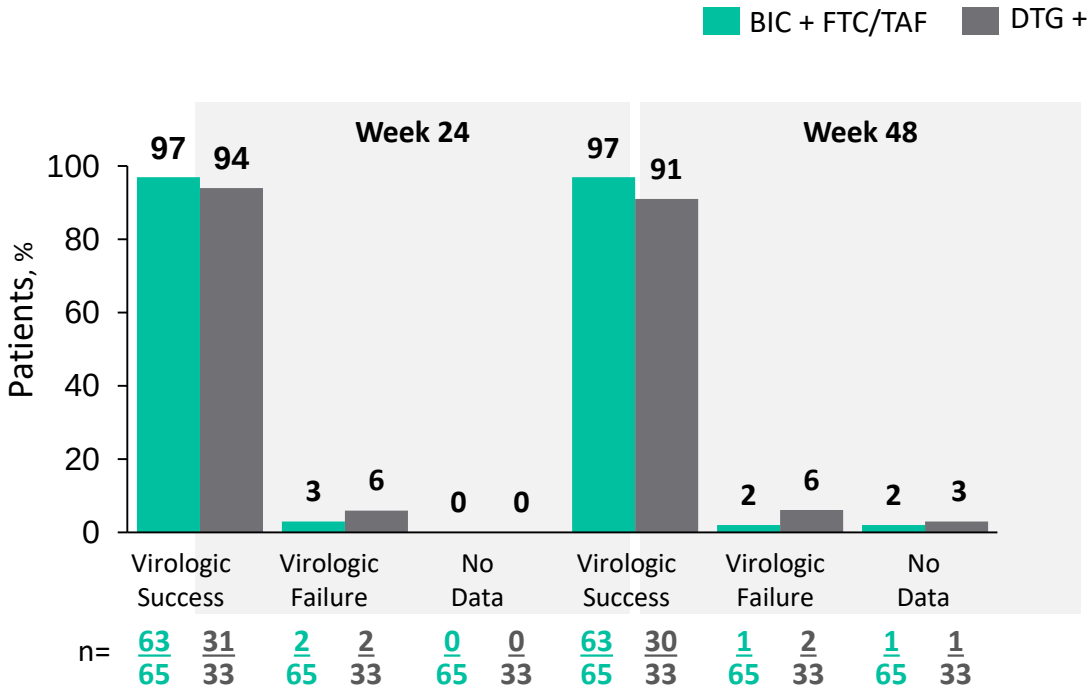
DTG, dolutegravir

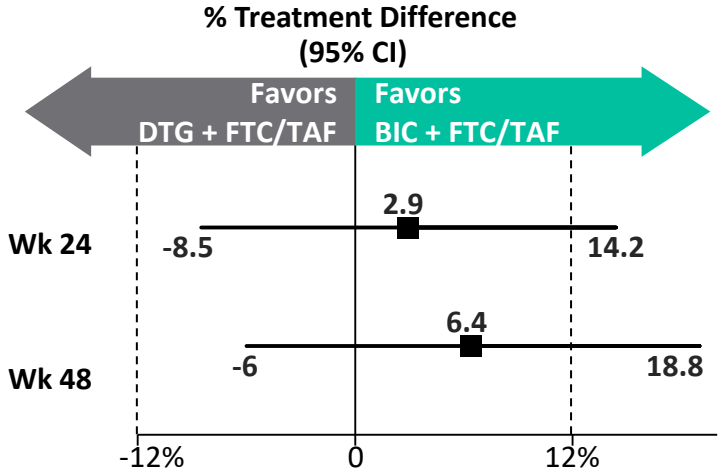
Results: Baseline Characteristics

Characteristic	BIC + FTC/TAF n=65	DTG + FTC/TAF n=33
Median age, years (range)	30 (19–68)	36 (21–61)
Male, %	98	91
Race, %		
White	58	55
Non-white	41	45
Median HIV-1 RNA, log_{10} copies/mL (IQR)	4.41 (4.01, 4.78)	4.48 (3.94, 4.82)
Baseline HIV-1 RNA >100,000 c/mL, %	15	21
Median CD4 Count, cells/mm^3 (IQR)	441 (316, 574)	455 (273, 677)
≤200 cells/mm^3, %	5	9
Median eGFR, mL/min (IQR)	130 (111, 148)	122 (97, 145)

- eGFR, estimated glomerular filtration rate by Cockcroft-Gault method.

Virologic Outcomes at Weeks 24 and 48 by FDA Snapshot HIV VL <50 c/mL





No resistance to study medications was detected in either arm

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Adverse Events

All Grades, ≥5% in either group	BIC + FTC/TAF n=65	DTG + FTC/TAF n=33
Diarrhea	12%	12%
Nausea	8%	12%
Headache	8%	3%
Upper respiratory tract infection	8%	0%
Fatigue	6%	6%
Arthralgia	6%	6%
Chlamydial infection	6%	3%
Back pain	6%	0%
Furuncle	5%	6%
Flatulence	2%	6%
Gastroenteritis	2%	6%
Costochondritis	0%	6%
Hemorrhoids	0%	6%
Pruritis	0%	6%

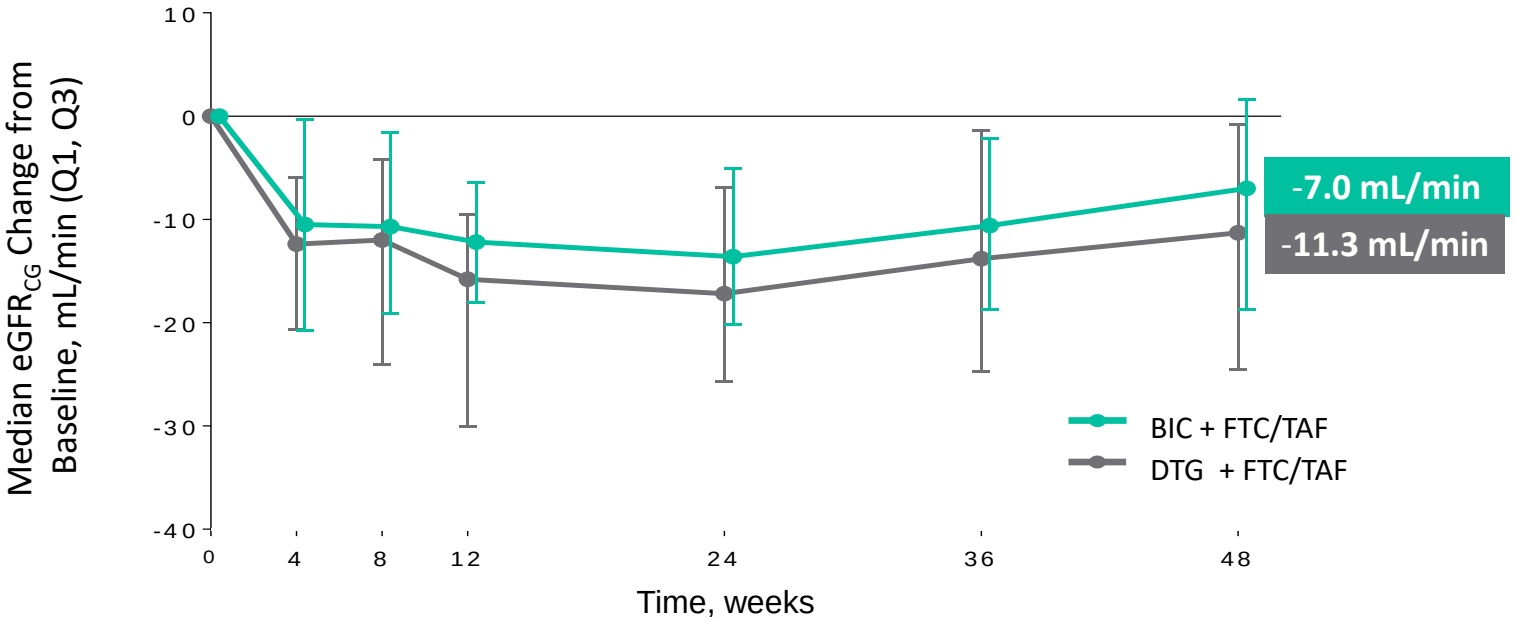
- 1 patient in the BIC + FTC/TAF group with a past history of urticaria and atopic dermatitis discontinued study drug after Week 24 due to urticaria

G2-4 Lab events

≥5% in either group	BIC + FTC/TAF n=64*	DTG + FTC/TAF n=32*
Creatine kinase (CK)	13%	9%
AST	9%	3%
Hyperglycemia	8%	13%
ALT	6%	0%
LDL	6%	9%
Amylase	5%	6%
Hematuria	3%	6%
Glycosuria	2%	6%

*The number of patients randomized and dosed with at least 1 post-baseline laboratory assessment, excluding assessments not specified for all patients at any given visit.

Results: Change in eGFR Over Time



- No discontinuations due to renal adverse events and no tubulopathy in either arm

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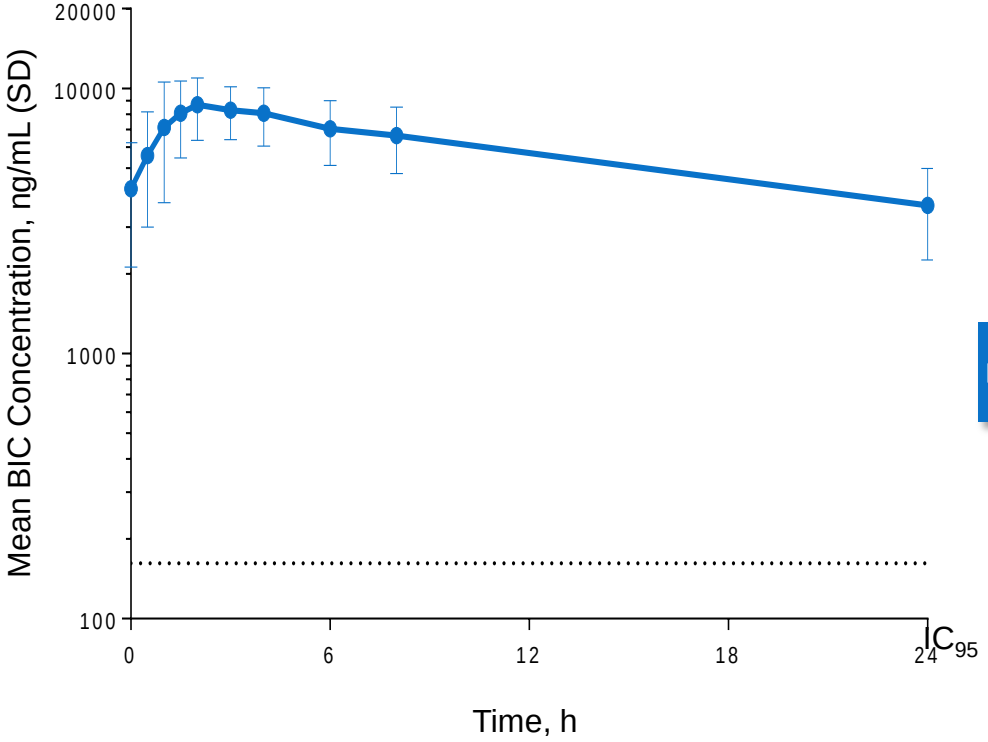
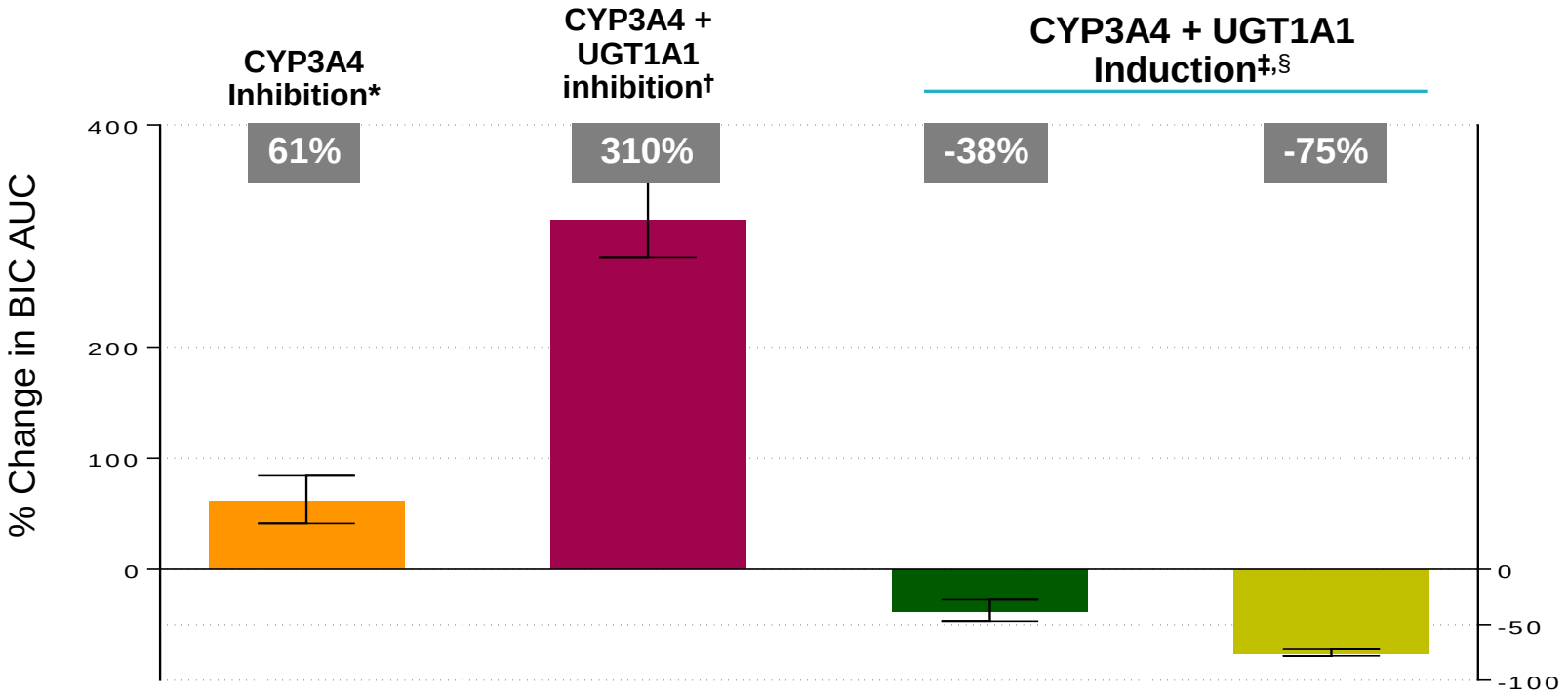
BIC Pharmacokinetic Profile HIV-infected Subjects
Phase 2: BIC 75 mg + F/TAF 200/25 mg
Heather Zhang



	BIC PK Parameters N=23		
	AUC_{τ}, h·ng/mL	C_{max}, ng/mL	C_{τ}, ng/mL
BIC 75 mg	140,000 (27)	9340 (27)	3510 (37)

*Data presented as mean (%CV).

Effects of other drugs ON BIC : Clinical Study Probing Effect of Inhibitors or Inducers



- *Voriconazole; †atazanavir; ‡rifabutin; §rifampin.

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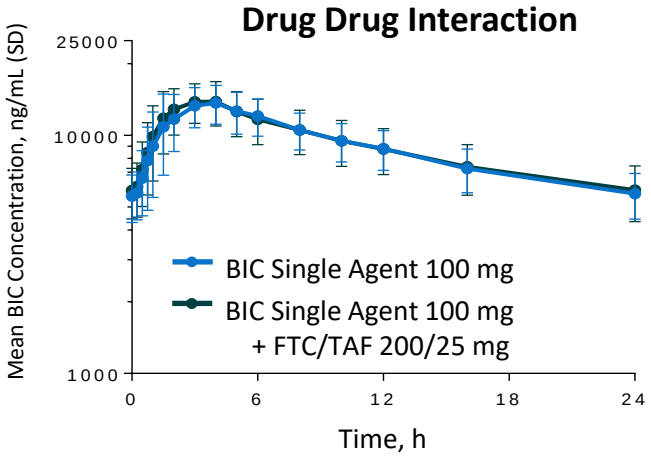
Effect of BIC ON other Co-administered Drugs

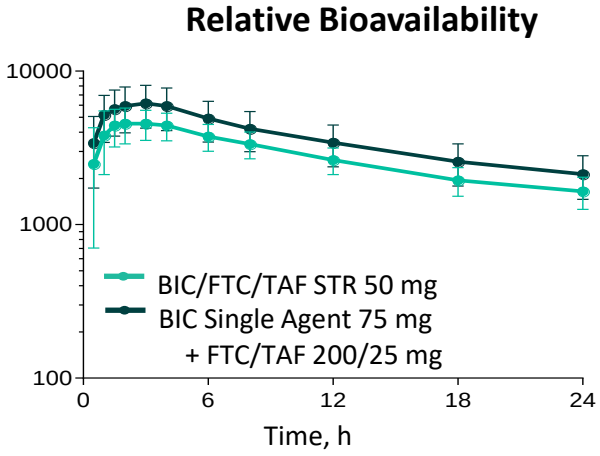
		Change in AUC
CYP3A4 Probe Substrate	Midazolam	↔
Representative Oral Contraceptive	Norelgestromin*	↔
	Ethinyl Estradiol	↔
Representative HCV DAA	Ledipasvir	↔
	Sofosbuvir	↔
OCT2/MATE1 Probe Substrate	Metformin	↑ 39%

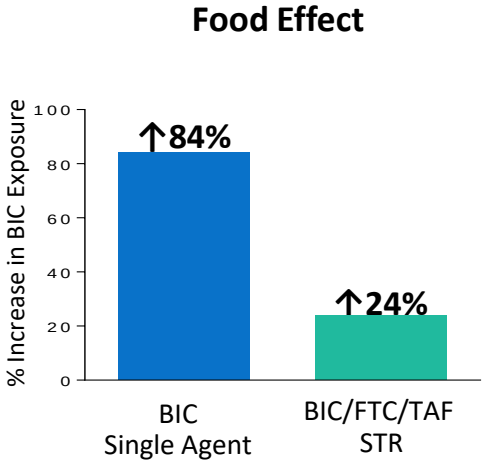
- Low potential to perpetrate DDIs
  - Not an inhibitor or inducer of CYP3A4 or UGT1A1
    - No effect on midazolam
  - No interaction with a representative oral contraceptive
    - No effect on norgestimate/ethinyl estradiol
  - No interaction with a representative HCV DAA
    - No effect on ledipasvir/sofosbuvir
  - Limited liability for inhibition of renal transporters (OCT2 and MATE1)
    - Modest increase in metformin exposure

- *Norelgestromin is circulating pharmacologically active progestin from norgestimate.
- 90% CI of GMR were within (↔) or extended above (↑) the predetermined protocol defined equivalence boundaries of 70–143%.

Co-formulation of BIC + F/TAF into Single Tablet Regimen (STR)







- Lack of DDI between BIC and FTC/TAF established
  - FTC/TAF 200/25 mg dose
- STR formulation development
  - Improved BIC bioavailability vs single agent Phase 2 formulation
  - Reduced food effect vs single agent Phase 2 formulation
  - STR with 50 mg BIC dose selected for Phase 3; administered with or without food

Coformulated BIC/FTC/TAF 50/200/25 mg STR under evaluation in Phase 3 studies

48 week Doravirine vs Darunavir/r in Naïve patients: DRIVE FORWARD STUDY
J Molina (K Squires)

J. Molina (K. Squires) CROI 2017

Study Design

Phase 3, multicenter, double-blind, randomized study in treatment-naïve adults with HIV-1 infection

Key Entry Criteria:

- HIV-1 RNA ≥1000 c/mL within 45 days before Day 1
- Antiretroviral naive
- No genotypic resistance to any study drugs
- Stratification factors: HIV-1 RNA > 100,000 and NRTI choice

Group 1: DOR 100 mg + DRV-PBO + r-PBO + 2 NRTIs — 14 Day Follow-up

Group 2: DOR-PBO + DRV 800 mg + r 100 mg + 2 NRTIs — 14 Day Follow-up

Primary Analysis Time Point

10% non inferiority margin

DOR = doravirine; DRV = darunavir; PBO = placebo; r = ritonavir
NRTIs = open-label TDF/FTC or ABC/3TC, as chosen by the investigator before randomization
All study therapy components were taken once daily

DRIVE FORWARD

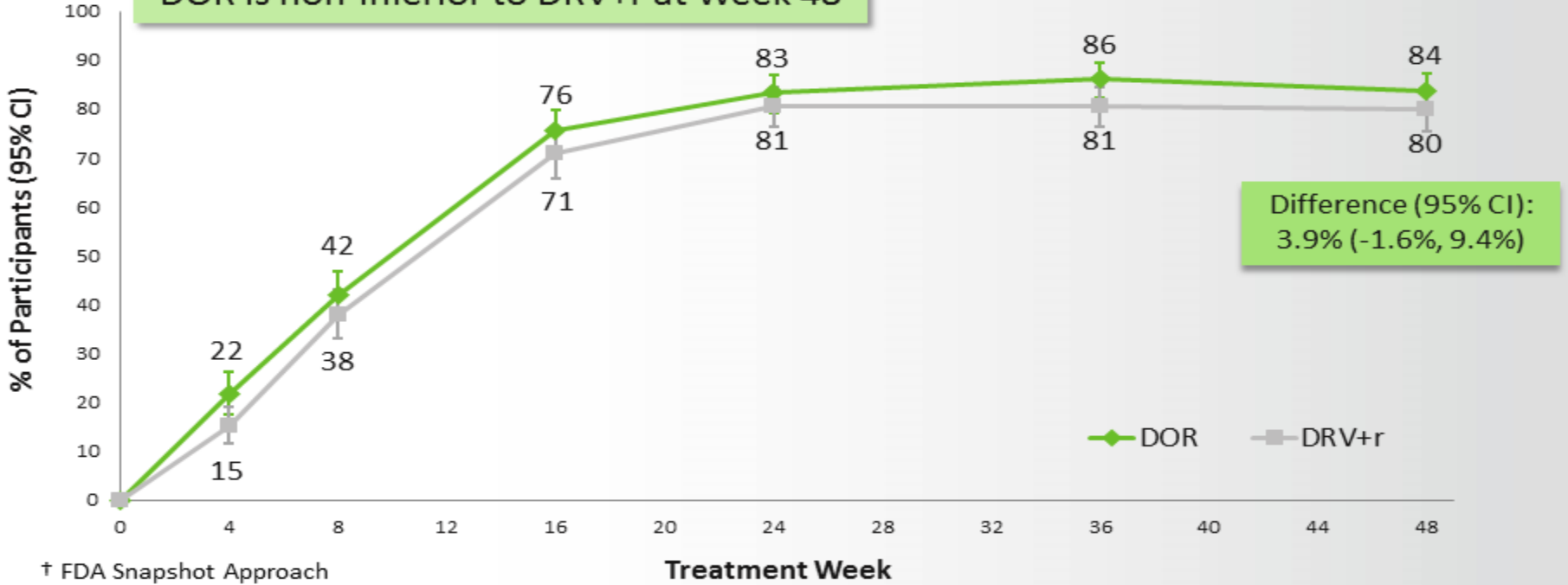
15% (56) on DOR discontinued after entry vs 19% (71) on DRV/r

Baseline Characteristics

	DOR (N=383)	DRV+r (N=383)
Mean age (SD), years	34.8 (10.5)	35.7 (10.7)
Male	83%	85%
Black/African American	22%	23%
Clinical history of AIDS	9%	10%
HIV-1 subtype B	69%	71%
Baseline HIV-1 RNA		
Mean (SD), $\log_{10}$ copies/mL	4.4 (0.7)	4.4 (0.7)
> 100,000 copies/mL	22%	19%
> 500,000 copies/mL	4%	3%
Baseline CD4+ T-cell count		
Mean (SD), cells/mm^3	433 (208)	412 (230)
≤ 200 cells/mm^3	11%	17%
NRTIs selected for use with blinded therapy		
TDF/FTC	87%	88%
ABC/3TC	13%	13%

Efficacy: Proportion with HIV-1 RNA <50 c/mL†

DOR is non-inferior to DRV+r at Week 48



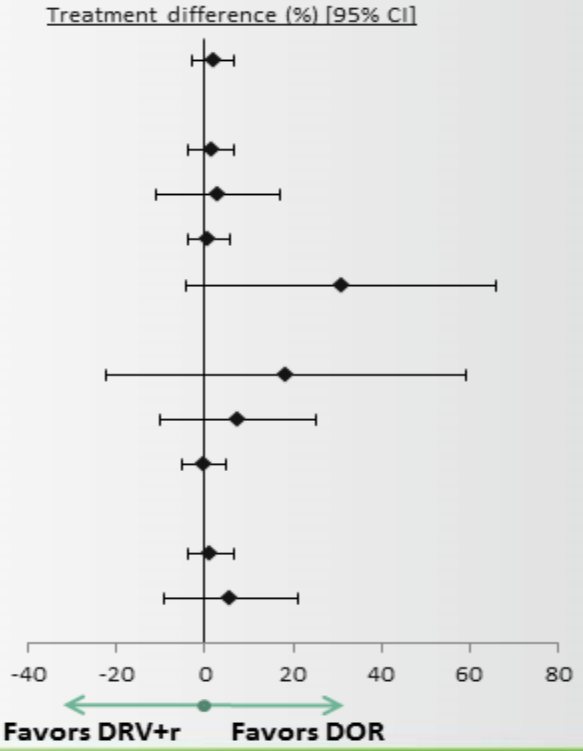
Difference (95% CI): 3.9% (-1.6%, 9.4%)

† FDA Snapshot Approach

DRIVE FORWARD

Efficacy by Subgroup, Observed Failure† Approach

	HIV-1 RNA <50 c/mL, % (N)	
	DOR	DRV+r
All Participants	88 (364)	86 (355)
Baseline HIV-1 RNA, c/mL		
≤100,000	90 (285)	89 (282)
>100,000	81 (79)	76 (72)
≤500,000	88 (347)	87 (342)
>500,000	82 (17)	50 (12)
Baseline CD4+ T-cell Count, cells/mm^3		
≤50	83 (6)	67 (18)
>50 and ≤200	83 (35)	74 (43)
>200	89 (323)	89 (294)
NRTI Component		
TDF/FTC	88 (316)	87 (312)
ABC/3TC	90 (48)	84 (43)



† Discontinuation due to lack of efficacy = failure; data missing for other reasons were excluded. N = number of participants in subgroup.

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Treatment-Emergent Drug Resistance – PDVF

	DOR (N=383)		DRV+r (N=383)	
Participants with PDVF[†], n (%)	19 (5%)		24 (6%)	
	Non-responder	Rebounder	Non-responder	Rebounder
	2	17	5	19
Genotype test successfully performed, n	7		8	
Primary NNRTI resistance	0		0	
Primary NRTI resistance	0		0	
Primary PI resistance	0		0	
Phenotype test successfully performed, n	6		8	
With any phenotypic drug resistance	0		0	

[†] Protocol defined virologic failure (PDVF): Confirmed HIV-1 RNA ≥ 50 c/mL after initial response of HIV-1 RNA <50 c/mL; or confirmed HIV -1 RNA ≥ 200 c/mL at Week 24 or Week 36; or confirmed HIV-1 RNA ≥ 50 copies/mL at Week 48.

- No genotypic or phenotypic drug resistance observed in participants with PDVF through Week 48

DRIVE FORWARD

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Summary of Clinical Adverse Events

	DOR (N=383) n (%)	DRV+r (N=383) n (%)
One or more AE	307 (80%)	300 (78%)
Drug-related AE	117 (31%)	123 (32%)
Serious AE	19 (5%)	23 (6%)
Discontinued due to AE	6 (2%)	12 (3%)
Most Common AE's (≥ 10% in either group)		
Diarrhea	54 (14%)	86 (22%)
Nausea	41 (11%)	46 (12%)
Nasopharyngitis	30 (8%)	39 (10%)
Headache	53 (14%)	41 (11%)
AEs of Clinical Interest		
Rash†	28 (7%)	32 (8%)
Neuropsychiatric‡	44 (11%)	50 (13%)

†Only 2 DOR participants and 1 DRV+r participant discontinued due to rash
‡Includes disturbance in attention, dizziness, somnolence, abnormal dreams, confusional state, depressed mood, depression, insomnia, major depression, nightmare, and psychotic disorder. No participants discontinued due to neuropsychiatric AEs

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Most Common† Laboratory Changes, Grade 3/4

Laboratory Test	Grade (criteria)	DOR, N=383 n (%)	DRV+r, N=383 n (%)
Fasting LDL-C	3 (≥190 mg/dL)	1 (<1%)	9 (3%)
Fasting Glucose	3 (>250 – 500 mg/dL)	4 (1%)	1 (<1%)
Creatinine	3 (>1.8 - <3.5 x ULN)	5 (1%)	10 (3%)
Aspartate aminotransferase	3 (5.0 - <10.0 x ULN)	2 (1%)	6 (2%)
Alanine aminotransferase	3 (5.0 - <10.0 x ULN)	4 (1%)	6 (2%)
Lipase	3 (3.0 - <5.0 x ULN)	6 (2%)	6 (2%)
	4 (≥5.0 x ULN)	4 (1%)	3 (1%)
Creatine kinase	3 (10.0 - <20.0 x ULN)	7 (2%)	7 (2%)
	4 (≥20.0 x ULN)	6 (2%)	7 (2%)

† reported in ≥4 participants in either treatment group.

DRIVE FORWARD

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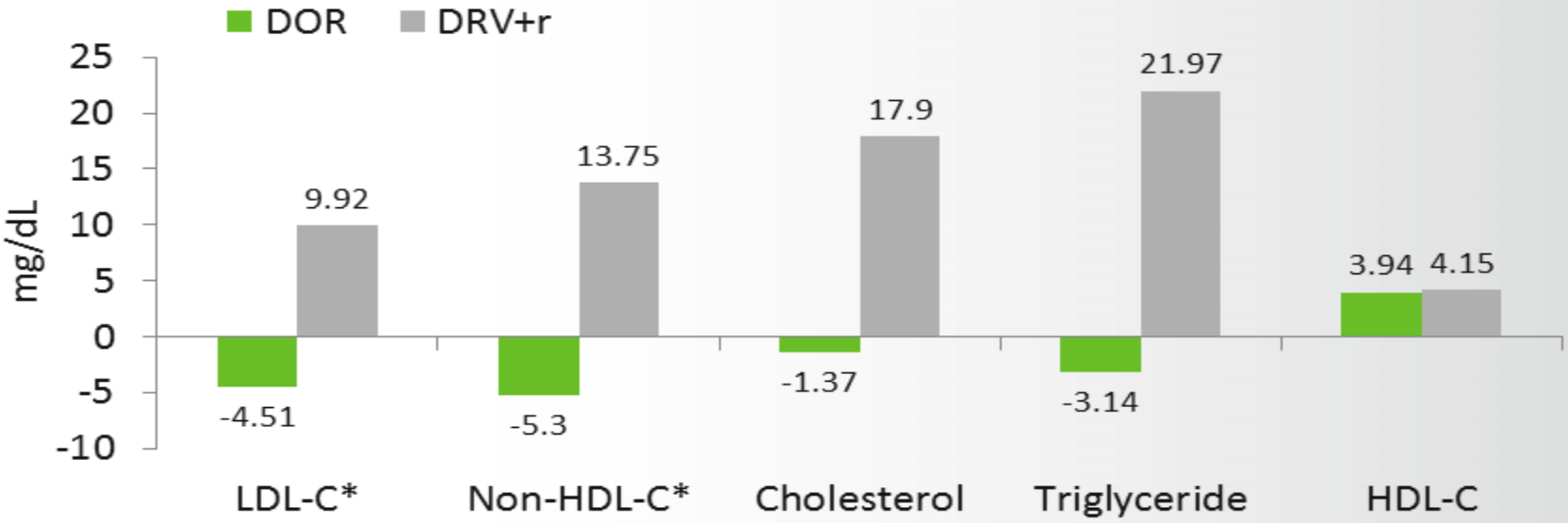
Fasting Lipids, Change from Baseline at Week 48



* P<0.0001 for DOR vs DRV+r. Statistical testing for other parameters was not prespecified.

DRIVE FORWARD

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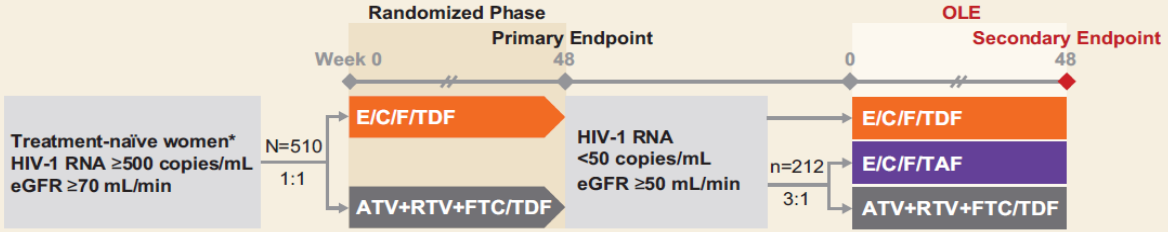
ART switch from TRU/ATV/r to E/C/F/TAF in women with undetectable viral loads

Study Design (GS-US-236-0128; NCT01705574)



*Women of childbearing potential had to agree to utilize protocol-recommended contraception methods, be nonheterosexually active, or practice sexual abstinence. eGFR, estimated glomerular filtration rate.

Demographics and Baseline Characteristics

		E/C/F/TAF n=159	ATV+RTV+FTC/TDF n=53
Median age, y (range)		36 (19–63)	36 (21–62)
Race, n (%)	Black	69 (43)	32 (60)
	White	65 (41)	16 (30)
	Asian	12 (8)	3 (6)
Latino/Hispanic, n (%)		15 (9)	3 (6)
Median CD4 count, cells/μL (range)		580 (58–1602)	687 (96–1168)
Median $eGFR_{CG}$, mL/min (range)		103 (53–260)	101 (35–229)
Proteinuria grade, n (%)*	1	15 (9)	3 (6)
	2	0	1 (2)
HBV surface antigen status, n (%)	Negative	154 (97)	52 (98)
	Positive	5 (3)	0
HCV antibody status, n (%)	Negative	145 (91)	48 (91)
	Positive	14 (9)	4 (8)

*No participants had Grade 3 or 4 proteinuria at baseline. CG, Cockcroft-Gault; HBV, hepatitis B virus; HCV, hepatitis C virus.

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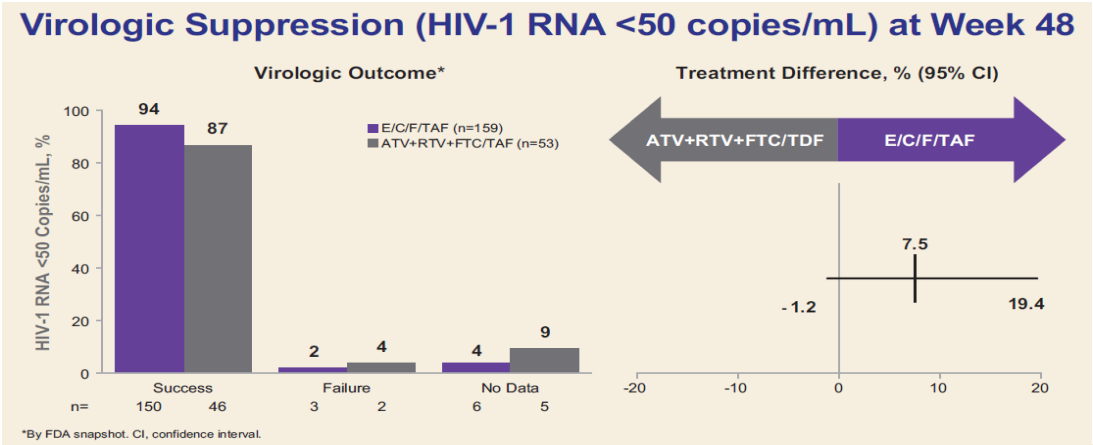
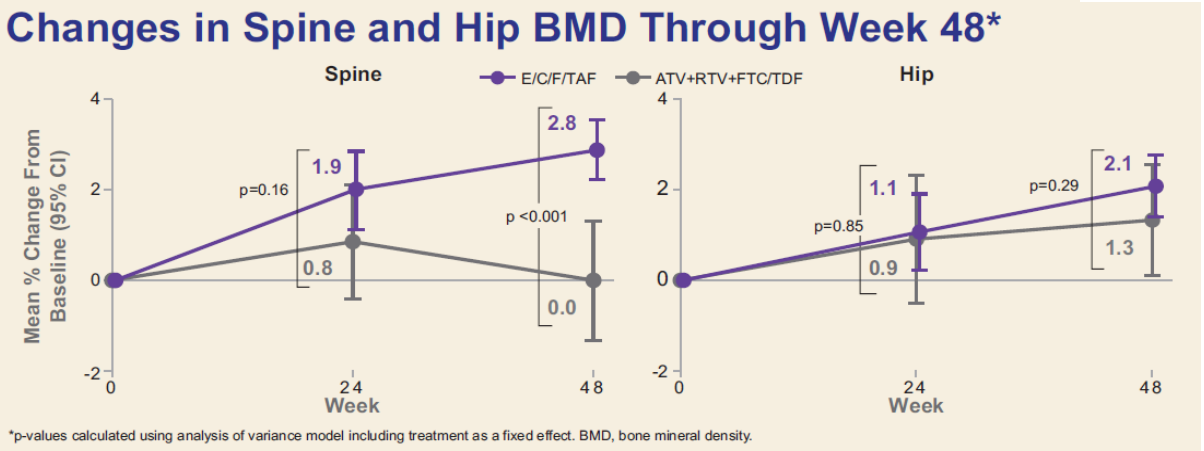
Switching from TRU/ATV/r to E/C/F/TAF maintains viral suppression and improves BMD





Pregnancies, n	E/C/F/TDF n=289
Live births	24*
Elective abortions	10†
Spontaneous abortions	7
Ectopic pregnancy	3
Ongoing pregnancy	1
No reported outcomes	1
	2

No deaths or AE in pregnancy

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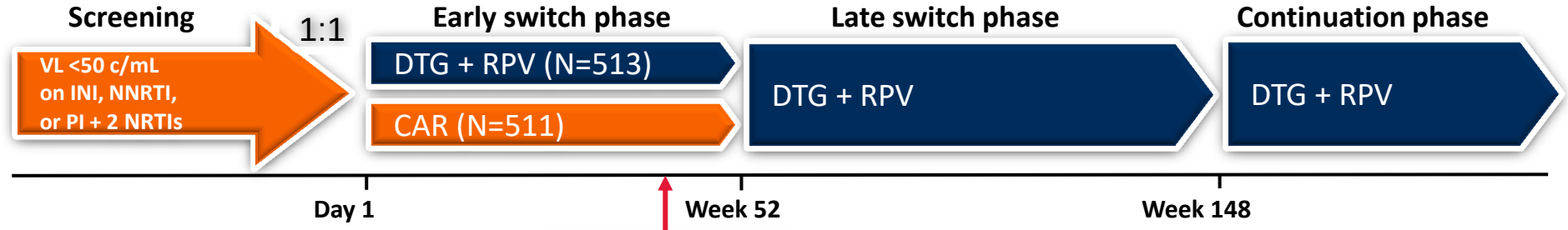
Treatment switches

SWORD 1 & 2: Switch to DTG + RPV Maintains Virologic Suppression Through 48 Weeks

JM Libre

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority phase III 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 during the 12 months before screening
- HBV negative

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

Countries

Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, United Kingdom, United States

- -8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies 513 (DTG+RPV) vs 511 (CAR) screened 486 vs 487 retained and contributed data to week 48 analysis

Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

Demographics and Baseline Characteristics

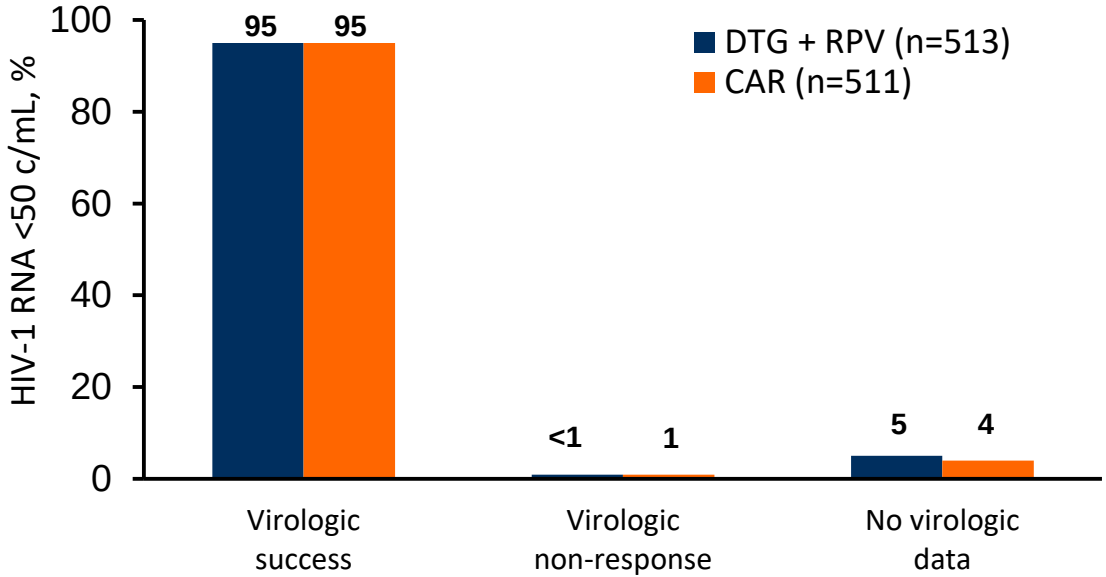
	DTG + RPV (n=513) n (%)	CAR (n=511) n (%)
Age, mean (SD)	43 (11.1)	43 (10.2)
≥50 years	147 (29)	142 (28)
Female	120 (23)	108 (21)
Race, non-white	92 (18)	111 (22)
CD4+ cell count, cells/mm³ (median)	611	638
≤500	165 (32)	149 (29)
>500	348 (68)	362 (71)
Baseline 3rd-agent class		
PI	133 (26)	136 (27)
NNRTI	275 (54)	278 (54)
INI	105 (20)	97 (19)
Baseline TDF use	374 (73)	359 (70)
Duration of ART prior to Day 1, median, months	51	53

Data pooled across SWORD-1 and SWORD-2.

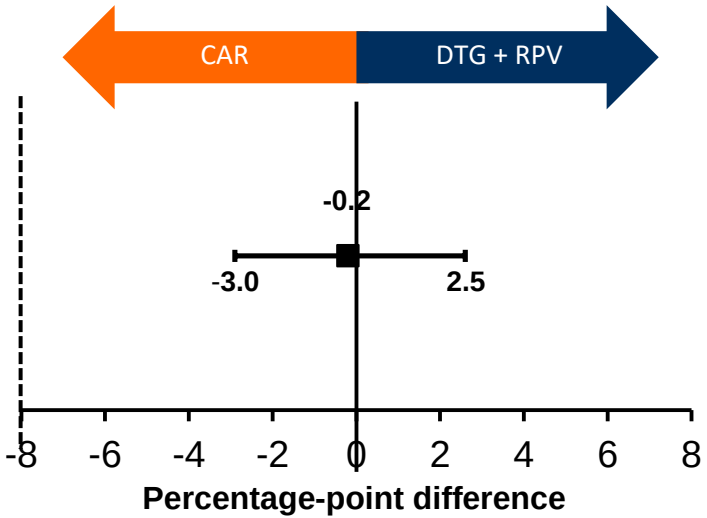
Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

Snapshot Outcomes at Week 48 (Pooled)

Virologic outcomes



Adjusted treatment difference (95% CI)[a]



DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48

[a]Adjusted for age and baseline 3rd agent.

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Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

Snapshot Outcomes at Week 48

	Early switch phase[a]	
	DTG + RPV n=513 n (%)	CAR n=511 n (%)
Virologic success	486 (95)	485 (95)
Virologic non-response	3 (<1)	6 (1)
Data in window not <50 c/mL	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	2 (<1)
Discontinued while VL not <50 c/mL	1 (<1)	1 (<1)
Change in ART	0	1 (<1)
No virologic data	24 (5)	20 (4)
Discontinued due to AE or death[1]	17 (3)	3 (<1)
Discontinued for other reasons	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)

	Early switch phase[a]	
	DTG + RPV n=513 n (%)	CAR n=511 n (%)
Confirmed Virologic Withdrawal (CVW)[b]	2 (<1)	2 (<1)

[a]Data pooled across SWORD-1 and SWORD-2.

[1] Two deaths in the study, both unrelated to study drug. DTG+RPV Kaposi's Sarcoma (N=1), CAR Lung cancer (N=1)

Adverse Events

	Early switch phase[a]	
	DTG + RPV (n=513) n (%)	CAR (n=511) n (%)
Any AE	395 (77)	364 (71)
AEs occurring in ≥5% of subjects in either group	49 (10)	50 (10)
Nasopharyngitis	41 (8)	23 (5)
Headache	24 (5)	37 (7)
Upper respiratory tract infection	32 (6)	27 (5)
Diarrhea	15 (3)	31 (6)
Back pain		
Any Serious AEs[1]	27 (5)	21 (4)
Drug-related AEs		
Grades 1-2	89 (17)	8 (2)
Grades 3-4	8 (2)	1 (<1)
AEs leading to withdrawal from the study	21 (4)	3 (<1)
CNS AEs leading to withdrawal	9 (2)	1 (<1)

Adverse Events Leading to Discontinuation

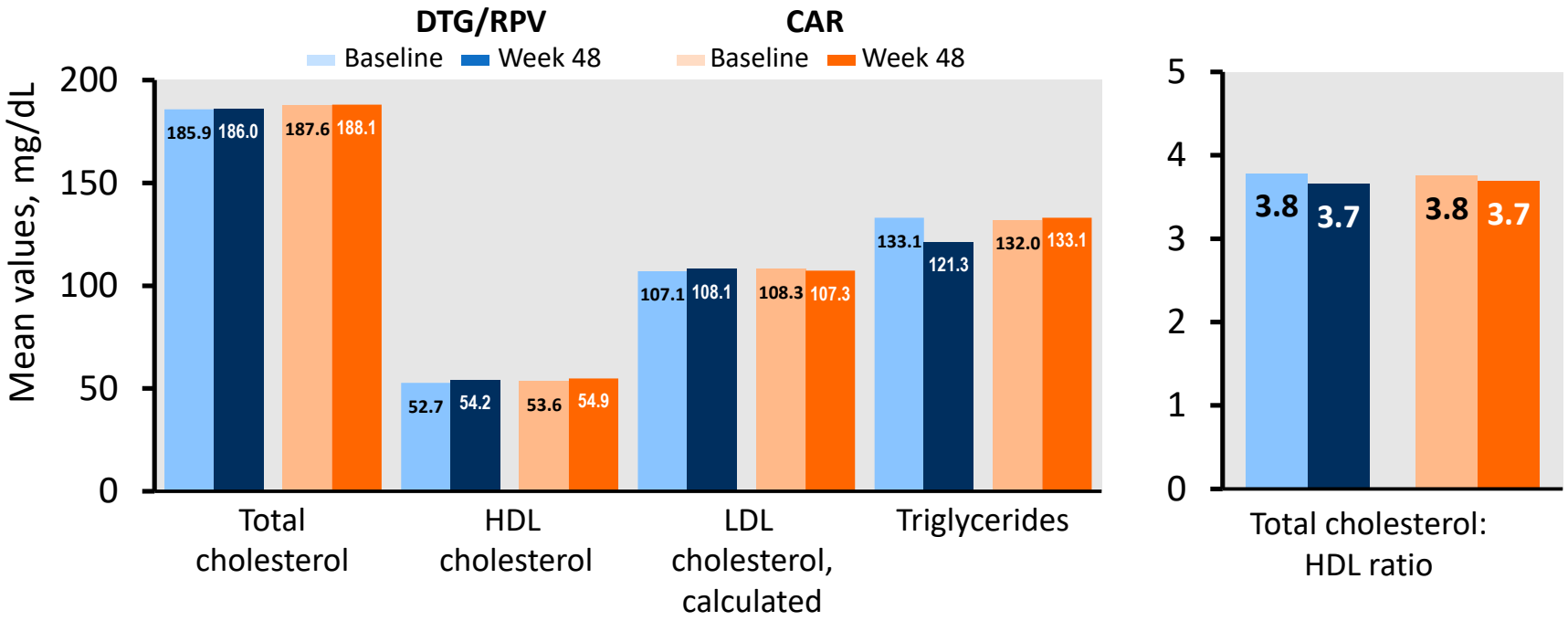
	DTG + RPV[a,b] (n=513) n (%)
Subjects with AEs leading to withdrawal from the study	21 (4)
Events Leading to Withdrawal (subject may report >1 AE)	
Anxiety	4 (<1)
Depression	3 (<1)
Abdominal distention	2 (<1)
Dyspepsia	2 (<1)
Insomnia	2 (<1)
Depressed mood	1 (<1)
Drug-induced liver injury	1 (<1)
Eosinophilic pneumonia, acute	1 (<1)
Gastrointestinal haemorrhage	1 (<1)
Headache	1 (<1)
Hodgkin's disease	1 (<1)
Kaposi's sarcoma	1 (<1)
Pancreatitis, acute	1 (<1)
Panic attack	1 (<1)
Peptic ulcer	1 (<1)
Plasmablastic lymphoma	1 (<1)
Tremor	1 (<1)
Suicidal ideation	

[a]Data pooled across SWORD-1 and SWORD-2 over 52 weeks.

[1]Two deaths in the study, both unrelated to study drug. DTG+RPV Kaposi's Sarcoma (N=1), CAR Lung cancer (N=1).

Change in Serum Lipids at Week 48

Pooled Data Early Switch Phase



Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

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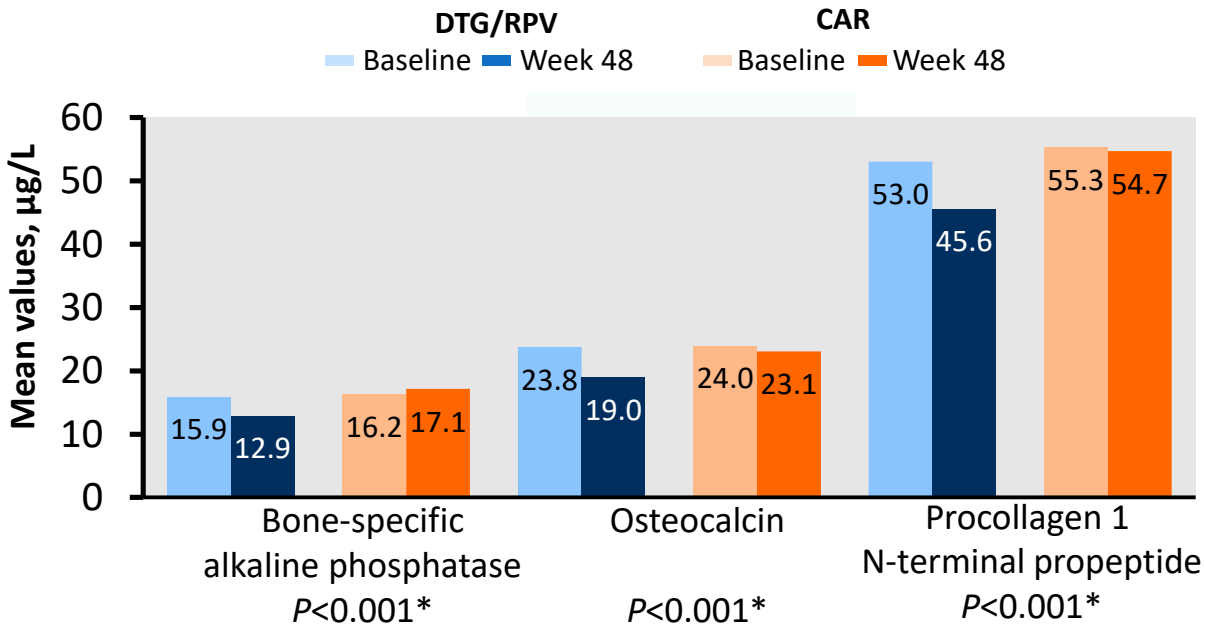
Change in Bone Markers at Week 48

Pooled Data Early Switch Phase



*Adjusted for baseline third agent, age, sex, body mass index, smoking status, and baseline biomarker level. Statistical model uses log-transformed data.

Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

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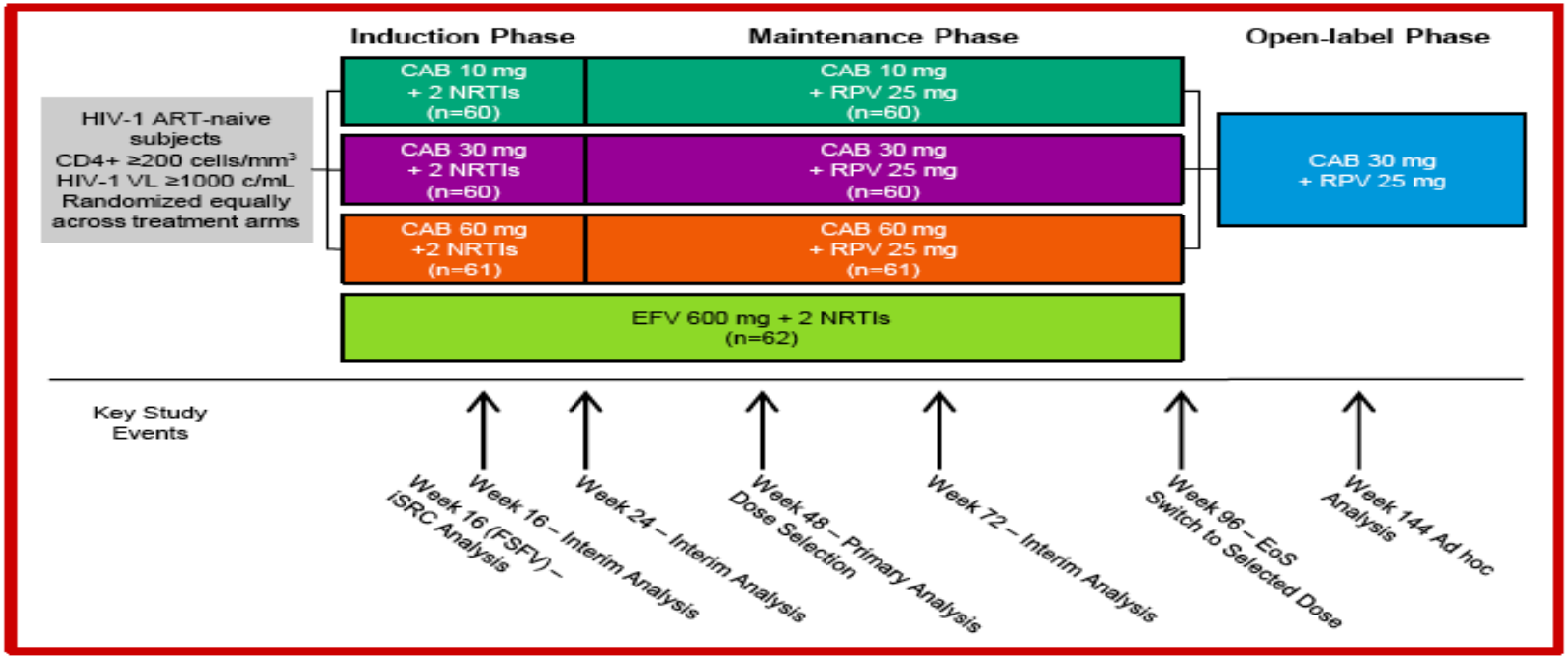
Long-term Safety and Efficacy of CAB and RPV as 2-Drug Oral Maintenance Therapy

Margolis D

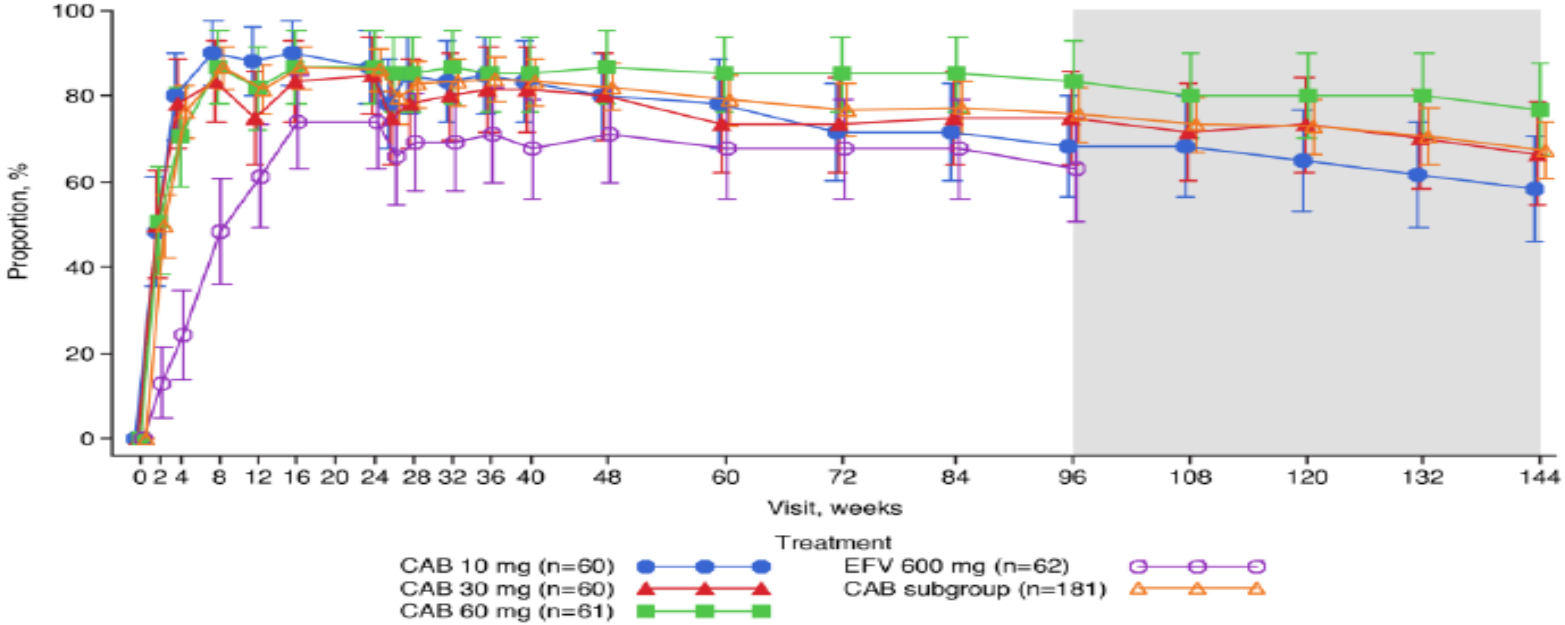
Study Design and Methods

Figure 1. LATTE Study Design



Proportion of Subjects With Plasma HIV-1 RNA <50 c/mL by Visit: Snapshot (MSDF) Analysis

- At W96, EFV Pts completed study participation
- Pts in the CAB arms who qualified for and chose to enter the OL phase were all switched to CAB 30 mg + RPV 25 mg (shaded area)



3 new PDVF's, between week 96 and 144.
2 with resistance mutations: both NNRTI and 1 INSTI

Margolis et al. CROI 2017; Seattle, WA. Poster 422.

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Table 3. Adverse Events Through Week 144

Maintenance safety population[a]	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
Grade 2-4 drug-related events (>3% in any arm)[b]	1 (2)	3 (6)	3 (5)	7 (4)
Depression	0	0	2 (4)	2 (1)
Serious AEs[c]	5 (10)	5 (9)	5 (9)	15 (9)
AEs leading to withdrawal (≥1 Pt)	1 (2)	2 (4)	1 (2)	4 (3)
Anxiety disorder	0	0	1 (2)	1 (<1)
Abnormal ECG	1 (2)	0	0	1 (<1)
Acute hepatitis C[d]	0	1 (2)	0	1 (<1)
Burkitt's lymphoma	0	1 (2)	0	1 (<1)
Grade 1-4 ALT abnormalities[e]	7 (13)	12 (23)	8 (15)	27 (17)
Select Grade 3-4 laboratory abnormalities				
Creatine kinase (CK)	5 (10)	4 (8)	3 (5)	12 (8)
Alanine aminotransferase (ALT)	0	1 (2)	0	1 (<1)
Lipase[f]	2 (4)	1 (2)	3 (5)	6 (4)
Total neutrophils[g]	2 (4)	1 (2)	1 (2)	4 (3)

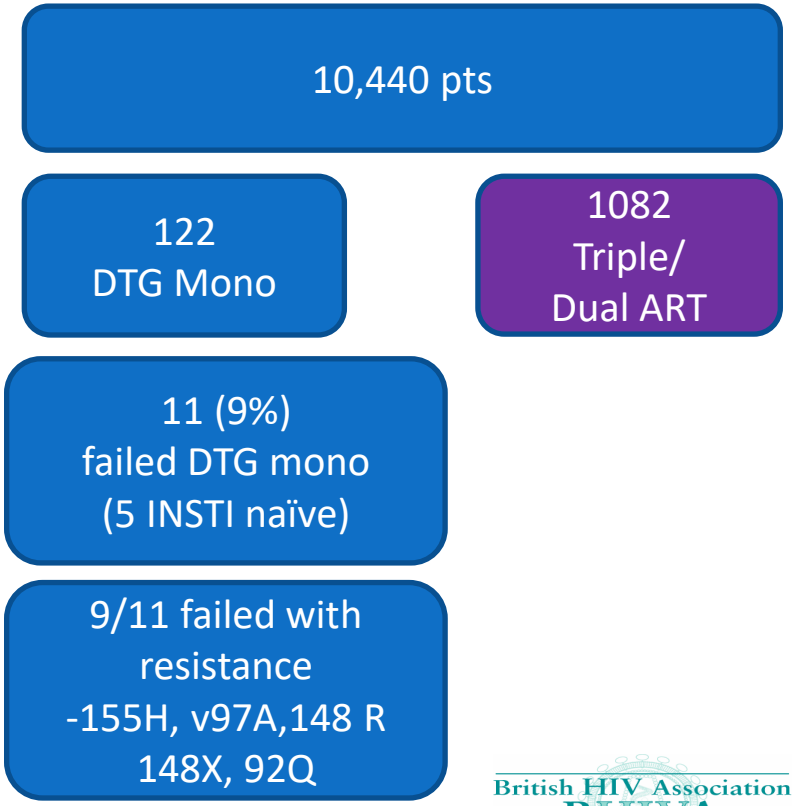
[a]The Maintenance Safety Population consists of all randomized Pts who were exposed to IP during the Maintenance and OL phases of the study. [b]All Grade 2; blood bilirubin increase (CAB 30 mg; n=1; not shown in table) was the only drug-related G2-4 AE added in OL phase (W96 through W144). [c]No SAEs were treatment related. [d]Acute Hep C was diagnosed in OL phase. [e]Less than 1% were ≥Grade 3; CAB 30 mg (n=2) and CAB 60 mg (n=1) were the only Grade 1-4 ALT abnormalities added in the OL phase. [f]CAB 10 mg (n=1) and CAB 60 mg (n=1); the only Grade 3-4 lipase abnormalities added in OL phase. [g]CAB 10 mg (n=1) was the only Grade 3-4 neutrophils abnormality added in OL phase.

Strategies /Methodology

Pathways for resistance in those failing DTG mono-therapy

Blanco J

- Aim:
  - To assess rate of failure with or without resistance in 3 large cohorts with complex DDI/comorbidity/toxicity
  - Describe resistance and outcomes for failing pts
- Pts from 3 centres, had to be VL<50 at switch,
- Exclusion : prior INSTI failure or no available resistance test
- Adherence was variable
- Most switched to DRV/r /triple



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ANRS 159 VIH-2 Pilot Study: Raltegravir & Truvada in HIV-2 infection

Inclusion criteria : HIV-2 infection only, with
- previous CDC group B or C defining event
- or CD4 count <500 cells/µL
- or CD4 decrease >50 cells/µL/year over the last 3 years, with a last value ± 10% of CD4 nadir
- or confirmed plasma HIV-2 RNA (pVL) ≥100 copies (cp)/mL

Primary endpoint : proportion of participants surviving at W48 without any of the following events :
- CD4 gain <100 cells/µL, as compared to baseline (W-4, W0) mean count
- pVL ≥40 cp/mL from W24 (confirmed within the next 4 weeks) (= virological failure)
- Raltegravir permanent discontinuation
- New B or C event

Missing data considered as failure

Main secondary endpoints:
- Mean gain in CD4 count at W12
- Evolution of CD4 count and percentage (W0-W48)
- Evolution of HIV-2 plasma RNA (W0-W48)
- Identification of selected resistance mutations (reverse transcriptase, integrase) and change in INI IC50 in case of virological failures, as compared to W0
- Evolution of ultrasensible pVL (us pVL) and total DNA (determined using "in-house" PCR assays) between W0 and W48
- Clinical progression
- Tolerance

Baseline characteristics

Sex, female, n (%)	20	(67)
Median age - years, (IQR)	49	(46 ; 53)
<35	1	(3)
[35;45[	5	(17)
[45;55[	17	(57)
[55;65[	4	(13)
≥ 65	3	(10)
Place of birth, n (%)		
West Africa	26	(87)
France	4	(13)
HIV-2 transmission, n (%)		
Heterosexual contacts	23	(77)
Transfusion	4	(13)
Unkwown	3	(10)
Time since HIV-2 diagnosis (years)(IQR)	11	(7.5 ; 13.9)
CDC stage - W-4, n (%)		
A	26	(86.7)
B	2	(6.7)
C	2	(6.6)
CD4 count cells/µL		
Median nadir (IQR)	351	(286.0 ; 455.0)
Median count (W-4, W0)	436	(314.0 ; 507.0)
< 200	3	(10.0)
[200-350[	6	(20.0)
[350-500[	13	(43.3)
≥ 500	8	(26.7)
CD4/CD8 ratio - W0, median (IQR)	0.9	(0.6-1.2)
Plasma HIV-2 RNA ≥ 40 cp/mL – n (%)	20	(67)
log_{10}cp/mL, median (IQR)	2.5	(1.8-3.2)

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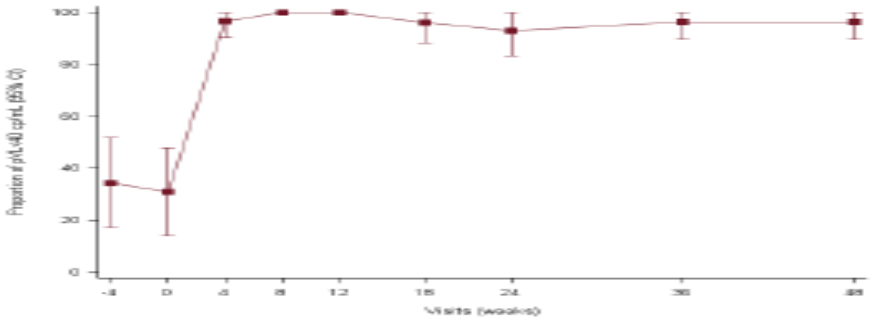
ANRS 159 VIH-2 Pilot Study: Results

At W48

- **Success was reached in 12/30 patients (40%)** ($CI_{95\%}$ 22.7- 59.4)
- **Failure was observed in 18/30 (60%) due to :**
  - **CD4 gain <100 cells/µL** **n=15**
    - median CD4 change (IQR) +38 (-5.5;+70)
    - CD4 loss n=5 (33%)
  - **pVL ≥40 cp/mL** **n= 1**
    - Viral failure at W18
    - Resistance mutations: E92Q, T97A, Y143C/G/H/R
  - **Withdrawal before W48** **n= 2**



Proportion of participants with HIV-2 RNA <40 cp/mL from W-4 to W48

- First-line treatment with Truvada / Raltegravir was well tolerated and resulted in 40% patients with VL<40 cp/ml at 1 year.
- Comparable to outcomes with PI regimens
- Failure driven by lower CD4 count gain

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Efficacy of initial ART

- The FDA Snapshot analysis defines success of ART by VL<50 without ART change
- ART changes are most commonly due to AE's
- Drug-related AE's may increase the risk of ART failure, but this has not been demonstrated

- Re-analysis of data from the SINGLE trial (ABC/3TC/DTG vs. TDF/FTC/EFV)
- Relationship between drug-related AE's and subsequent ART failure
- "Snapshot plus" algorithm that regards Grade 2= drug related AE's as ART failure

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Drug-related AE's (grade 2+) predict subsequent ART failure

Table 1. Odds of failure by Snapshot at Weeks 48, 96 and 144 for participants experiencing any grade, or any grade 2-4, drug-related AE through to Week 12.

WEEK AND GROUP	ANY GRADE AE			GRADE 2-4 AE	
	OR (95%CI)	P		OR (95%CI)	P
All participants					
Week 48	1.07 (0.73 – 1.55)	0.73		2.68 (1.75 – 4.11)	<0.001
Week 96	1.12 (0.82 – 1.55)	0.48		2.55 (1.73 – 3.75)	<0.001
Week 144	1.05 (0.79 – 1.41)	0.74		2.47 (1.76 – 3.58)	<0.001
VL <5log$_{10}$ copies/mL					
Week 48	1.08 (0.67 – 1.76)	0.64		3.00 (1.77 – 5.08)	<0.001
Week 96	1.24 (0.83 – 1.86)	0.30		2.74 (1.72 – 4.37)	<0.001
Week 144	1.08 (0.76 – 1.55)	0.66		2.78 (1.79 – 4.30)	<0.001
VL ≥5log$_{10}$ copies/mL					
Week 48	1.07 (0.59 – 1.94)	0.83		2.47 (1.16 – 5.26)	0.02
Week 96	0.97 (0.57 – 1.65)	0.91		2.44 (1.20 – 4.96)	0.01
Week 144	1.00 (0.60 – 1.65)	0.99		1.93 (0.96 – 3.90)	0.07

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ART failure as defined by “FDA Snapshot” and “Snapshot Plus”

Table 2. Odds of failure by Snapshot analysis at Weeks 48, 96 and 144 for study participants experiencing any grade, or any grade 2-4, drug-related AE through to Week 12.

	SNAPSHOT				SNAPSHOT-PLUS				
	% Responders		Mean diff (95%CI)*	Chi-square P	% Responders		Mean diff (95%CI)*	Chi-square P	McNemar's P
All participants	ABC-3TC-DTG (N=414)	TDF-FTC-EFV (N=419)			ABC-3TC-DTG (N=414)	TDF-FTC-EFV (N=419)			
Week 12	83.8	54.2	29.6 (23.7 – 35.6)	<0.0001	76.2	43.4	32.7 (26.4-38.9)	<0.0001	<0.0001
Week 48	87.9	80.6	7.3 (2.3-12.2)	0.004	76.6	62.8	13.8 (7.6-20.0)	<0.0001	<0.0001
Week 96	80.4	72.3	8.1 (2.4-13.9)	0.006	70.3	56.6	13.7 (7.3-20.2)	<0.0001	<0.0001
Week 144	71.5	63.2	8.3 (1.9 – 14.6)	0.01	62.6	50.4	12.2 (5.5-18.9)	<0.004	<0.0001
HIV-RNA <5log$_{10}$ c/mL	N=280	N=288			N=280	N=288			
Week 12	91.8	65.9	25.8 (19.5 – 32.2)	<0.0001	81.8	52.4	29.4 (22.0 – 36.7)	<0.0001	<0.0001
Week 48	90.4	82.6	7.7 (2.1 – 13.3)	0.007	77.9	62.9	15.0 (7.6 – 22.4)	<0.0001	<0.0001
Week 96	85.0	72.6	12.4 (5.8 – 19.1)	0.0003	73.2	55.6	17.7 (9.9 – 25.4)	<0.0001	<0.0001
Week 144	72.9	64.2	8.6 (1.0 – 16.2)	0.03	63.6	50.4	13.2 (5.2 – 21.3)	0.002	<0.0001
HIV-RNA ≥5log$_{10}$ c/mL	N=134	N=131			N=134	N=131			
Week 12	67.2	28.2	38.9 (27.8 – 50.0)	<0.0001	64.2	23.7	40.5 (29.6 – 51.4)	<0.0001	<0.0001
Week 48	82.8	76.3	6.5 (-3.2 to 16.2)	0.19	73.9	62.6	11.3 (0.2 – 22.4)	0.048	<0.0001
Week 96	70.9	71.8	-0.9 (-11.8 to 10.3)	0.87	64.2	58.8	5.4 (-6.3 to 17.1)	0.37	<0.0001
Week 144	68.7	61.1	7.6 (-3.9 to 19.1)	0.20	60.5	50.4	10.1 (1.8 to 22.0)	0.10	<0.0001

*Mean difference in the proportion of responders in the ABC-FTC-DTG vs TDF-FTC-EFV arm

Early drug-related events are clinically important, and “Snapshot Plus” may be a more relevant measure of ART efficacy

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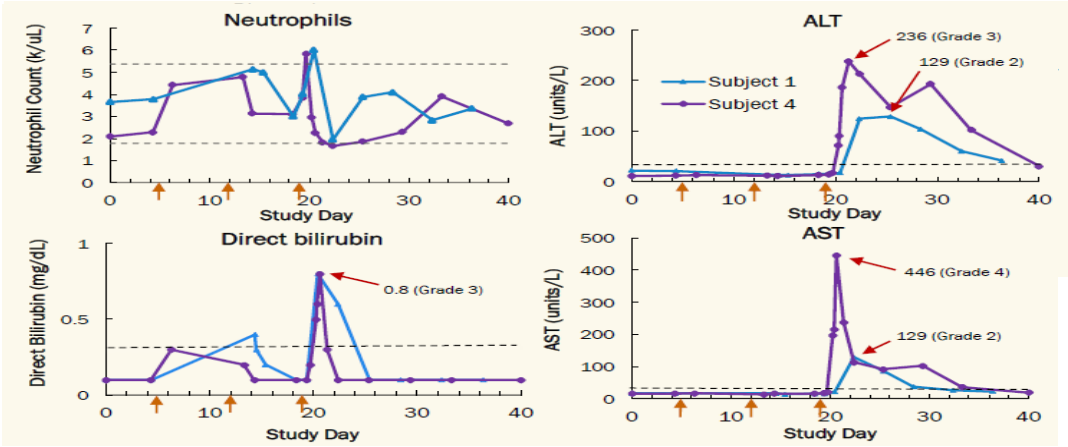
- PK

Drug Interactions – DTG and RPT/INH

DTG and RPT/INH (412)

RPT/INH once-weekly used in US for LTBI
PK study to assess DDI between RPT/INH (weekly x 3) and DTG (50mg od)

Healthy volunteer study



Terminated following serious toxicities after 3rd dose in 2/4 patients:

- 1 subject N/V, headache, fever (39.1°C)
- 1 subject N/V, fever (39.5°C), hypotension (79/51mmHg, hospitalised, iv fluids)
- Both subjects had ↑ALT/AST/bilirubin, L shift in WBC, ↑ IL6/TNFα/IFNγ/CRP
- Resolved 72h post-dose

- No clear PK signal, (INH levels slightly higher in both subjects)
- Mechanism ?

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Drug Interactions – RTV vs Cobi boosting

Dabigatran (409)

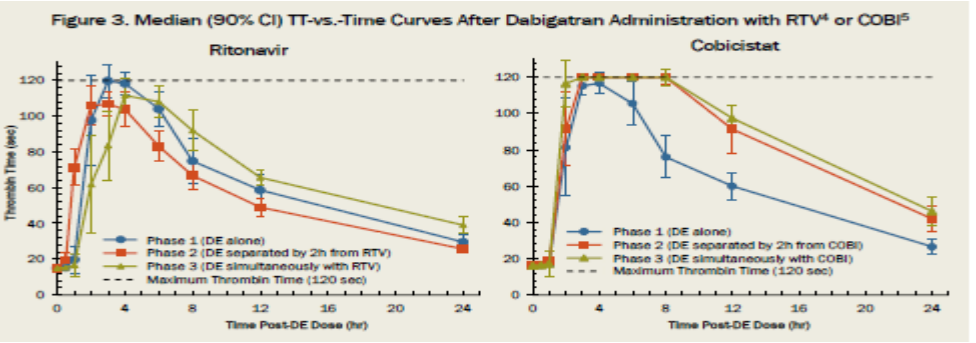
- Dabigatran etexilate (DE; prodrug) is PgP substrate
- DDIs affect bioavailability

- **Cobi** inhibits Pgp - ↑ [Dabigatran]

- **RTV** – mixed inducer/inhibitor, little net effect

- **Reflected in thrombin times – affected by cobi, not RTV**

	RTV	Cobi
Simultaneous (GMR AUC)	1.11 (0.89-1.33)	2.31 (1.83-2.78)
Separated 2h (GMR AUC)	0.71 (0.60-0.81	2.14 (1.65-2.63)



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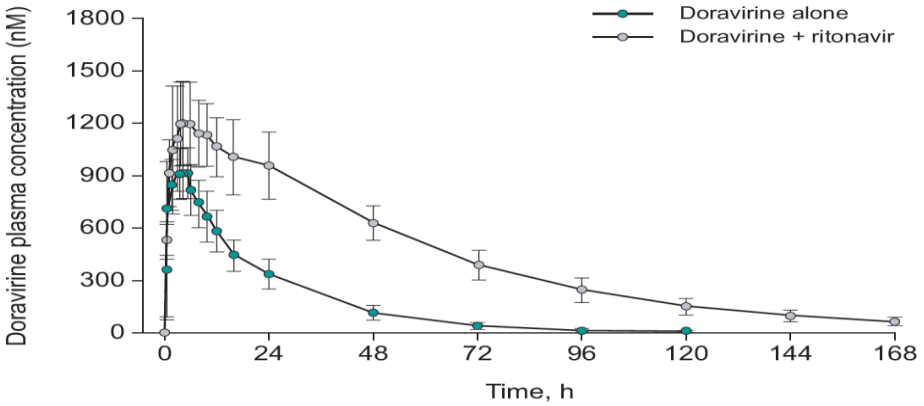
Drug Interactions – This and that

Doravirine (412)

CYP3A metabolised
(PgP substrate in-vitro)
Predicted DDI with RTV (and cobi)

RTV (multiple dosing)
↑ [DOR] AUC (GMR 3.54)



Pharmacology and Practice - Mums

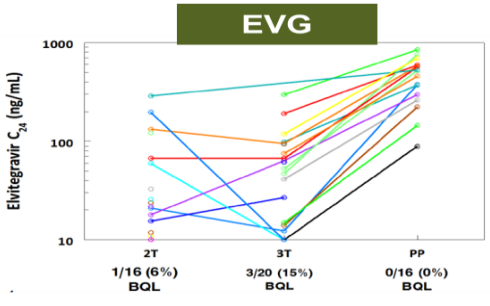
Rilpivirine(412)
PANNA consortium (N=16)
Significant reduction in RPV exposure compared with PP
2/16 mums had subtherapeutic levels

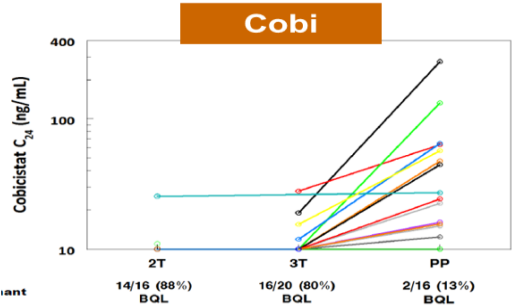
	T3**	Neonates
RPV	↓ 45%	Cord:maternal blood 50%

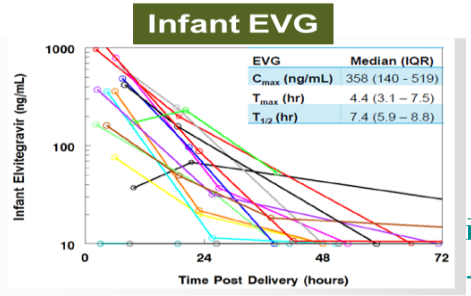
** vs post-partum

Rilpivirine(412) IMPAACT P1026s (N=20)
Significant reduction in EVG and cobi
[EVG]<10th centile: T2 (50%), T3 (55%)
EVG readily crosses placenta, not cobi
2/26 congenital anomalies (amniotic band/microcephaly/IUGR ; polydactyly)

	T2**	T3**	Neonates
EVG	↓ 49%	↓ 42%	↓ 42%
Cobi	↓ 54%	↓57%	undetectable







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Pharmacology and Practice - Kids

3TC syrup (412)

Syrup bioequivalent to tablets (GSK), ….. *but* ……..
ARROW - ↑VF with 3TC syrup, bioavailability ↓37% compared to tablets

Sorbitol (present in ABC, NVP, TMP-SMZ)
AUC 3TC ↓ 20-44% with increasing concentrations of sorbitol

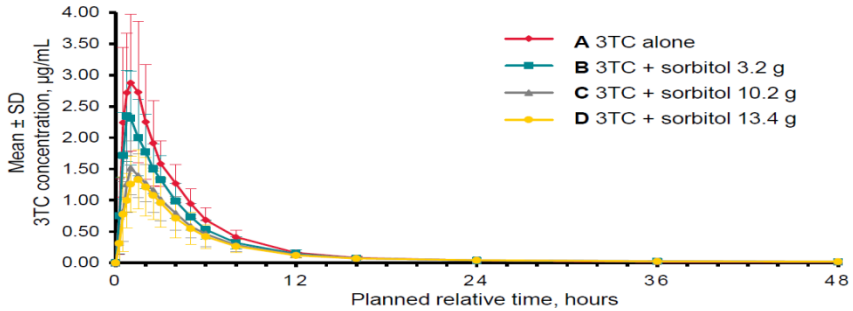
Other paediatric PK data

DTG granules in kids 2-6years (806)

RAL dosing in the neonate (757)

Genvoya (adult FDC) in 6-12y (424)

ATVc or DRVc 12-18 years (425)



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New Drugs

New Drugs

Discovery *Preclinical* *First in Man*

Capsid inhibitor (38)
Potent at pM concentrations,
targets capsid assembly and disassembly.
One to watch

Humanised monoclonals
PRO140 (437)- anti- CCR5 mAb. Weekly s/c injection
Ibalizumab (438) – anti-CD4 receptor mAb. Bi-weekly IM

Oral, non-boosted PI (433)
GS-PI1. EC50 4.9nM, high genetic barrier to resistance. Long half-life in animals

Non-catalytic site INI (434)
GS-9882. EC50 3.0 nM. Superior resistance profile. PK- qd dosing.
Problem with urothelial toxicity in monkeys

NRTTI (NRT translocation inhibitor)
MK8591 /EFdA (435) – enriches in lymphoid tissue, penetrates vaginal/rectal tissue and cells.
continues to impress. Proposed oral dosing 10mg/w. Implants under assessment

NRTI
GS 9131 (prodrug) potent EC50 0.29-113 nM
Favourable resistance profile K65R, L74V, M184V or their combinations (EC50 fold change < 1)

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BHIVA ‘Best of CROI’ Working Party 2017

Dr Tristan Barber
Dr Sanjay Bhagani
Dr David Chadwick
Dr Duncan Churchill
Mr Simon Collins
Dr Alessia Dalla Pria
Dr Sarah Duncan
Dr Julie Fox
Dr Andrew Freedman
Professor Saye Khoo
Professor Clifford Leen
Dr Rebecca Metcalfe
Professor Chloe Orkin
Dr Katrina Pollock
Dr Adrian Palfreeman
Dr Frank Post
Dr Iain Reeves
Dr Rebecca Simons
Ms Sonali Sonecha
Professor Graham Taylor
Dr Steve Taylor
Dr Hiten Thaker

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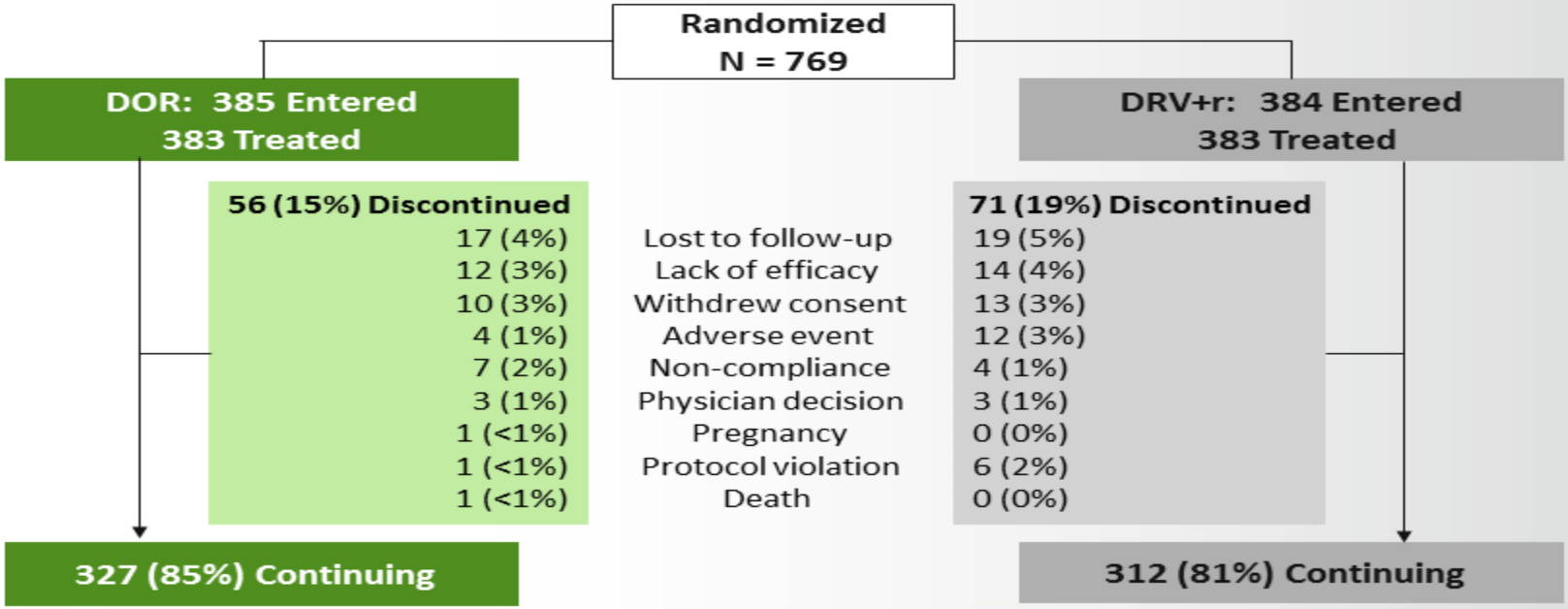
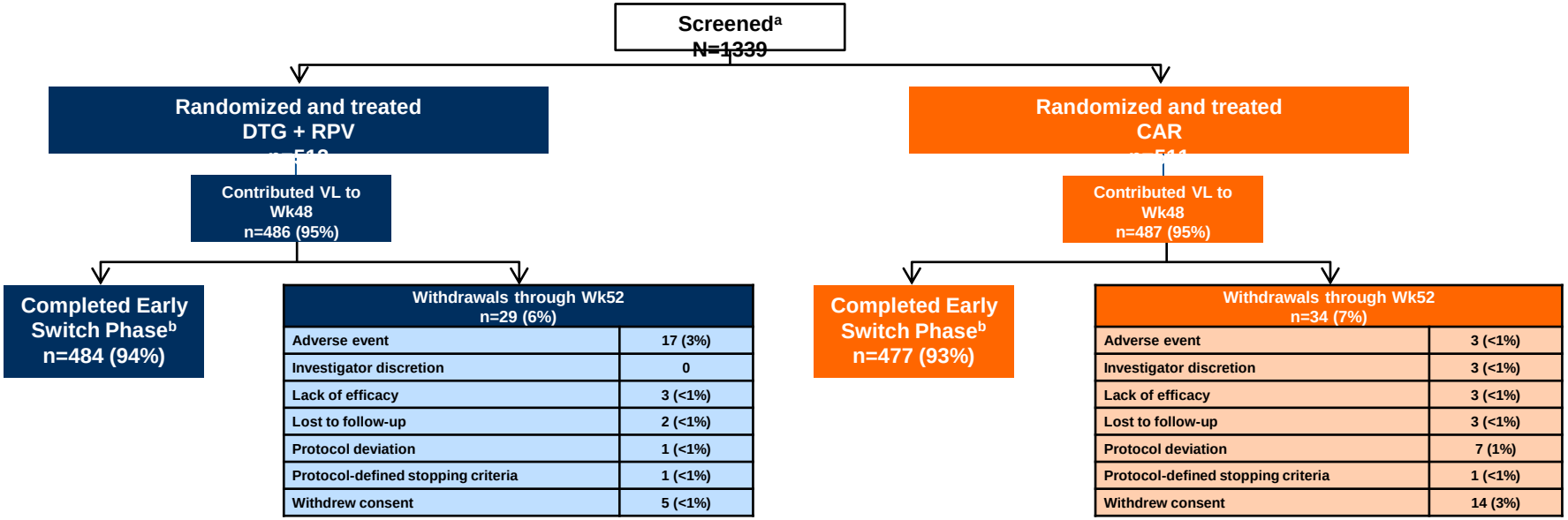
Back up slides if needed

Disposition, Week 48



DRIVE FORWARD

Subject Disposition: Early Switch Phase (Through Wk 52)



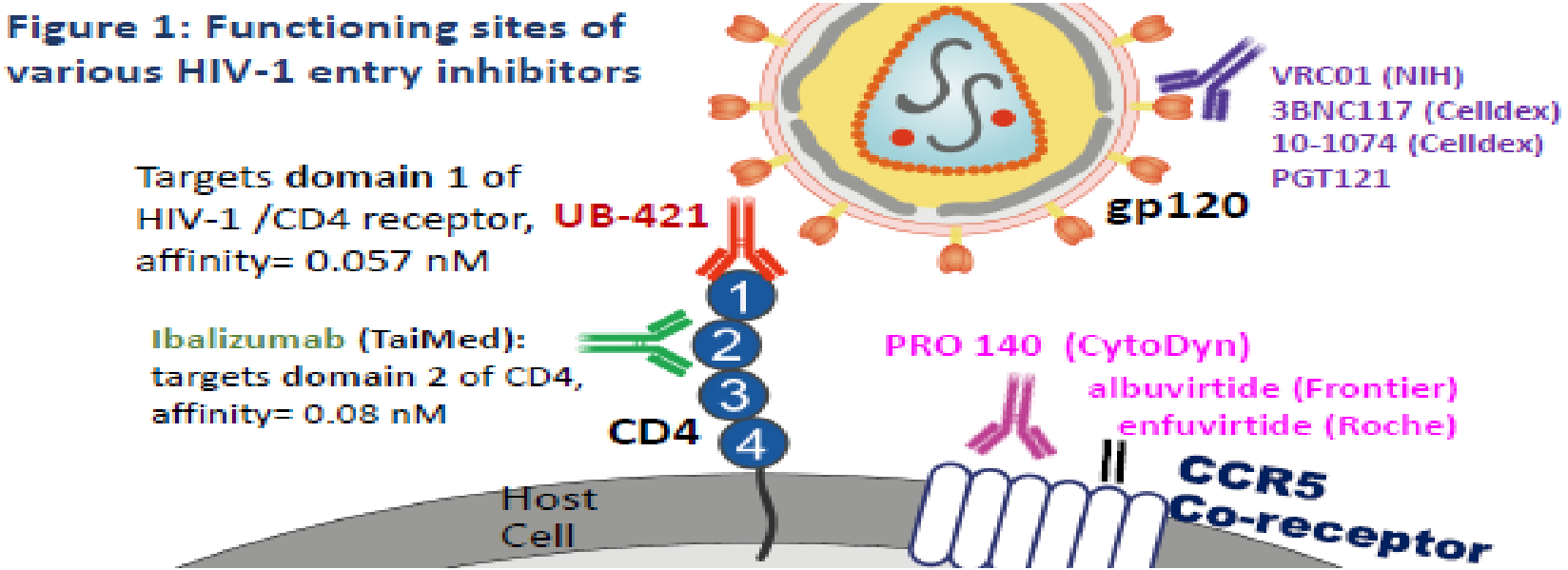
Withdrawals through Wk52 n=29 (6%)	
Adverse event	17 (3%)
Investigator discretion	0
Lack of efficacy	3 (<1%)
Lost to follow-up	2 (<1%)
Protocol deviation	1 (<1%)
Protocol-defined stopping criteria	1 (<1%)
Withdrew consent	5 (<1%)

Withdrawals through Wk52 n=34 (7%)	
Adverse event	3 (<1%)
Investigator discretion	3 (<1%)
Lack of efficacy	3 (<1%)
Lost to follow-up	3 (<1%)
Protocol deviation	7 (1%)
Protocol-defined stopping criteria	1 (<1%)
Withdrew consent	14 (3%)

[a]Data pooled across SWORD-1 and SWORD-2. [b]Early switch phase ends at Week 52.

Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

Functioning sites of various HIV-1 entry inhibitors



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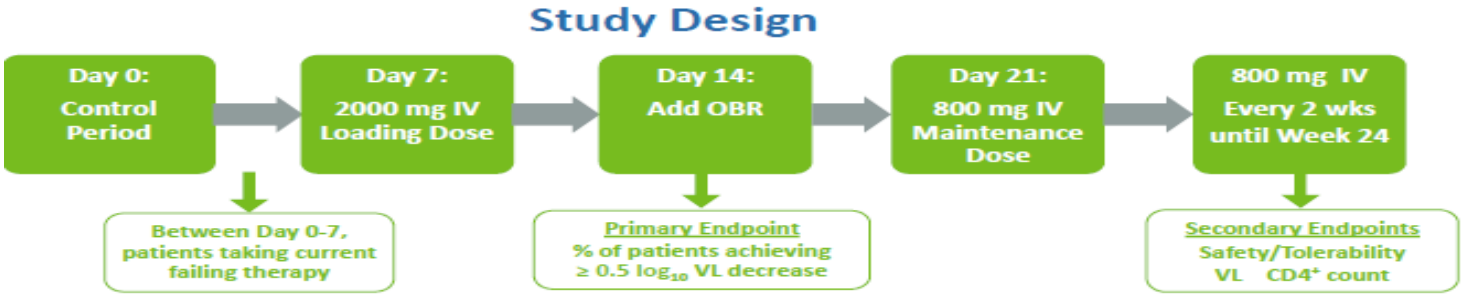
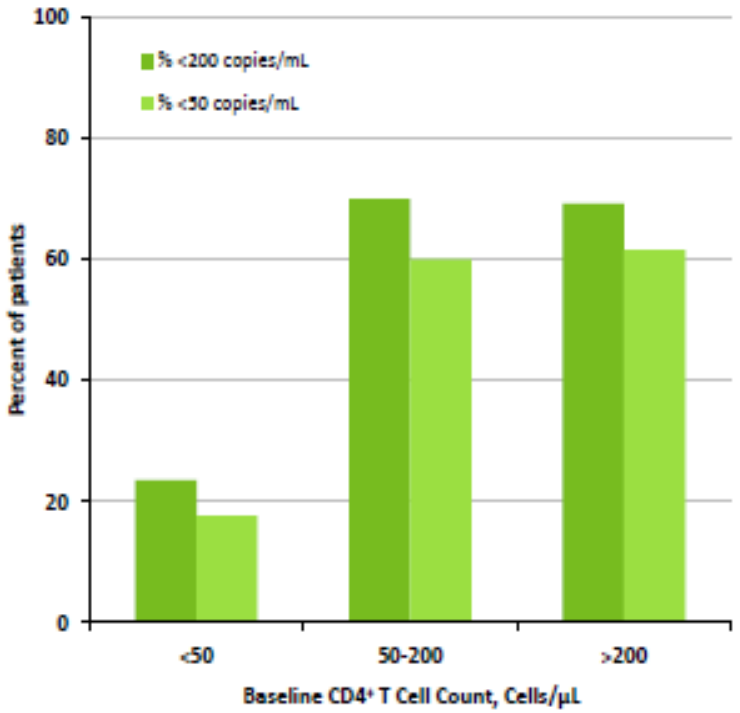
TMB-301: Ibalizumab in patients with multi-drug resistant HIV-1 infection – 24 week data

- Ibalizumab (IBA) is a long-acting, immunoglobulin G4 monoclonal antibody that blocks HIV entry into CD4 cells whilst preserving normal immune function
- Single arm, phase 3 registration study over 24 weeks (n=40)
  - addition of IBA to a physician selected, optimised background regimen (OBR)
  - Most common OBR included DRV/r 600mg/100mg BD and dolutegravir. T-20 also used in some cases
  - 43% patients required fostemsavir (via compassionate release)



Results



- Mean VL decrease 1.6 $\log_{10}$ from baseline
- 43% with undetectable VL<50 cp/ml
- 10 discontinuations
  - 1 drug-related IRIS
  - 4 deaths
  - 3 consent withdrawals
  - 1 lost to follow up
- Rolling over to expanded access & FDA application

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