Corevih Ile-de-France Ouest

Comité de coordination régionale de la lutte contre les IST et le VIH

eCROI 2021

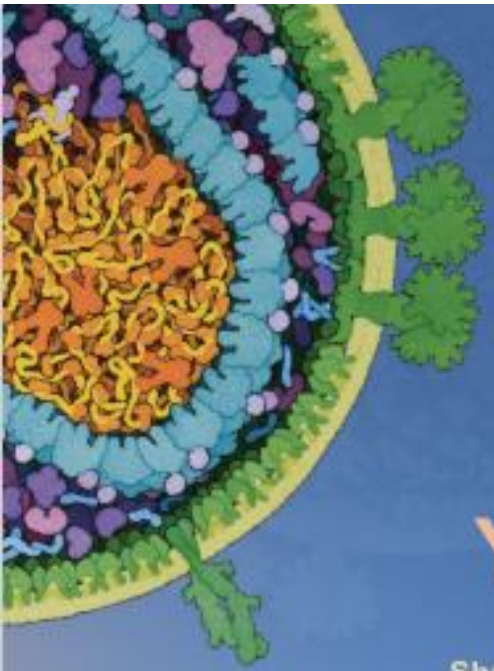
P de Truchis

Hopital Raymond Poincaré

Garches 92

eCROI 2021

Traitements ARV: stratégies 1ère ligne



SCIENCE SPOTLIGHT™

DURABLE EFFICACY OF DTG + 3TC IN GEMINI-1&-2: YEAR 3 SUBGROUP ANALYSES

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Disclosure: Dr Chloe Orkin has received lecture fees, fees for advisory boards, travel bursaries, and research grants to her institution from ViiV Healthcare, Gilead, Merck & Co, and Janssen.

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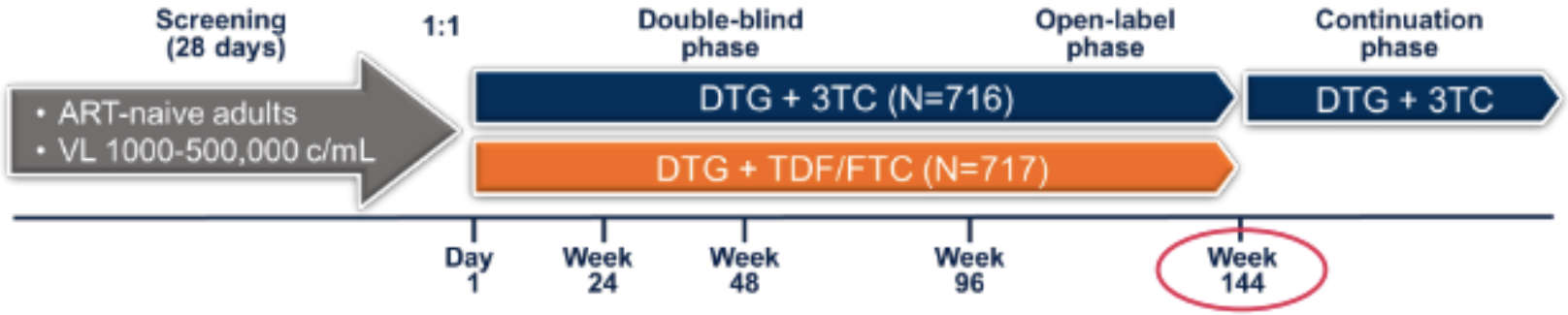
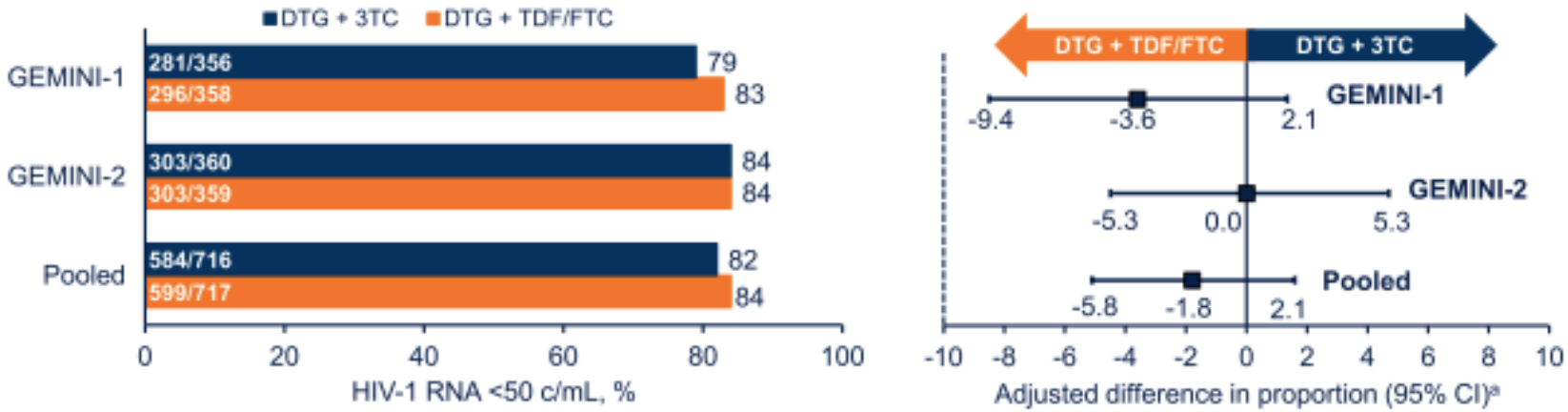
Background

- The GEMINI-1 and -2 studies (NCT02831673 and NCT02831764, respectively) are ongoing phase III, non-inferiority trials evaluating the efficacy and safety of initiating the 2-drug regimen DTG + 3TC in treatment-naive adults with HIV-1 infection compared with the 3-drug regimen DTG + TDF/FTC[1,2]
- In the Weeks 48, 96, and 144 analyses of the GEMINI studies, DTG + 3TC demonstrated non-inferior efficacy vs DTG + TDF/FTC in ART-naive adults through 3 years of treatment[3-5]
- Here we present rates of virologic suppression (Snapshot) and safety results through Week 144 by demographic and baseline characteristics



1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed January 27, 2021. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed January 27, 2021. 3. Cahn et al. *Lancet*. 2019;393:143-155. 4. Cahn et al. *J Acquir Immune Defic Syndr*. 2020;83:310-318. 5. Cahn et al. HIV Glasgow 2020; Virtual. Poster P018.

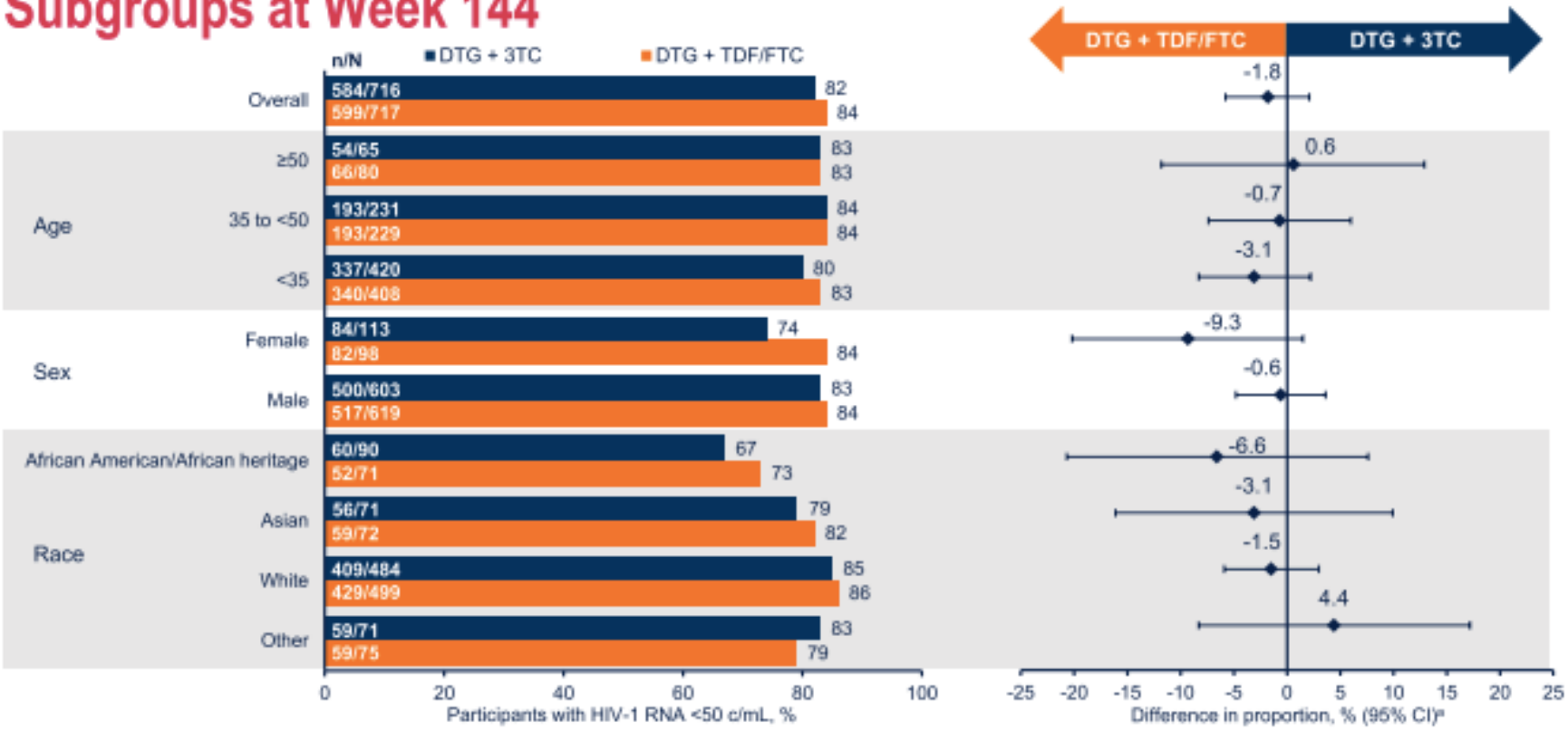
DTG + 3TC Is Non-inferior to DTG + TDF/FTC at Week 144



- Through Week 144, 12 participants in the DTG + 3TC group and 9 in the DTG + TDF/FTC group met protocol-defined CVW criteria; there were no treatment-emergent INSTI or NRTI resistance mutations
- 1 non-CVW participant with reported intermittent non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG

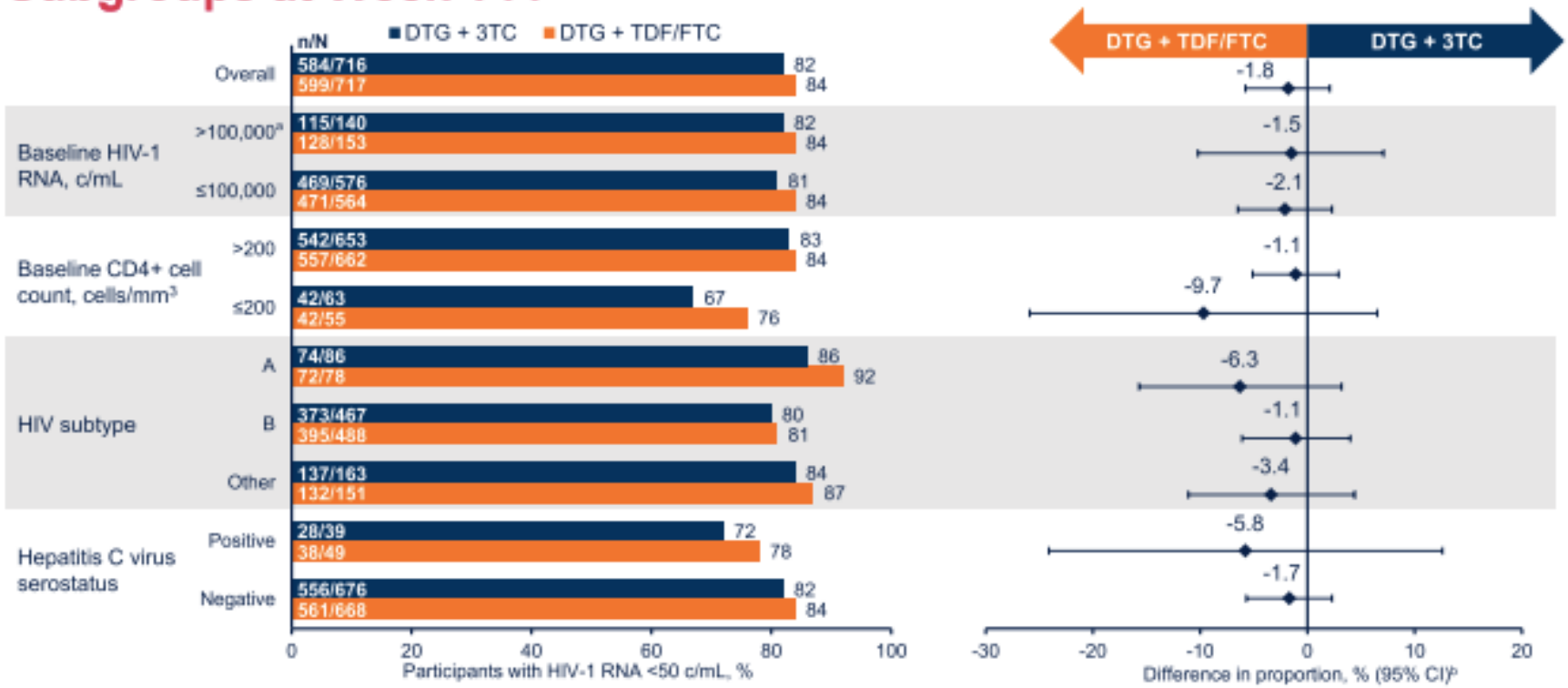
CVW, confirmed virologic withdrawal.
[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and baseline CD4+ cell count (≤200 vs >200 cells/mm³). The pooled analysis was also adjusted for study (GEMINI-1 vs GEMINI-2).
Cahn et al. HIV Glasgow 2020; Virtual. Poster P018.

HIV-1 RNA <50 c/mL Was Comparable Across Demographic Subgroups at Week 144



aAdjusted difference (95% CI) for overall population (DTG + 3TC − DTG + TDF/FTC). Unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC.

HIV-1 RNA <50 c/mL Was Comparable Across Baseline Disease Subgroups at Week 144



[a]Includes values for HIV-1 RNA >250,000 c/mL (DTG + 3TC, 41/51 [80%]; DTG + TDF/FTC, 37/46 [80%]), HIV-1 RNA >400,000 c/mL (DTG + 3TC, 15/18 [83%]; DTG + TDF/FTC, 19/24 [79%]), and HIV-1 RNA >500,000 c/mL (DTG + 3TC, 10/13 [77%]; DTG + TDF/FTC, 12/15 [80%]). [b]Adjusted difference for overall population (DTG + 3TC − DTG + TDF/FTC). Unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC.

Weight Gain by Subgroup Through Week 144: Safety Population[a]

Variable	Subgroup	DTG + 3TC n	DTG + 3TC Mean (SD)	DTG + TDF/FTC n	DTG + TDF/FTC Mean (SD)
Change in weight from baseline, kg					
Overall	—	588	3.7 (6.8)	599	2.4 (7.6)
Sex	Female	86	2.7 (6.7)	79	1.8 (6.6)
	Male	502	3.8 (6.8)	520	2.5 (7.8)
Race	White	412	3.3 (6.8)	431	1.8 (7.4)
	African American/African heritage	62	3.9 (8.6)	51	4.2 (10.8)
	Asian	56	5.1 (5.9)	59	3.9 (6.3)
	Other	58	4.8 (5.4)	58	4.0 (6.4)
Change in BMI from baseline, kg/m^2					
Overall	—	587	1.2 (2.3)	599	0.8 (2.8)
Sex	Female	86	1.1 (2.6)	79	0.7 (2.4)
	Male	501	1.3 (2.2)	520	0.8 (2.8)
Race	White	411	1.1 (2.3)	431	0.6 (2.8)
	African American/African heritage	62	1.3 (2.8)	51	1.4 (3.5)
	Asian	56	1.7 (2.0)	59	1.4 (2.2)
	Other	58	1.6 (1.9)	58	1.4 (2.2)

[a]Post hoc analysis.

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D/C/F/TAF vs DTG/ABC/3TC FOR INITIAL TREATMENT IN HIV+ ADULTS: A RANDOMIZED STUDY

Podzamczer D[*1], Mican R[2], Tiraboschi J[1], Portilla J[3], Domingo P[4], Llibre JM[5], Ribera E[6], Vivancos MJ[7], Morano L[8], Masiá M[9], Gomez-Ayerbe C[10], Navarro A[1], Caicedo A[11], Moreno S[7], for the SYMTRI Study Group **(PreECIRIS-57)**

1:Hospital U. de Bellvitge, 2: Hospital U. La Paz, 3: Hospital Gral. U. de Alicante, 4: Hospital de Sant Pau, 5: Hospital U. Germans Trias i Pujol, 6: Hospital U. Vall d'Hebron, 7: Hospital U. Ramón y Cajal, 8: Hospital U. Álvaro Cunqueiro. 9: Hospital Gral. U. de Elche, 10:Hospital U. Virgen de la Victoria, 11: Red de Investigación en SIDA.

Disclosure: Daniel Podzamczer has received research grants and/or honoraria for advisories and/or conferences from MSD, Gilead ViiV, and Janssen.

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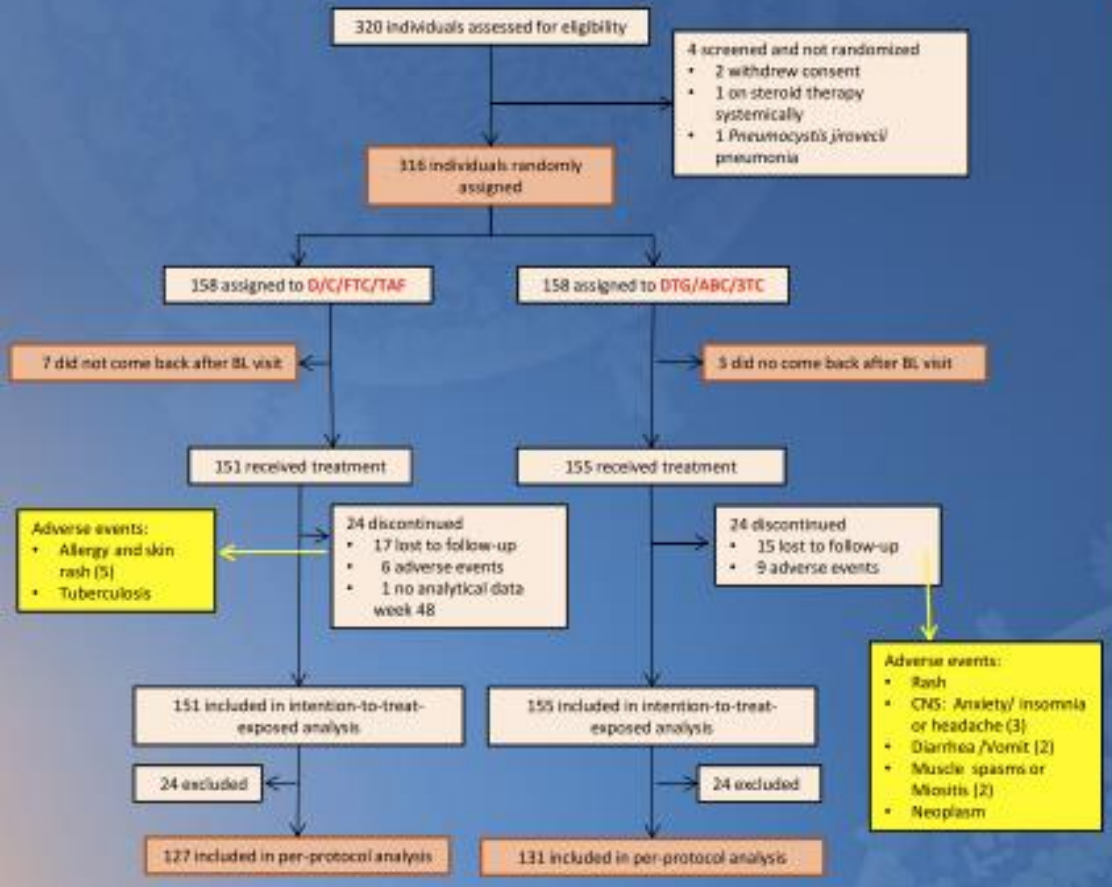
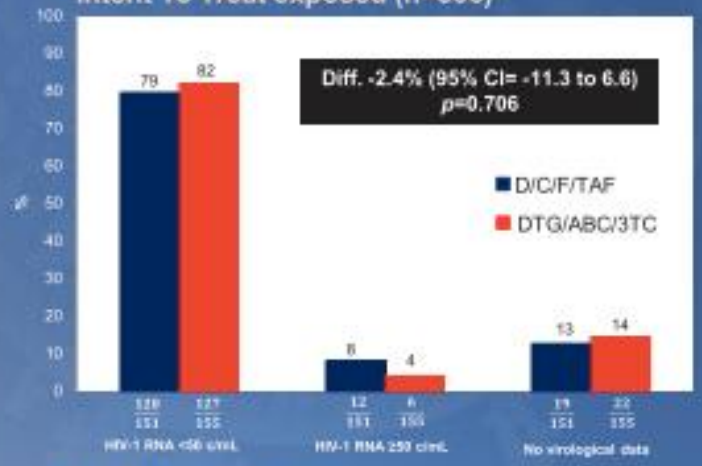
Trial Profile and baseline characteristics



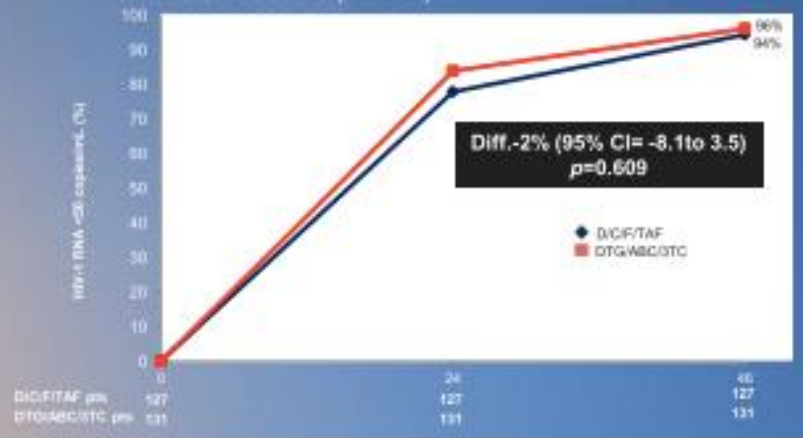
		D/C/FTC/TAF (n=151)	DTG/ABC/3TC (n=155)
Median age, years		34 (27-41)	36 (31-43)
Gender (male) (n, %)		146 (97%)	142 (92%)
Risk practice (n, %)	MSM	127 (84%)	115 (74%)
	Heterosexuals	16 (11%)	31 (20%)
	Intravenous drug use	2 (1%)	2 (1%)
	Others | Unknown	6 (4%)	7 (4%)
AIDS (opportunistic diseases) (n, %)		0 (0%)	0 (0%)
Median CD4+ cell count (x10E6/µL)		420 (286-608)	383 (247-569)
CD4+ cell count (n, %)	<200 x10E^6/µL	17 (11%)	22 (14%)
	200-350 x10E^6/µL	40 (26%)	44 (28%)
	>350 x10E^6/µL	94 (62%)	89 (57%)
Median HIV-1 RNA (copies/mL)		63096 (13534-233000)	65900 (24786-212000)
HIV-1 RNA concentration (n, %)	<100000 c/mL	91 (60%)	93 (60%)
	≥100000 c/mL	60 (40%)	62 (40%)
Hepatitis C virus infection (n, %)		5 (3%)	5 (3%)
Median weight (kg)		72.95 (64-79.97)	72.75 (64.5-80)
Median Body Mass Index (kg/m^2)		23.78 (21.77-26.3)	23.81 (22.04-26.08)

Results

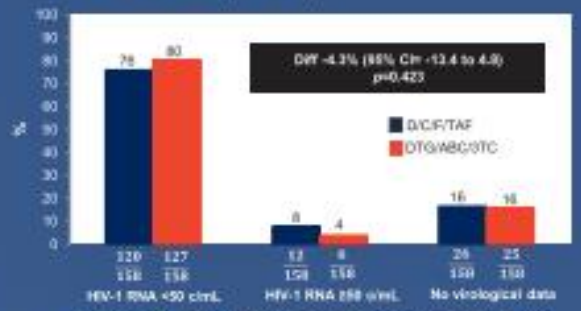
Intent To Treat exposed (n=306)



Per Protocol (n=258)

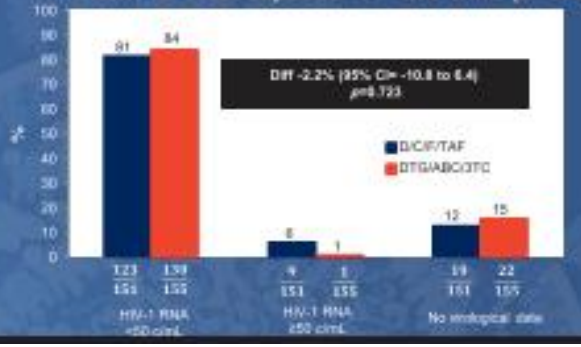


Intent To Treat (n=316)



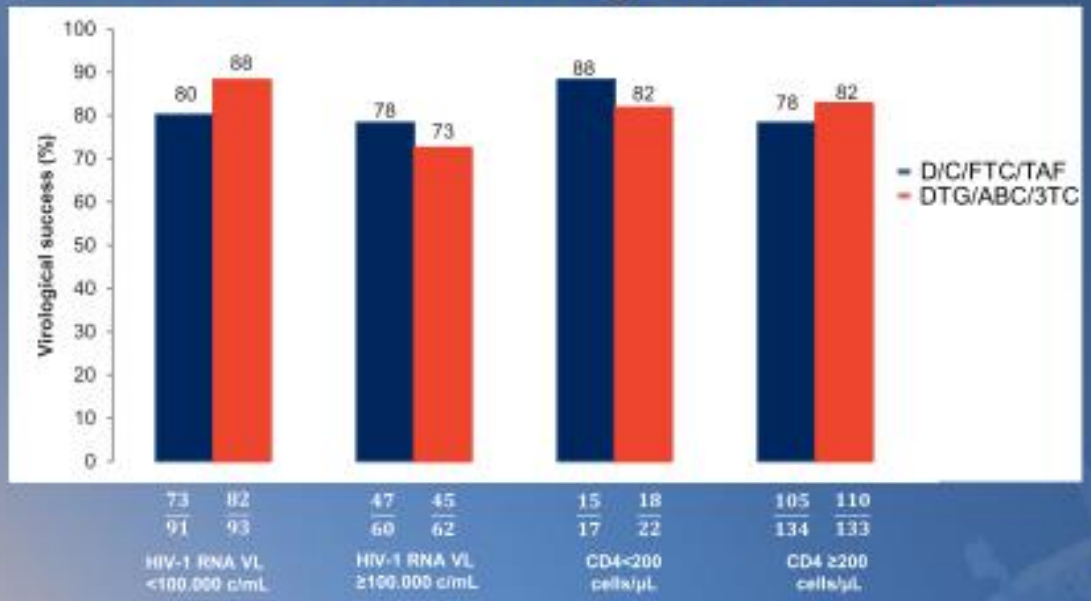
Intent To Treat Missing=Excluded (n=265)

Intent To Treat exposed=VL<200 c/mL (n=306)

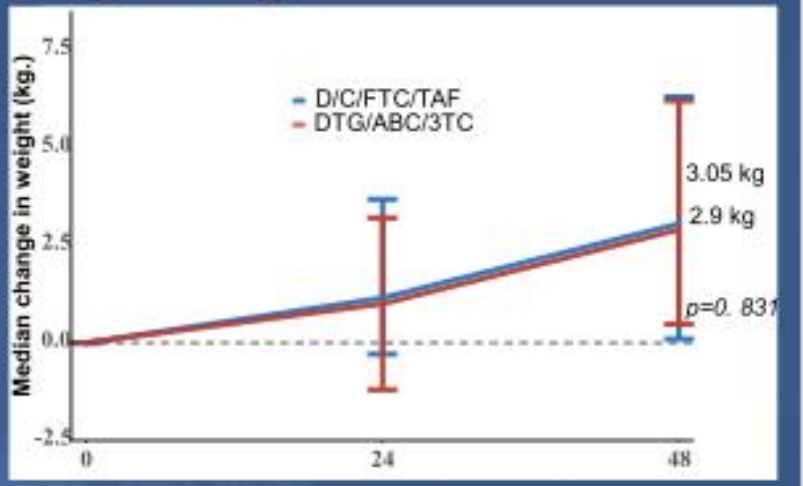


Results

% of VL < 50 c/mL according to BL VL and CD4

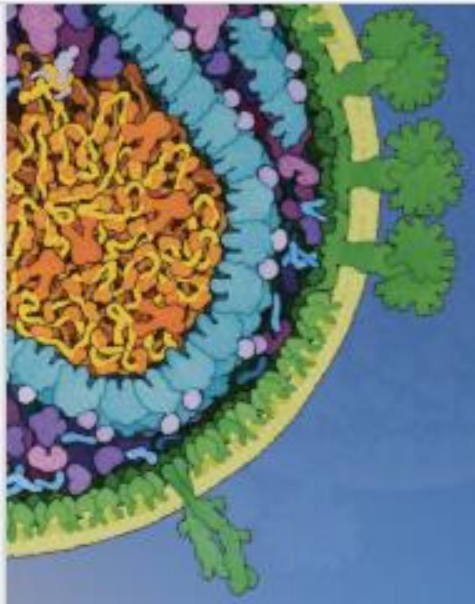


Weight change*



- *Similar changes for BMI were observed

- After 48w a non significant difference in CD4 count increase was observed : 226 cells/uL (D/C/FTC/TAF) vs 260 cells/uL (DTG/ABC/3TC); *p=0.106.*



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DOLUTEGRAVIR VS. DARUNAVIR/r-BASED ART IN VERY ADVANCED PATIENTS: 48-WEEK RESULTS

Jose M. Miro on behalf of Advanz-4 investigators

Hospital Clinic – IDIBAPS. University of Barcelona. Barcelona, Spain

Disclosure: The study was funded by ViiV Healthcare.

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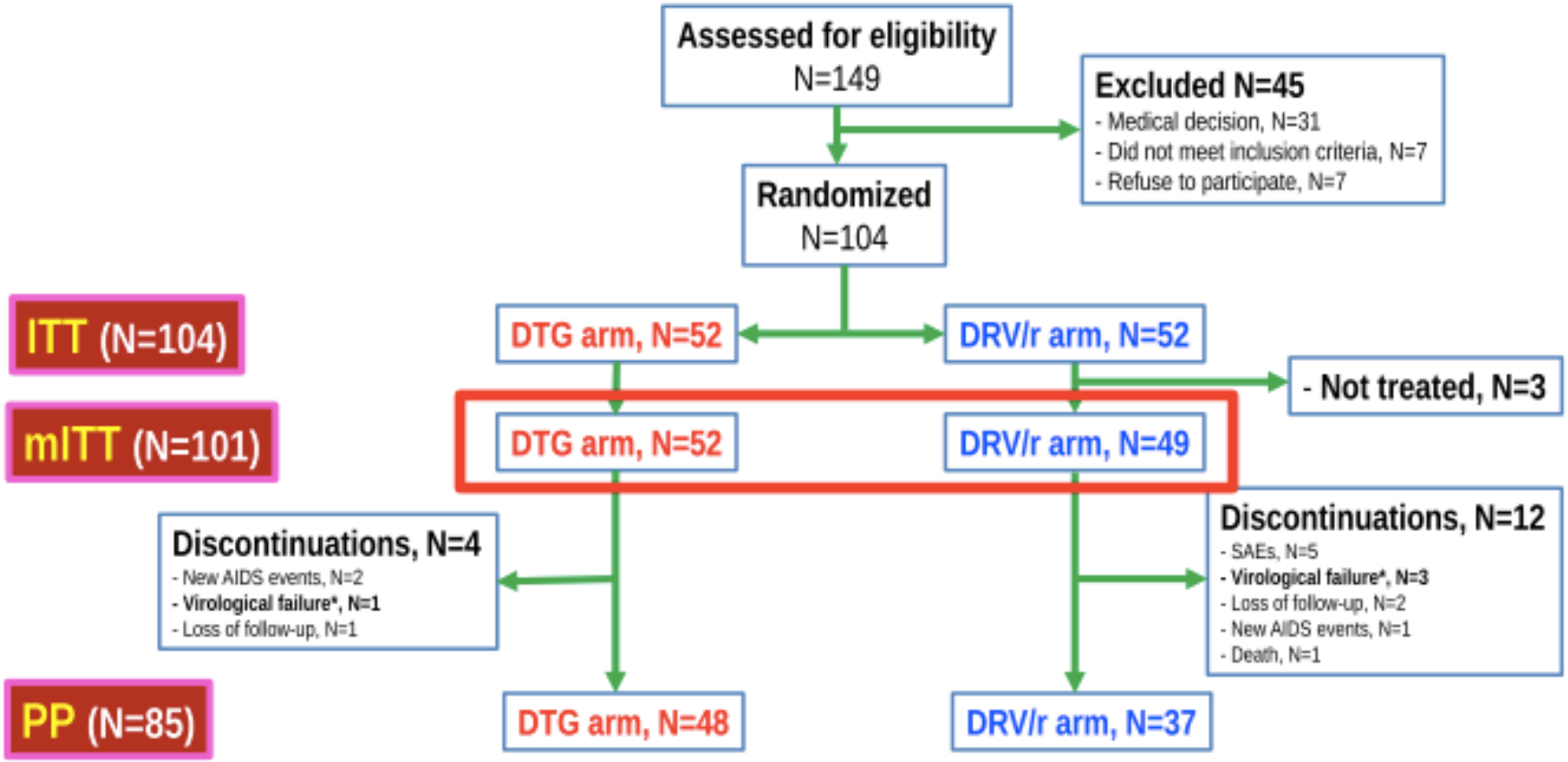
Results (I): Participants disposition



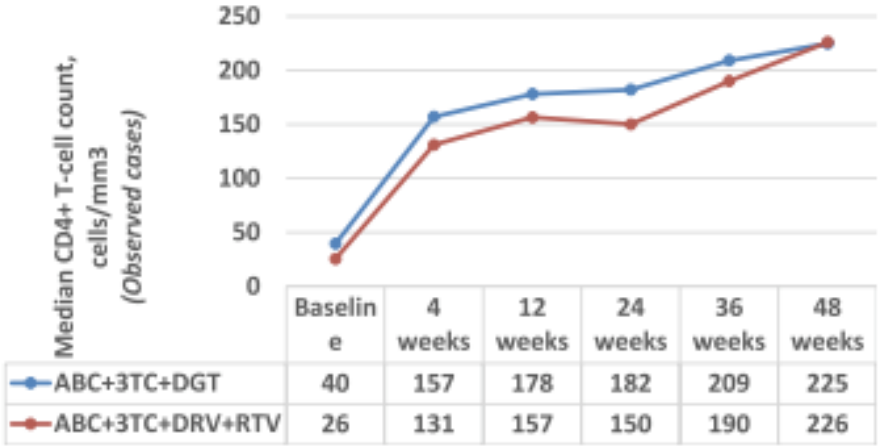
ITT: Intention-to-treat; mITT: modified ITT; PP: Per protocol analysis; *Virological failure: Two consecutive plasma VL samples >200 copies/mL. The four samples could not be amplified for genotypic resistance studies.

Results (II): mITT (M=F) analysis

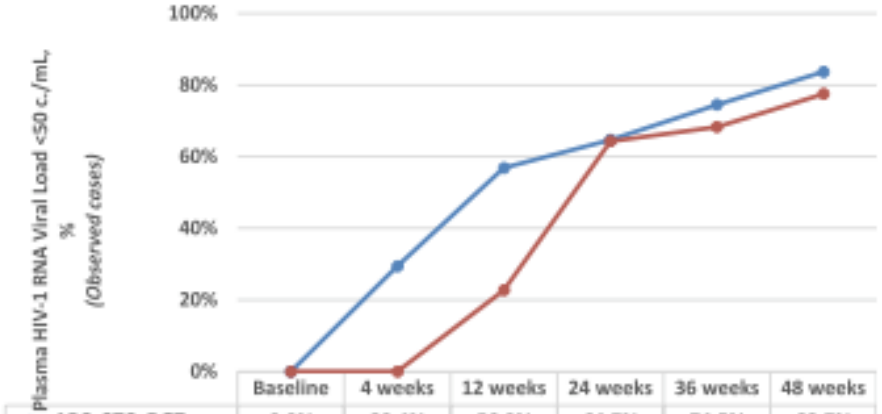
	Dolutegravir N=52	Darunavir/rtv N=49	p-value
• Age, yr., median (IQR)	40 (30;48)	41 (34;46)	NA*
• Male gender, n (%)	44 (87)	46 (88.5)	
• Men who have sex with men (MSM), n (%)	31 (60)	25 (51)	
• Baseline AIDS-defining events (ADE), n (%)	22 (42)	24 (46)	
• Baseline RNA HIV VL, median (IQR) log10/mL	5.47 (4.79;6.10)	5.67 (5.14;6.12)	
• Baseline CD4, median (IQR) cells/mm^3	41 (18; 67)	30 (11; 54)	
• **48-wk CD4 increase (median delta, IQR)**	**172.50 (118; 255)**	**157 (66; 277)**	**0.430**
• **48-wk RNA HIV VL <50 copies/ml, n (%)**	**40 (77)**	**31 (63)**	**0.191**
• **IRIS, n (%)**	**5 (10)**	**6 (12)**	**0.911**
• **New ADEs/death, n (%)**	**4 (8)**	**6 (12)**	**0.666**
• **Treatment discontinuation (any reason), n (%)****	**4 (8)**	**12 (24.5%)**	**0.029**

*NA: not applicable for baseline measurements; ** See previous slide with patients disposition flow-chart.

Results (III): mITT (M=F) analysis



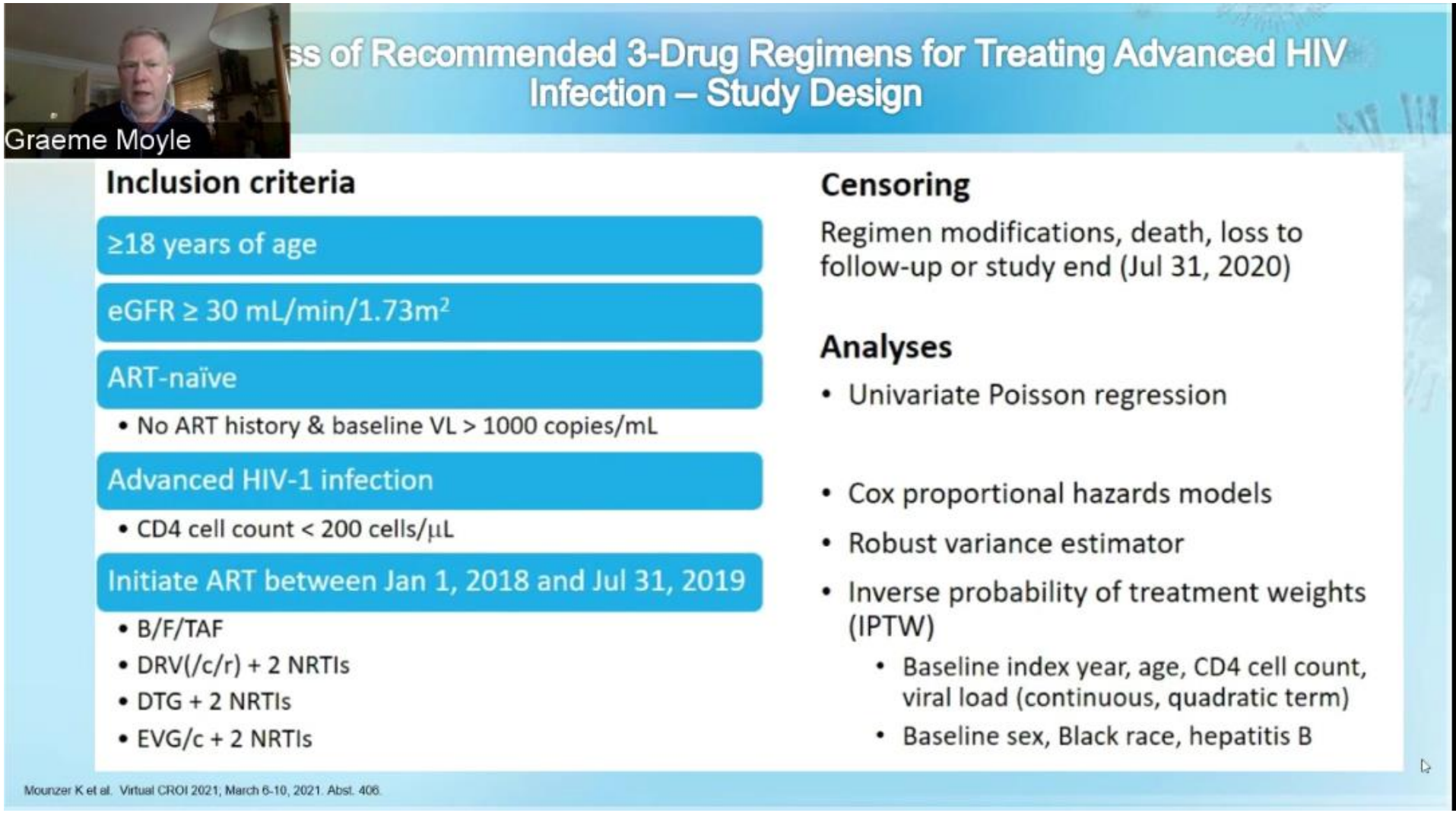
	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	48 weeks
ABC+3TC+DGT	40	157	178	182	209	225
ABC+3TC+DRV+RTV	26	131	157	150	190	226



	Baseline	4 weeks	12 weeks	24 weeks	36 weeks	48 weeks
ABC+3TC+DGT	0,0%	29,4%	56,9%	64,7%	74,5%	83,7%
ABC+3TC+DRV+RTV	0,0%	0,0%	22,7%	64,3%	68,3%	77,5%

- **Median (IQR) increase in the CD4** count after 48 weeks by **mITT (M=F)** analysis was +172 (118; 255) and 157 (66; 277) cells/mm^3 in the **DTG** and **DRV/r** arms, respectively (p=0.430).
- **Plasma HIV-1 RNA VL suppression** (<50 copies/ml) was significatively faster in the **DTG** arm at 4 and 12 weeks. **At week 48**, the rate of suppressed patients by **mITT (M=F)** analysis was **77% vs. 63% (p=0.191)** for **DTG** and **DRV/r** arms, respectively.
- **Inflammation** (TNF-alpha, IL-6, hsCRP), **immune activation** (CD8+CD38+ T cells, CD8+CD38+DR+) and **apoptotic** (annexin-V) **markers** were similar at baseline and declined significantly and similarly in both ART arms (P>0.05 for all comparisons).
- A greater reduction in **bacterial translocation** (srCD14) marker in patients treated with **DTG** was found (-802 [-1302; -398] vs. -396 [-924, 0.00] ng/mL; p=0.011).

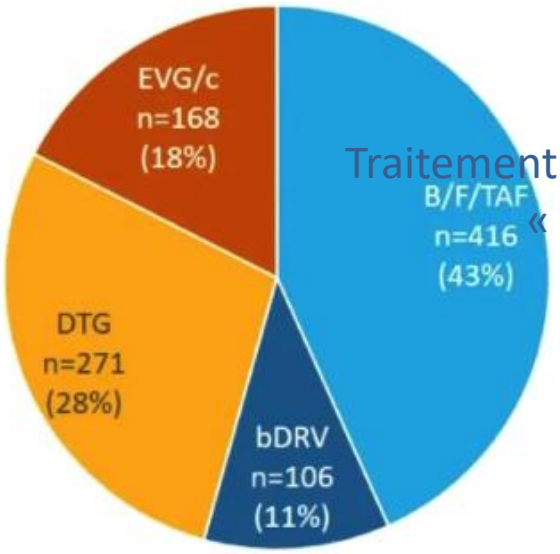
Traitement de 1ère ligne chez des patients « avancés » (CD4<200)

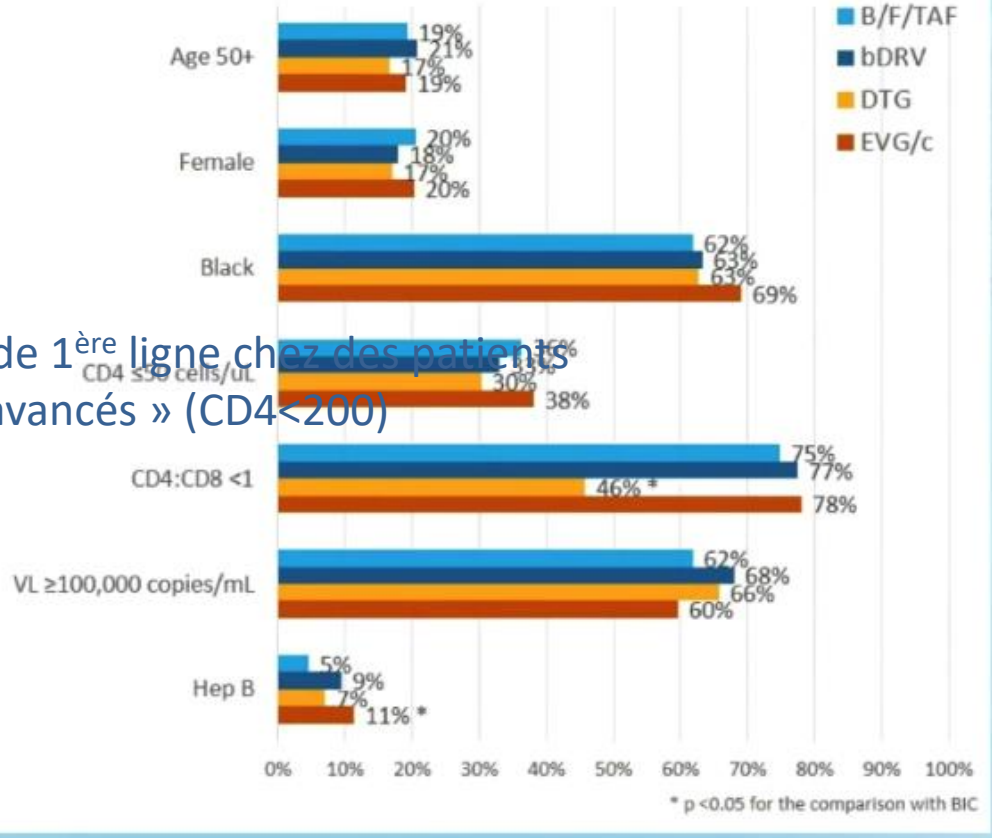


Traitement de 1ère ligne chez des patients « avancés » (CD4<200)

Study Characteristics

Study population (N=961)





Traitement de 1ère ligne chez des patients « avancés » (CD4<200)

Mounzer K et al. Virtual CROI 2021, March 6-10, 2021. Abst. 406.

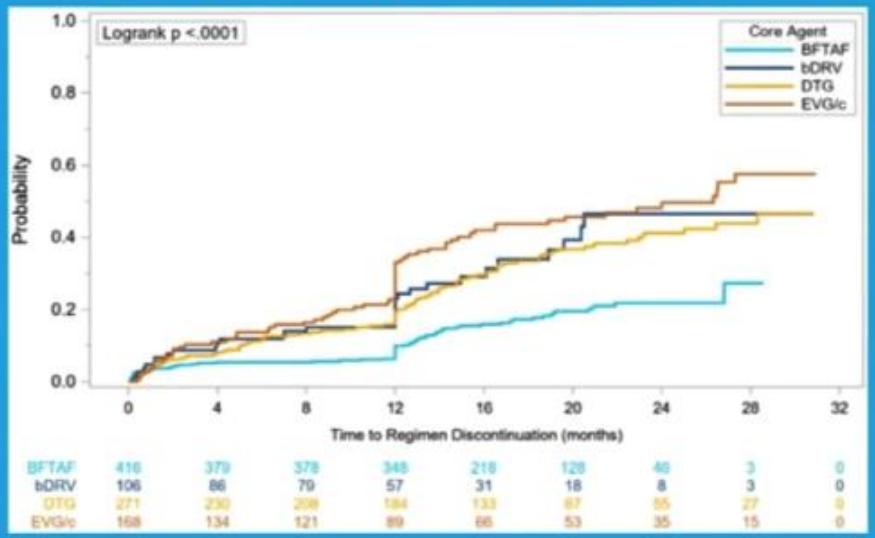
Traitement de 1ère ligne chez des patients « avancés » (CD4<200)

Third Agent Discontinuation

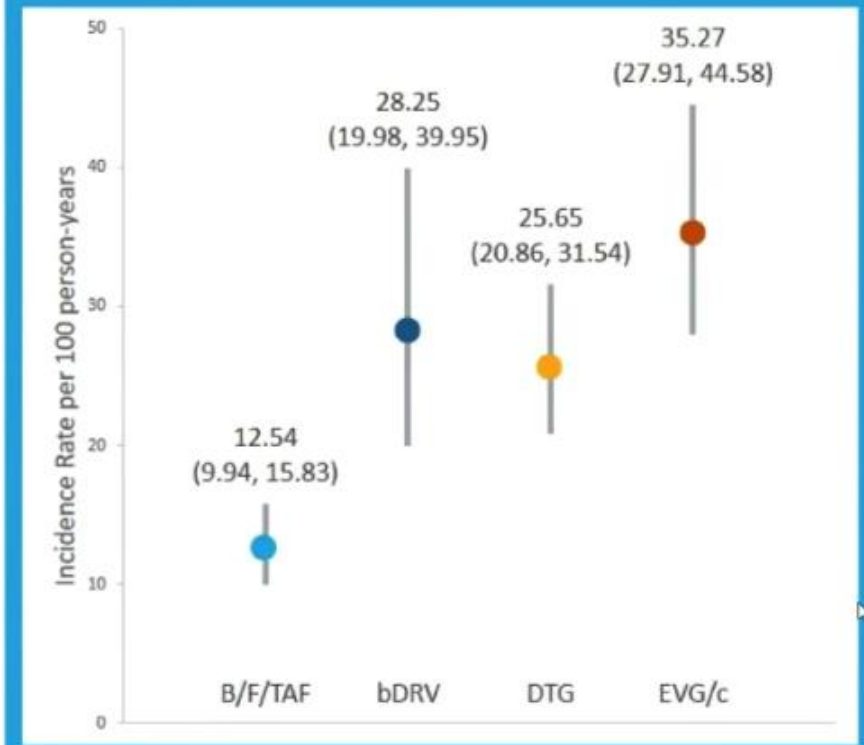
Duration of follow-up (months)

	BFTAF	bDRV	DTG	EVG/c
Median	17	13	16	12
IQR	(13-21)	(7-18)	(11-22)	(6-23)

Unadjusted cumulative probability of discontinuation



Unadjusted incidence rate of discontinuation

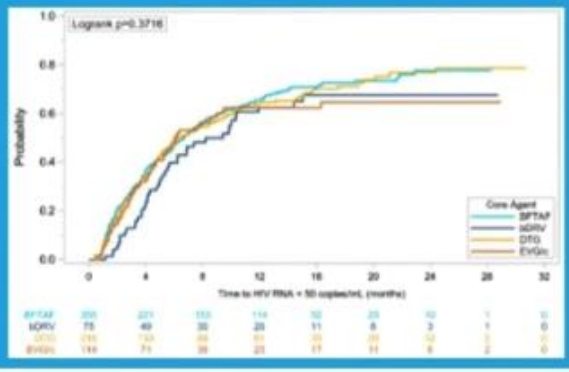


Mounzer K et al. Virtual CROI 2021; March 6-10, 2021. Abst. 406.

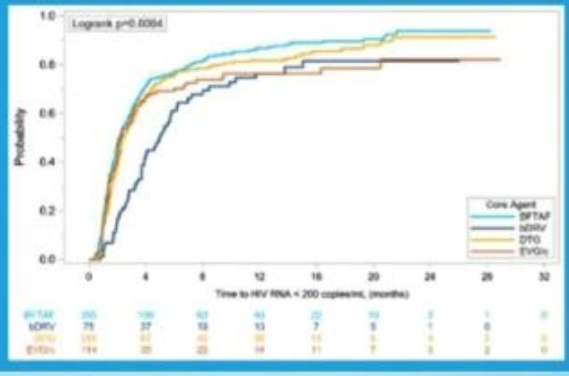
Traitement de 1ère ligne chez des patients « avancés » (CD4<200)

Virologic Effectiveness

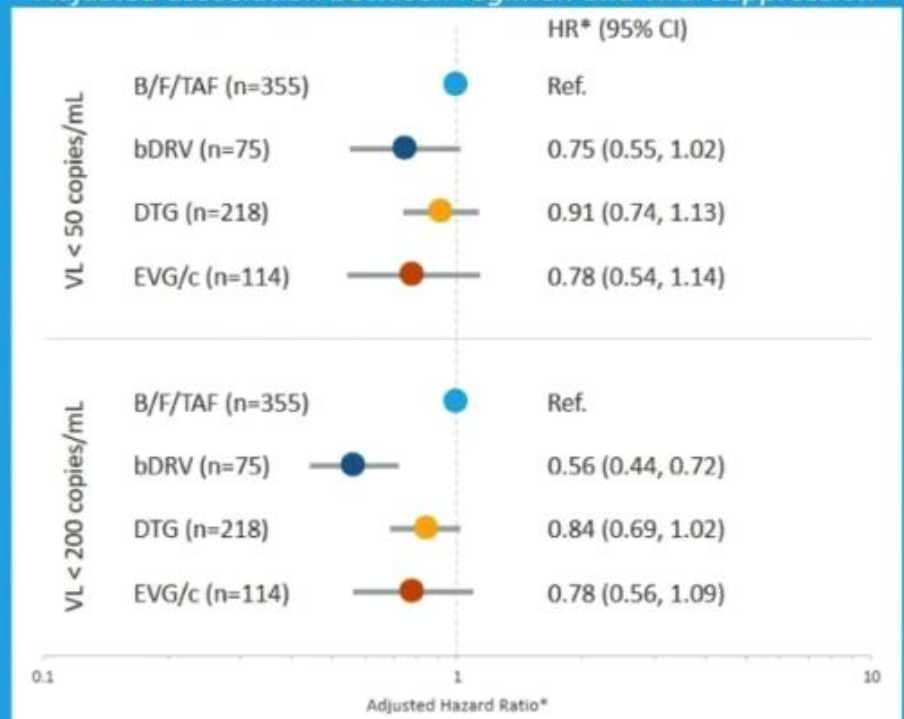
Unadjusted cumulative probability of VL <50 copies/mL



Unadjusted cumulative probability of VL <200 copies/mL

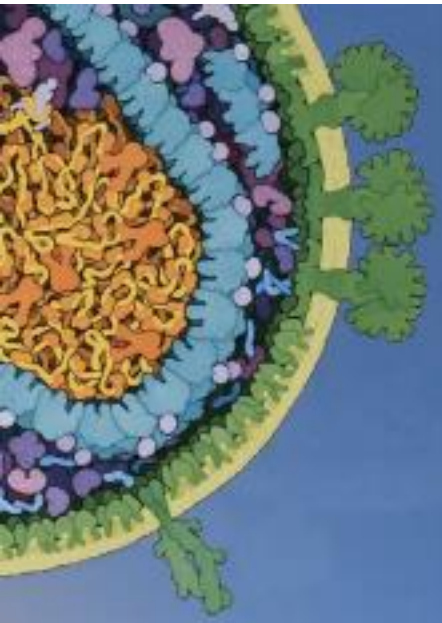


Adjusted association between regimen and viral suppression



*Marginal structural model with sIPTW controlling for baseline index year, age, CD4 cell count, viral load, sex, race, HBV; among 762 individuals with follow-up viral load

Mounzer K et al. Virtual CROI 2021; March 6-10, 2021. Abst. 406.



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FOUR-YEAR OUTCOMES OF B/F/TAF IN TREATMENT-NAÏVE ADULTS

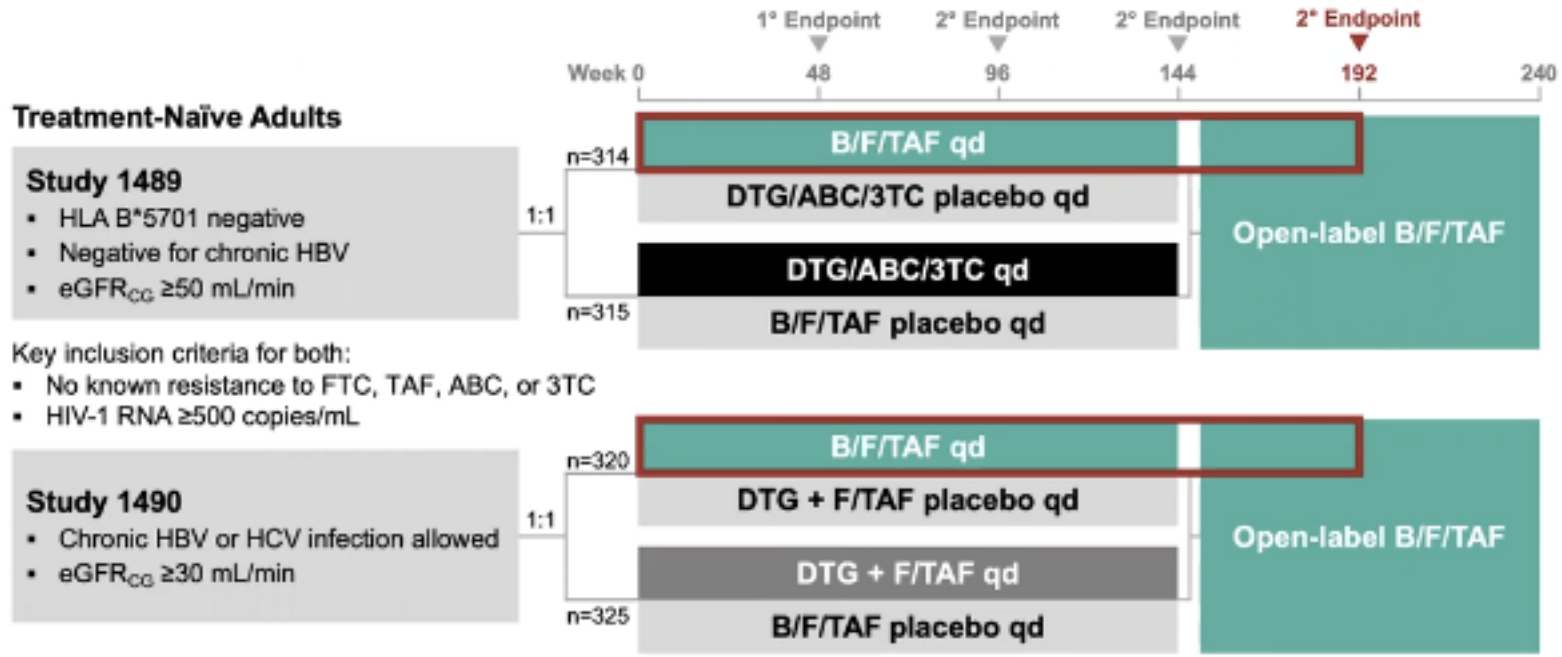
Kimberly Workowski

Emory University, Atlanta, GA

Disclosure: Clinical Trials- Gilead, Acuris, DMID

00:09

Study Designs: Randomized, Double Blind, Active Controlled



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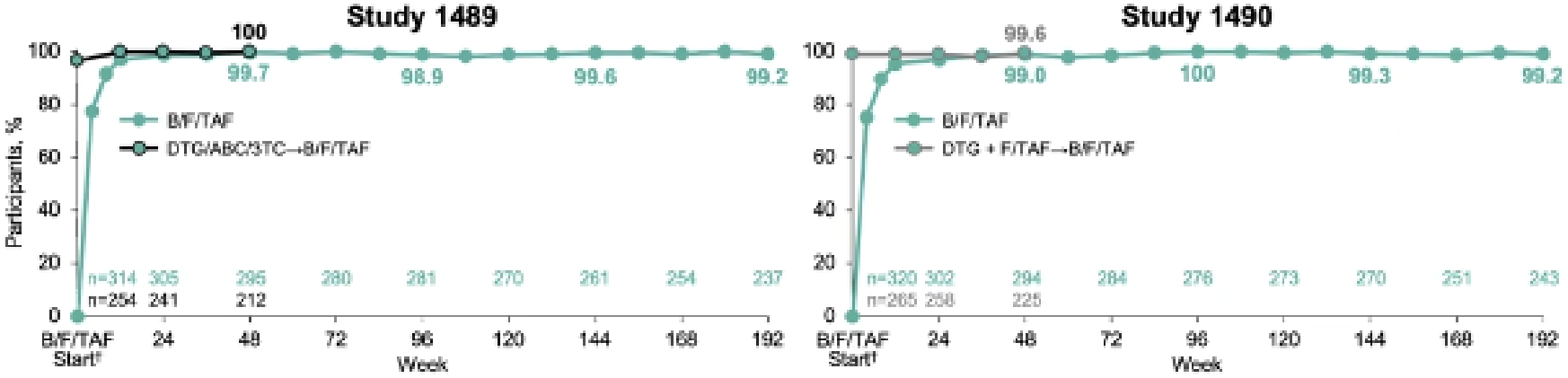
Virologic Outcomes Through Week 192 on B/F/TAF

HIV-1 RNA <50 Copies/mL, Missing = Excluded*



*Calculated using US FDA Snapshot algorithm; †B/F/TAF group were treatment-naive at B/F/TAF start; DTG groups switched from DTG-containing regimens to B/F/TAF.

- Efficacy was >98% after Week 48 at each study visit through Week 192 in both studies for all participants
- HIV-1 RNA <50 copies/mL was maintained in participants who switched from DTG-containing regimens to B/F/TAF at Weeks 144–192

Virologic Resistance Through Week 192

	Week 144 to Unblinding				OLE B/F/TAF			
	Study 1489		Study 1490		Study 1489		Study 1490	
Participants, n	B/F/TAF	DTG/ABC/3TC	B/F/TAF	DTG + F/TAF	B/F/TAF	DTG/ABC/3TC→B/F/TAF	B/F/TAF	DTG + F/TAF→B/F/TAF
Met criteria for resistance testing*	0/263	4/269†	0/268	1/261	0/252	1/254	0/254	1/265
NRTI-R detected	0	1 (M184V) ‡	0	0	0	0	0	0
INSTI-R detected	0	0	0	0	0	0	0	0

*Resistance testing performed for participants with confirmed HIV-1 RNA ≥200 copies/mL or ≥200 copies/mL at last visit, with no resuppression of HIV-1 RNA to <50 copies/mL while on study drug;

AEs Through Week 192*

Participants, %		Study 1489 B/F/TAF: n=314	Study 1490 B/F/TAF: n=320
Any AE		96	92
>10% in either group	Diarrhea	19	23
	Headache	16	20
	Nasopharyngitis	17	18
	URTI	16	15
	Syphilis	15	14
	Nausea	14	11
	Arthralgia	13	13
	Cough	13	12
	Back pain	13	12
	Fatigue	12	9
	Anxiety	11	6
	Rash	11	5
	Insomnia	11	10
	Influenza	8	11

Study Drug-Related AEs Through Week 192*

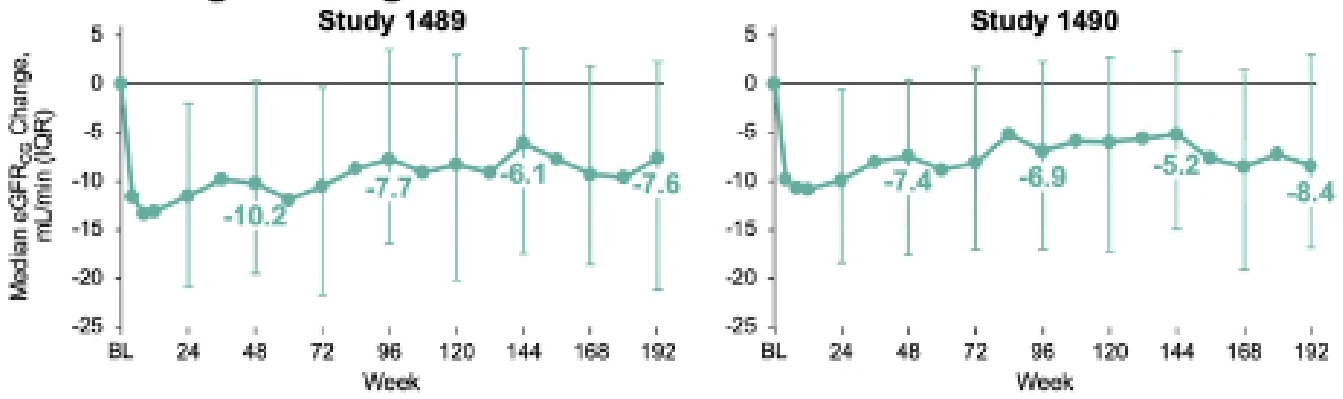
Participants, %		Study 1489 B/F/TAF: n=314	Study 1490 B/F/TAF: n=320
Any study drug-related AE		32	24
>5% in either group	Diarrhea	6	3
	Headache	5	5
	Nausea	5	3

AEs Leading to D/C Through Week 192*

Study 1489 B/F/TAF: n=1/314 (<1%)	Study 1490 B/F/TAF: n=6/320 (2%)
Intervertebral discitis (Day 1366)	Cardiac arrest (Day 28)
	Paranoia (Day 299)
	Chest pain (Day 1)
	Depression (Day 337)
	Abdominal distension (Day 1)
	Sleep disorder, dyspepsia, and tension headache (Day 15); *depressed mood and insomnia* (Day 63)

Italics indicate AEs considered study drug-related by investigator; *red shading* indicates events that occurred after Week 144.

eGFR Changes Through Week 192 on B/F/TAF*

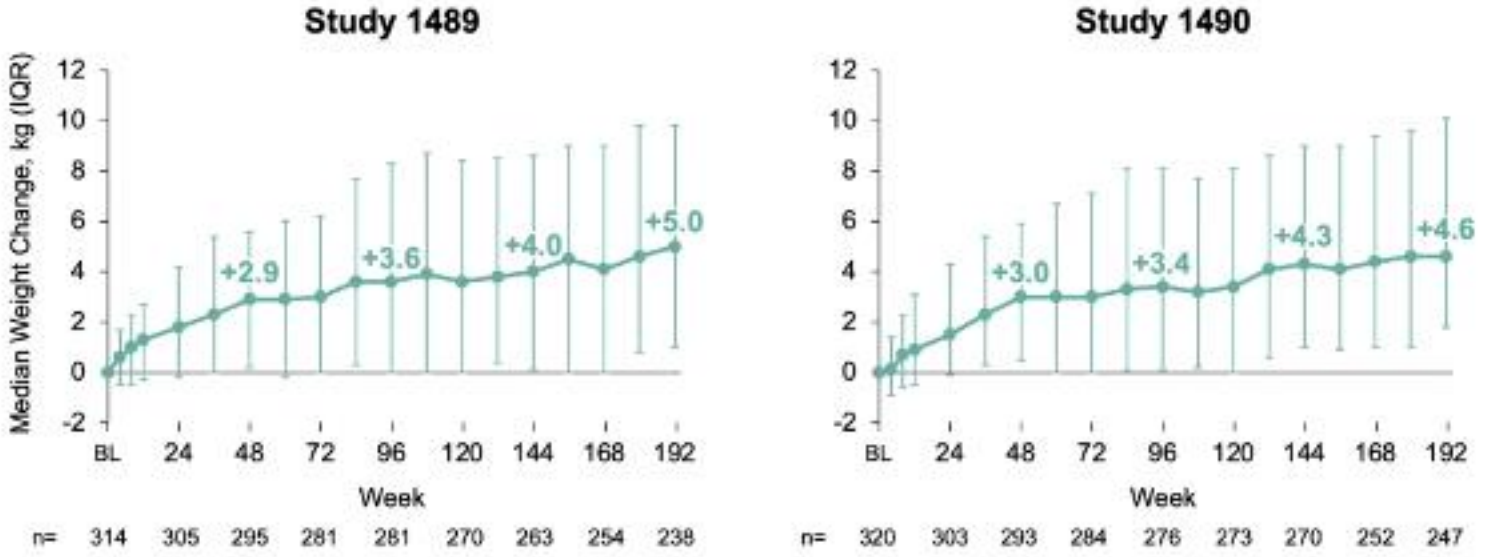


Mean BMD % change (95% CI) at Week 192 in Study 1489 participants initially randomized to B/F/TAF

- Spine: -0.9% (-1.7, -0.2)
- Hip: -1.4% (-2.2, -0.7)

*Includes only participants initially randomized to B/F/TAF.

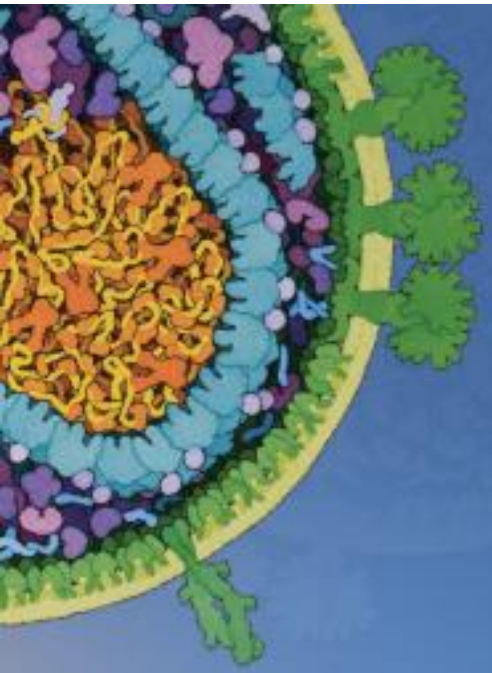
Weight Changes From Baseline Through Week 192 on B/F/TAF*



- From baseline through 144 weeks of the randomized phase, participants originally assigned B/F/TAF in Study 1489 had a median weight change (IQR) of +4.0 kg (0.1, 8.6), and in Study 1490 +4.3 kg (1.0, 9.0)
- Between Weeks 144 and 192, median weight increased +1.0 kg in Study 1489, +0.3 kg in Study 1490

eCROI 2021

Traitements ARV: stratégies 2è ligne/switches



SCIENCE SPOTLIGHT™

SWITCHING TO DTG/3TC FDC IS NON-INFERIOR TO TAF-BASED REGIMENS FOR 96 WEEKS: TANGO SUBGROUP ANALYSES

Paul Benson,[1] Clifford Kinder,[2] María Jesús Pérez Elías,[3] Don E. Smith,[4] Stefan Scholten,[5] Mounir Ait-Khaled,[6] Keith A. Pappa,[7] Ruolan Wang,[7] Jonathan Wright,[8] Brian Wynne,[7] Michael Aboud,[6] Jean van Wyk,[6] Kimberly Y. Smith[7]

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Disclosure: Paul Benson participates in speakers bureaus for ViiV Healthcare.

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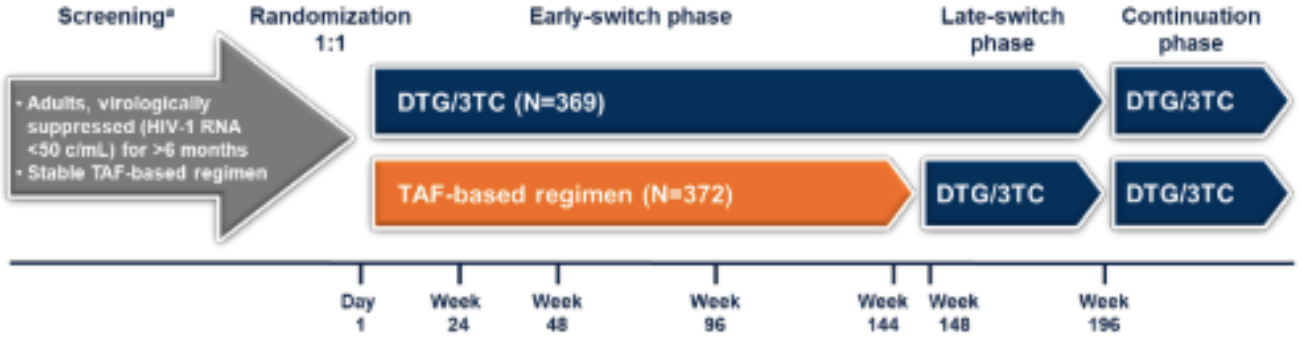
Background

- TANGO (NCT03446573) is an ongoing phase III, non-inferiority trial evaluating efficacy and safety of a switch to DTG/3TC fixed-dose combination in adults with HIV-1 infection who are virologically suppressed on a 3- or 4-drug TAF-based regimen[1]
- In the Week 48 primary analysis and Week 96 analysis of TANGO, switching to DTG/3TC FDC was non-inferior to remaining on a TAF-based regimen in ART-experienced, virologically suppressed adults[2,3]
- Here we present rates of virologic suppression (Snapshot) through Week 96 by demographic characteristics, baseline third agent class, and disease characteristics

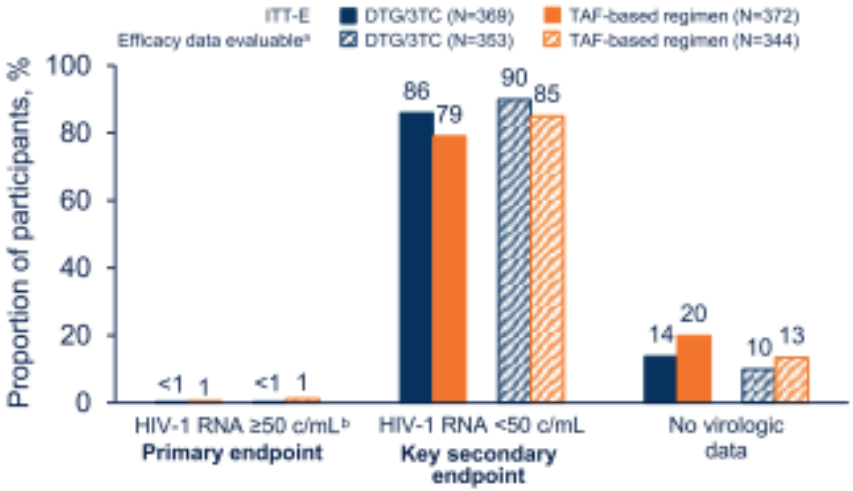


[a]Participants were eligible if they had ≥2 documented HIV-1 RNA measurements <50 c/mL, no HBV infection or need for HCV therapy, no prior VF and no documented NRTI or INSTI resistance, and TAF/FTC + PI or INSTI or NNRTI as initial regimen.

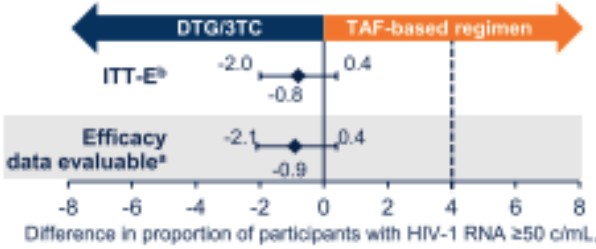
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03446573. Accessed January 26, 2021. 2. van Wyk et al. *Clin Infect Dis.* 2020;71:1920-1929. 3. van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441.

DTG/3TC Is Non-inferior to TAF-Based Regimen at Week 96

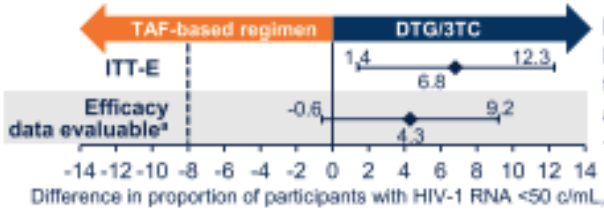
Virologic outcomes (Snapshot analysis)



Adjusted treatment difference (95% CI)[c]



HIV-1 RNA ≥50 c/mL
DTG/3TC is non-inferior to TAF-based regimen at Week 96 based on a 4% non-inferiority margin

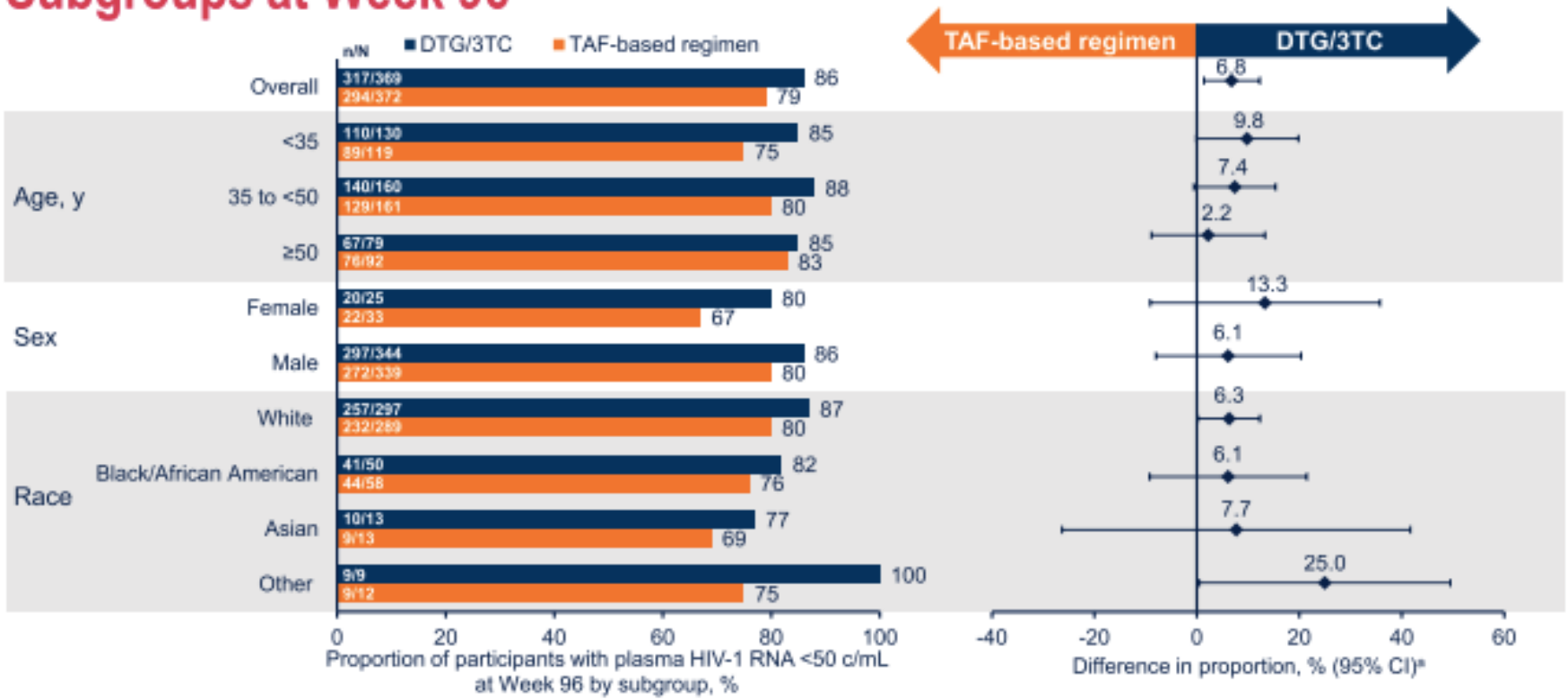


HIV-1 RNA <50 c/mL
DTG/3TC is non-inferior to TAF-based regimen at Week 96 based on a −8% non-inferiority margin

- Superiority was demonstrated in the **per-protocol analysis**: 0/348 participants in the DTG/3TC group and 4/351 in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 96 (adjusted difference, −1.1%; 95% CI, −2.3% to −0.0%; *P*=0.044)
- In the DTG/3TC group, there were no cases of confirmed virologic withdrawal through Week 96 and 3 cases in the TAF-based regimen group; no resistance mutations were observed

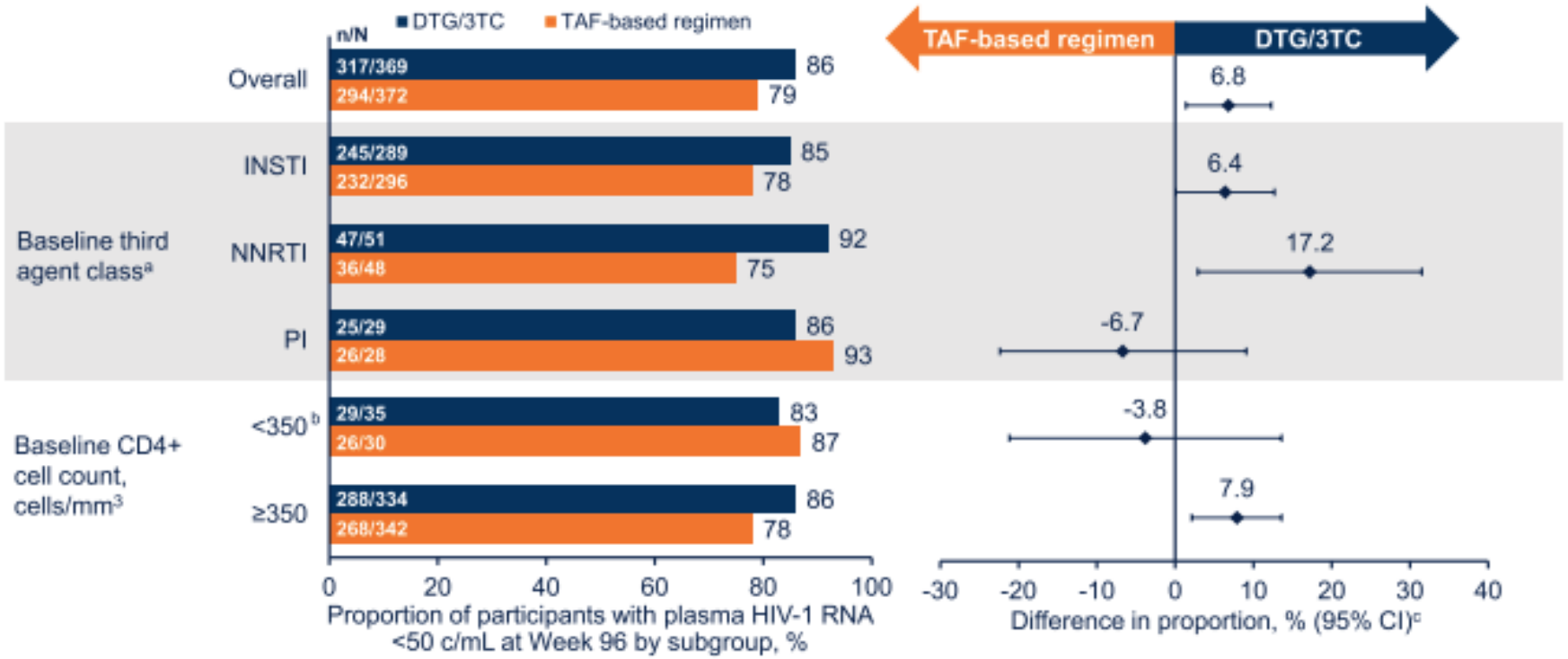
[a]Sensitivity analysis excluding 16 and 28 participants in the DTG/3TC and TAF-based regimen groups, respectively, because of no Week 96 HIV-1 RNA data due to effects of the COVID-19 pandemic. [b]Primary endpoint (Snapshot virologic non-response, ITT-E). [c]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − TAF-based regimen) adjusting for baseline third agent class.

HIV-1 RNA <50 c/mL Was Comparable Across Demographics Subgroups at Week 96

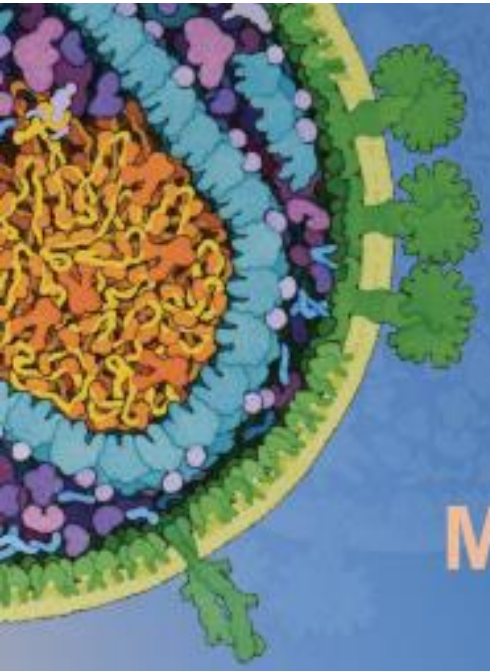


aAdjusted difference for overall population (DTG/3TC − TAF-based regimen) and 95% CI are based on a stratified analysis (adjusting for baseline third agent class) using Cochran-Mantel-Haenszel weights (meeting non-inferiority based on −8% margin). Unadjusted difference for subgroups calculated by proportion on DTG/3TC − proportion on TAF-based regimen.

HIV-1 RNA <50 c/mL Was Comparable Across Baseline Characteristics Subgroups at Week 96



[a]The study population was stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]Includes 14 participants with baseline CD4+ cell count <200 cells/mm³: 71% (5/7) in the DTG/3TC group and 100% (7/7) in the TAF-based regimen group. [c]Adjusted difference for overall population (DTG/3TC − TAF-based regimen) and 95% CI are based on a stratified analysis (adjusting for baseline third agent class) using Cochran-Mantel-Haenszel weights (meeting non-inferiority based on −8% margin). Unadjusted difference for subgroups calculated by proportion on DTG/3TC − proportion on TAF-based regimen.



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W96 EFFICACY OF 4/7DAYS MAINTENANCE ART STRATEGY: ANRS-170 QUATUOR TRIAL

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Université de Paris, INSERM, IMEA, Hôpital Bichat-Claude Bernard, AP-HP, Paris, France

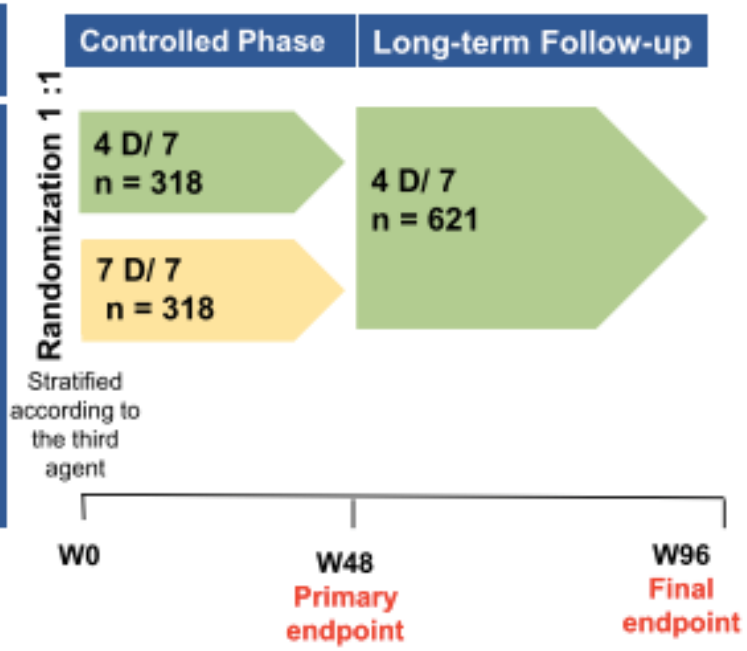
Disclosure: Research grant from Viiv Healthcare, Inc., Gilead Science, Inc., Merck & Co, Inc

CROI 2021

QUATUOR - STUDY DESIGN
RANDOMIZED, MULTICENTER, NATIONAL, OPEN-LABEL, NON-INFERIORITY STUDY IN ADULTS WITH HIV-1 VIROLOGICAL SUPPRESSION

Screening Phase

- VL < 50 c/mL for ≥12 months
- No genotype resistance
- CD4 > 250 cells/mm^3
- PI-, NNRTI- ou INI- based regimen with a 2 NRTI backbone



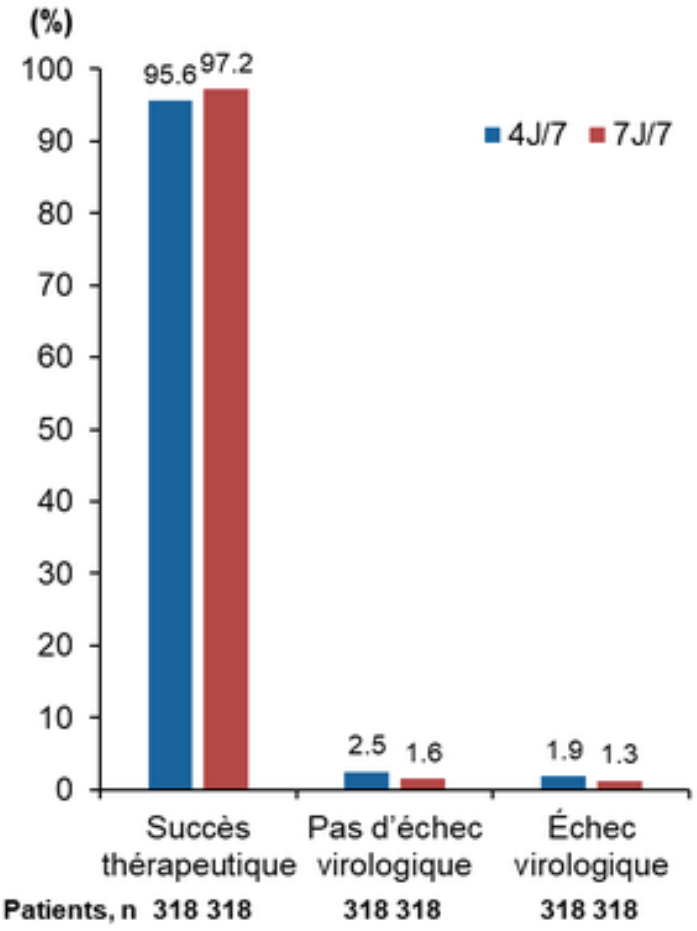
Baseline Characteristics	Total 4/7 Days n=621
Age, year, median (IQR)	49 (41 – 55)
Male sex, n (%)	525 (84.5)
CD4 at screening (cells/mm^3), median (IQR)	692 (532 - 884)
Duration on ARV, year, median (IQR)	6.9 (4.0 – 12.4)
Duration of virological suppression (<50 c/mL), year, median (IQR)	5.8 (3.4 – 9.7)
Baseline NRTI , n (%)	
- TDF-TAF/FTC	452 (72.8)
- ABC/3TC	169 (27.2)
Baseline third agent class , n (%)	
- INI (DTG/EVG/RAL)	300 (48.3)
- NNRTI (RPV/EFV/ETR)	286 (46.1)
- PI (DRV/ATV/LPV)	35 (5.6)

OBJECTIVES :

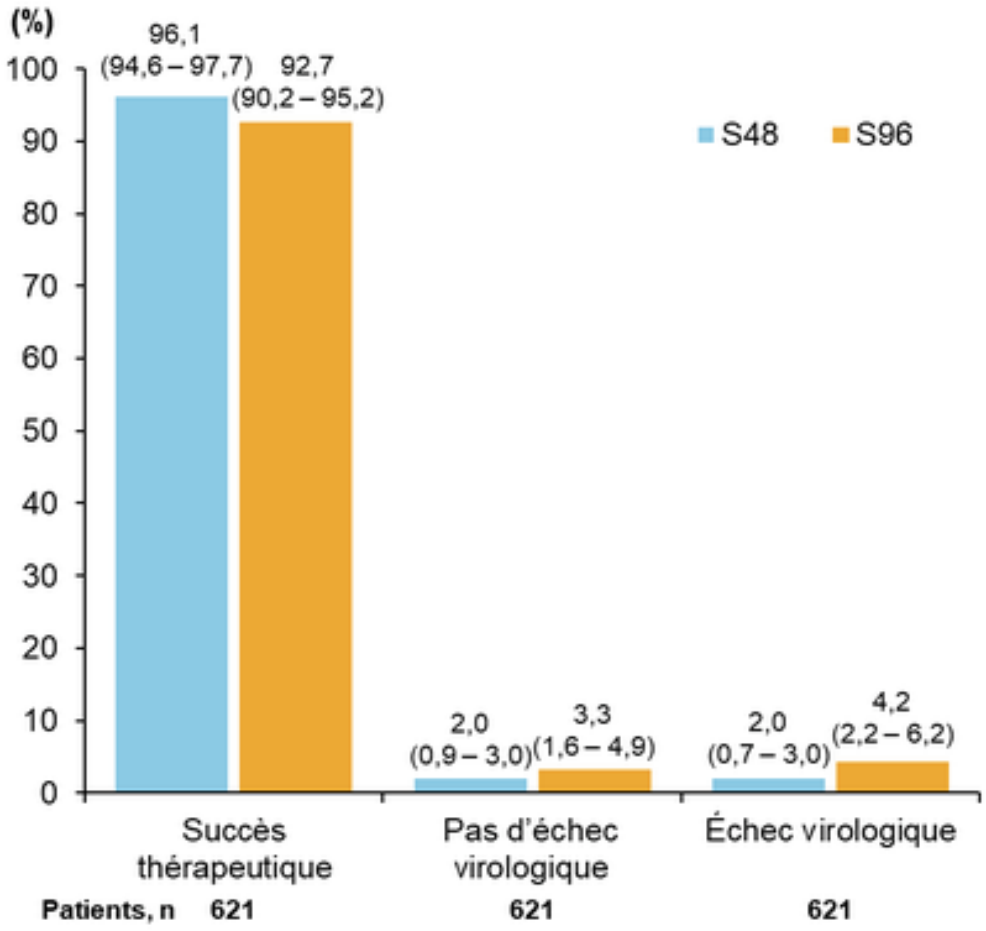
- **W48 : to establish non-inferiority of antiviral activity of 4D/7 versus 7D/7with 5% non inferiority margin between groups**
- **W96 : long term follow-up efficacy and tolerance of 4D/7**

QUATUOR (ANRS-170) : RÉSULTATS

Phase randomisée de J0 à S48



Suivi à long terme de J0 à S96 (n = 621) sous 4J/7



(EV défini par 2 CV consécutives ≥ 50 copies/mL)

Selon le 3e agent, l'échec virologique (EV) a été observé chez 5,3 % (1,9 – 8,6) sous INNTI, et 2,4 % (0,6 – 4,1) sous INI à S96

QUATUOR - VIROLOGICAL FAILURE AND TOLERANCE: WEEK 96

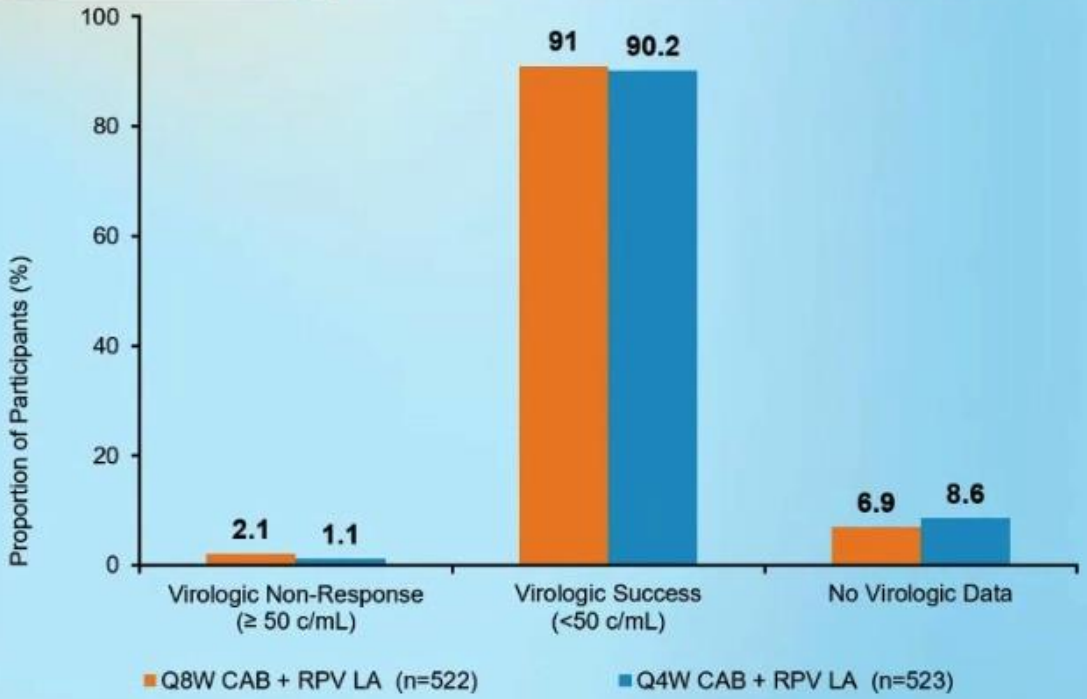
Virological failure / New drug resistance mutations

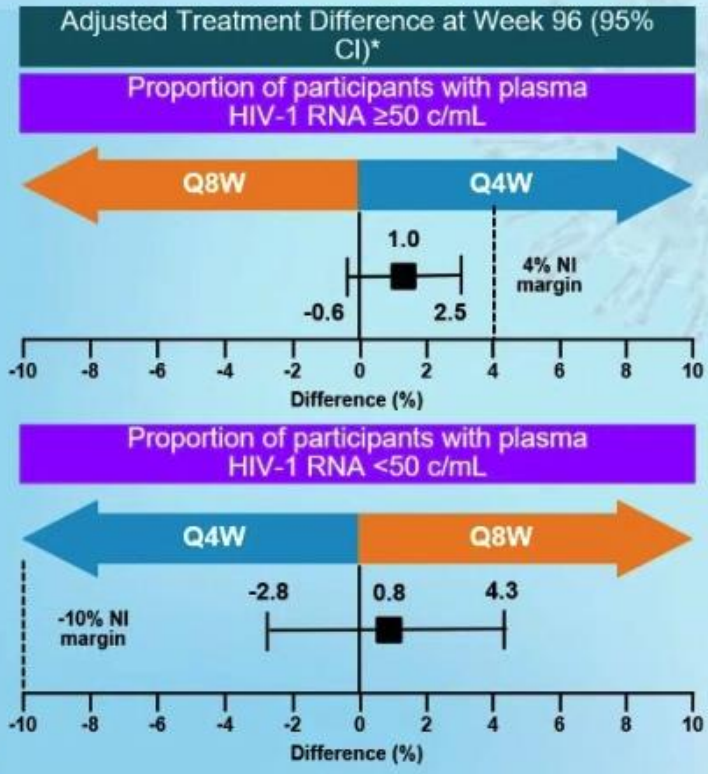
Follow-up period	Virological failure	Patients with new DRM	Treatment at failure
D0-W48	6 /318	3 /6 : - M184I, E138K, Y188L - M184V, E138K, V179I, H221Y - M184I, N155H	 - TDF+FTC+RPV - TDF+FTC+RPV - ABC+3TC+RAL
W48-W96	13/621	4/13 : - M184I - E138K, M184V - M184I/M - K65K/R, E138K/E, V179I, K219E, F227F/C	 - TDF+FTC+EFV - TDF+FTC+RPV - TAF+FTC+EVG/c - TAF+FTC+RPV

Tolerance

- No significant adverse events, biological changes were observed with the 4/7-days strategy until W96, except a gain of +4 ml/min (IQR -2;+6) in eGFR, $p<0.001$
- Strategy interruption for adverse event (n=3) and death (n=5 – 2 cancers, 1 domestic accident, 1 stroke, 1 myocardial infarction)

ATLAS-2M Study: 96 Week Update





*Based on CMH stratificed analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH Cochran-Mantel-Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Jaeger, et al. Virtual CROI 2021; March 6-10, 2021. Abst. 401

ATLAS-2M Study: Results

Overall Summary of CVFs through Week 96

	n	CVFs n (%)	CVFs with RPV RAMS*	RPV RAMs observed at failure	CVFs with IN RAMs*	IN RAMs observed at failure
Q8W	522	9 (1.7)	7/9	K101E, E138E/K, E138A, Y188L, Y181C	5/9	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

One additional participant, who was in the Q8W arm, met the CVF criterion between Week 48 and 96 (Week 88)‡

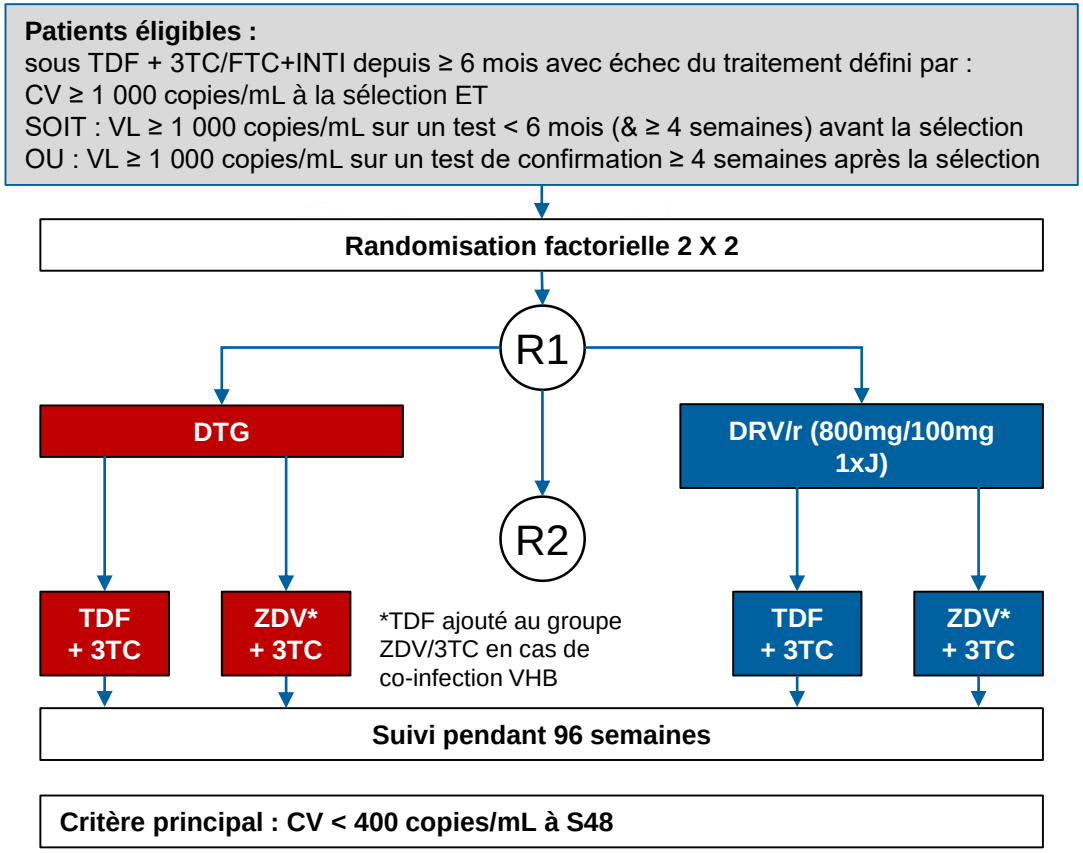
- NNRTI RAM K103N and RPV RAM Y181C were detected at virologic failure in the plasma sample and retrospectively at baseline in the PBMC sample
- No INSTI RAMs were present at virologic failure in the plasma sample or in the baseline PBMC sample; IN substitution L74L/I was present at baseline
- 10/11 CVFs resuppressed on alternative regimens (one participant was non-adherent to PI-based ART)

Jaeger, et al. Virtual CROI 2021, March 6-10, 2021. Abst. 401

ÉTUDE NADIA : DTG OU DRV/R + INTI EN 2E LIGNE (1)

Réalisée en Afrique – patients en échec d'INNTI+ TDF/3TC

- Objectifs :
  - non-infériorité du DTG versus DRV/r en 2e ligne ?
  - non-infériorité de TDF/3TC versus ZDV/3TC en 2e ligne ?
  - Chez des patients avec une résistance potentielle aux INTI : pas de test de résistance à l'inclusion, suivi allégé de la CV : S24, S48 – pour les patients avec CV ≥ 1 000 cp/mL, conseils intensifs d'adhérence au traitement + répéter dosage CV après 12 (10-16) semaines



CROI 2021 - D'après Paton N et al., LBA94, actualisé

ÉTUDE NADIA : DTG/DRV/R + INTI EN 2E LIGNE (2)

Caractéristiques à l'inclusion

Caractéristiques	Groupe dolutégravir (n = 235)	Groupe darunavir (n = 229)	Groupe ténofovir (n = 233)	Groupe zidovudine (n = 231)	Tous (n = 464)
Sexe féminin, n (%)	140 (59,6)	142 (62,0)	140 (60,1)	142 (61,5)	282 (60,8)
Âge médian (IQR), années	33 (28 – 40)	35 (28 – 42)	34 (28 – 43)	35 (28 – 40)	34 (28 – 41)
Taux médian de lymphocytes CD4+ (IQR), par mm^3	189 (58 – 388)	202 (84 – 357)	200 (77 – 388)	191 (58 – 340)	194 (68 – 367)
< 50 par mm^3, n (%)	54 (23,0)	39 (17,0)	45 (19,3)	48 (20,8)	93 (20,0)
50 – 199 par mm^3, n (%)	71 (30,2)	74 (32,3)	70 (30,0)	75 (32,5)	145 (31,3)
200 – 349 par mm^3, n (%)	43 (18,3)	56 (24,5)	47 (20,2)	52 (22,5)	99 (21,3)
> 350 par mm^3, n (%)	64 (28,5)	60 (26,2)	71 (30,5)	56 (24,2)	127 (27,4)
CV médiane (IQR), log_{10} copies/mL	4,5 (3,9 – 5,1)	4,4 (3,8 – 5,1)	4,4 (3,9 – 5,1)	4,4 (3,9 – 5,1)	4,4 (3,9 – 5,1)
< 100 000	169 (71,9)	167 (72,9)	171 (73,4)	165 (71,4)	336 (72,4)
≥ 100 000	66 (28,1)	62 (27,1)	62 (26,6)	66 (28,6)	128 (27,6)
K65R/N présente à l'inclusion, n (%)	120 (52,9)	107 (47,6)	116 (50,7)	111 (49,8)	227 (50,2)
M184V/I présente à l'inclusion, n (%)	196 (86,3)	195 (86,7)	201 (87,8)	190 (85,2)	391 (86,5)
Résistance au TDF Int./élevée, n (%)	139 (61,2)	125 (55,8)	132 (57,9)	132 (59,2)	264 (58,5)
Résistance à la ZDV Int./élevée, n (%)	45 (19,8)	38 (17,0)	41 (18,0)	42 (18,8)	83 (18,4)
Résistance au 3TC Int./élevée, n (%)	213 (93,8)	202 (90,2)	212 (93,0)	203 (91,0)	415 (92,0)

CROI 2021 - D'après Paton N et al., LBA94, actualisé

ÉTUDE NADIA : DTG/DRV/R + INTI EN 2E LIGNE (3)

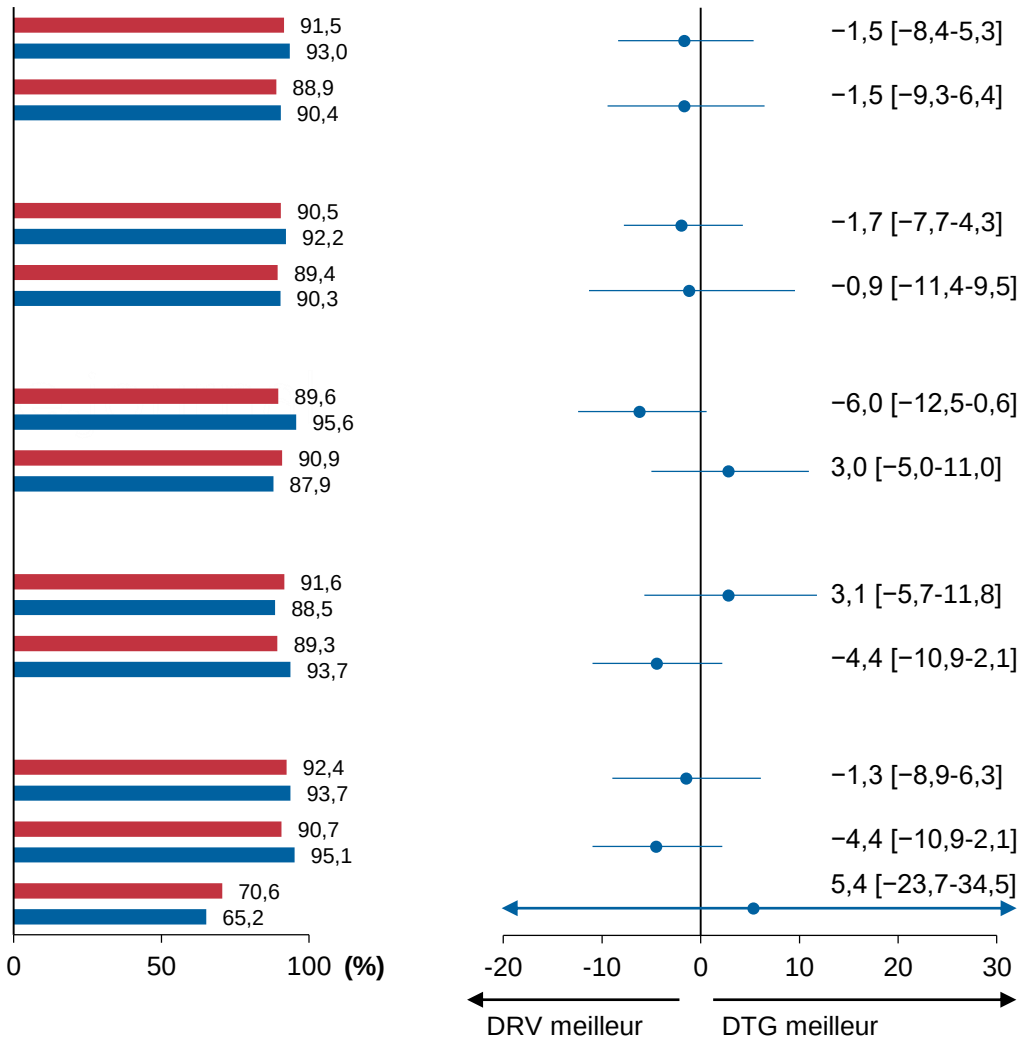
Efficacité : DTG versus DRV/r

Critères	Groupe dolutégravir (n = 235)	Groupe darunavir (n = 229)	Différence (IC_{95}), %	p
CV (critère principal), n (%)				
< 400 copies/mL (ITT)	212 (90,2)	210 (91,7)	−1,49 [−6,7-3,7]	0,576
≥ 400 copies/mL	20 (8,5)	16 (7,0)	-	
Pas de données virologiques - Retrait pour EI/décès - Retrait pour autres raisons	3 (1,3) 2 (0,9) 1 (0,4)	3 (1,3) 3 (1,3) 0	-	
Niveau de CV (analyses de sensibilité, secondaires, autres critères), n (%)				
< 400 copies/mL (ajusté)	88,2	89,8	−1,6 [−6,9-3,6]	0,541
VL < 400 copies (per protocole)	205 (92,3)	204 (93,2)	−0,8 [−5,6-4,0]	0,744
VL < 1 000 cp/mL (ITT)	217 (92,3)	213 (93,0)	−0,7 [−5,4-4,1]	0,781
VL < 50 cp/mL (ITT)	190 (80,9)	182 (79,5)	1,4 [−5,9-8,6]	0,710
Rebond viral (critère secondaire), n (%)				
Rebond CV ≥ 1 000 cp/mL, confirmé (ITT)	14 (6,0)	13 (5,7)	0,3 [−4,0-4,5]	0,897
Rebond CV ≥ 1 000 cp/mL, confirmé avec ≥ 1 mutation de résistance majeure au DTG ou DRV	4*	0	-	-

*≥ 1 mutation majeure de résistance au DTG : 4 (1) T66TA, G118R, E138K, G149GA, (élevé) ; (2) E138K, G140A, Q148R (élevé) ; (3) T66I, G118R, E138K, G149GA (élevé) ; (4) R263K, M50I (intermédiaire).
≥ 1 mutation majeure de résistance au DRV : 0

ÉTUDE NADIA : DTG/DRV/R + INTI EN 2E LIGNE (4)

Efficacité - analyse de sous-groupes : DTG versus DRV/r



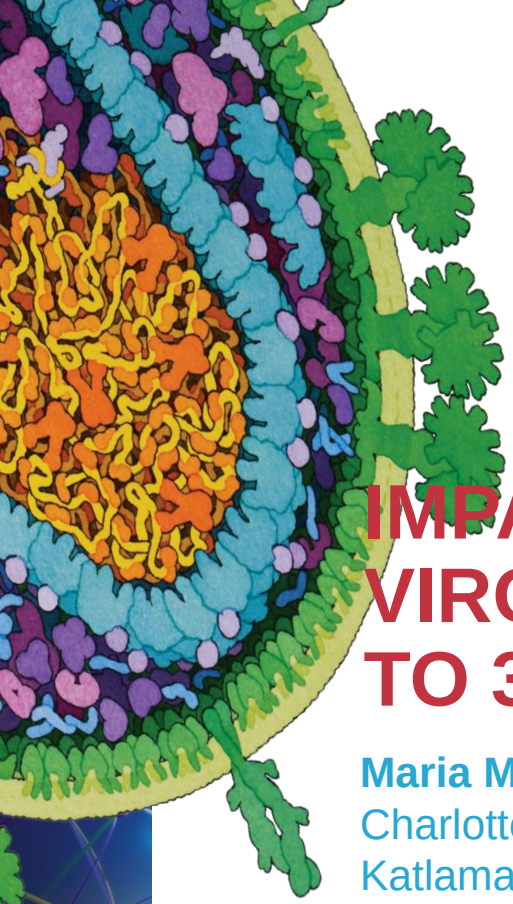
CROI 2021 - D'après Paton N et al., LBA94, actualisé

ÉTUDE NADIA : DTG/DRV/R + INTI EN 2E LIGNE (5)

Efficacité : TDF versus ZDV

Critères	Groupe ténofovir (n = 233)	Groupe zidovudine (n = 231)	Différence (IC_{95}), %	p
CV (critère principal), n (%)				
< 400 copies/mL (ITT)	215 (92,3)	207 (89,6)	2,7 [−2,6-7,9]	0,317
≥ 400 copies/mL	15 (6,4)	21 (9,1)	-	
Pas de données virologiques - Retrait pour EI/décès - Retrait pour autres raisons	3 (1,3) 3 (1,3) 0	3 (1,3) 2 (0,9) 1 (0,4)	-	
Niveau de CV (analyses de sensibilité, secondaires, autres critères), n (%)				
< 400 copies/mL (ajusté)	88,2	85,4	2,8 [−2,5-8,0]	0,304
VL < 400 copies (per protocole)	20,9 (93,7)	200 (91,7)	2,0 [−2,9-6,8]	0,423
VL < 1 000 cp/mL (ITT)	219 (94,0)	211 (91,3)	2,6 [−2,1-7,4]	0,274
VL < 50 cp/mL (ITT)	188 (80,7)	184 (79,7)	1,0 [−6,2-8,3]	0,780
Rebond viral (critère secondaire), n (%)				
Rebond CV ≥ 1 000 c/mL, confirmé (ITT)	11 (4,7)	16 (6,9)	−2,2 [−6,5-2,1]	0,310
Rebond CV ≥ 1 000 c/mL, confirmé avec ≥ 1 mutation de résistance majeure au DTG ou DRV*	1	3	-	-

*≥1 mutation majeure de résistance au DTG : 4
≥ 1 mutation majeure de résistance au DRV : 0



SCIENCE SPOTLIGHT™

IMPACT OF M184V ON THE VIROLOGICAL EFFICACY OF SWITCH TO 3TC/DTG IN REAL LIFE

Maria M. Santoro[1], Daniele Armenia[2], Elisa Teyssou[3], José Ramón Santos[4], Charlotte Charpentier[5], Sidonie Lambert-Niclot[6], Andrea Antinori[7], Christine Katlama[3], Diane Descamps[5], Carlo F. Perno[8], Vincent Calvez[3], Roger Paredes[4], Francesca Ceccherini-Silberstein[1], Anne Geneviève Marcelin[3], for LAMRES Study Group

[1]University of Rome Tor Vergata, Rome, Italy; [2]Saint Camillus International University of Health Sciences, Rome, Italy; [3]Hôpital Pitié-Salpêtrière, Paris, France; [4]Hospital Germans Trias i Pujol, Barcelona, Spain; [5]Hôpital Bichat-Claude-Bernard, Paris, France; [6]Saint-Antoine Hospital, Paris, France; [7]National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy; [8]Bambino Gesu Children's Hospital, Rome, Italy.

Disclosure: Maria Mercedes Santoro has received funds for attending symposia, speaking and organizing educational activities from ViiV Health Care and Janssen-Cilag.

AIM: **To assess the efficacy of 3TC/DTG in a large set of virologically suppressed patients with or without past M184V**

Methods

This **European retrospective study** included **several clinical and virological centers** involved in HIV care from **France**, **Italy** and **Spain**.

Patients were included according to the following criteria:

- ✓To be **virologically suppressed** (plasma HIV-RNA ≤50 copies) at **switching to dual therapy including 3TC/DTG**.
- ✓Availability of at least one previous HIV-RNA and/or HIV-DNA genotypic resistance test (GRT).
- ✓Virological follow up after switching to 3TC/DTG.

Survival analysis was used to evaluate **the role of past M184V on experiencing a virological failure** (**VF**: HIV-RNA >50 cps/mL in 2 consecutive determinations or ≥200 cps/mL in a single determination) or **a blip** (a single HIV-RNA in the range 51-199 cps/mL preceded and followed by ≤50 cps/mL measurements) after 3TC/DTG switch.

Moreover, **demographic, viro-immunological and therapeutical variables** were evaluated **as other potential factors associated with VF or blips**.

Resistance at VF was also evaluated.

LAMRES:Characteristics of the population studied

Demographic characteristics

Variables	Overall (N=533)
Male, n (%)	422 (79.2)
Risk factor, n (%)	
Homosexual	252 (47.3)
Heterosexual	169 (31.7)
Drug abuse	62 (11.6)
Sexual	23 (4.3)
Other/unknown	27 (5.1)
Ethnicity, n (%)	
Caucasian	391 (73.4)
Black	23 (4.3)
Hispanic	18 (3.4)
Other/unknown	101 (18.9)
Adherence, n (%)	
High	130 (24.4)
Medium/Low	22 (4.1)
Unknown	381 (71.5)

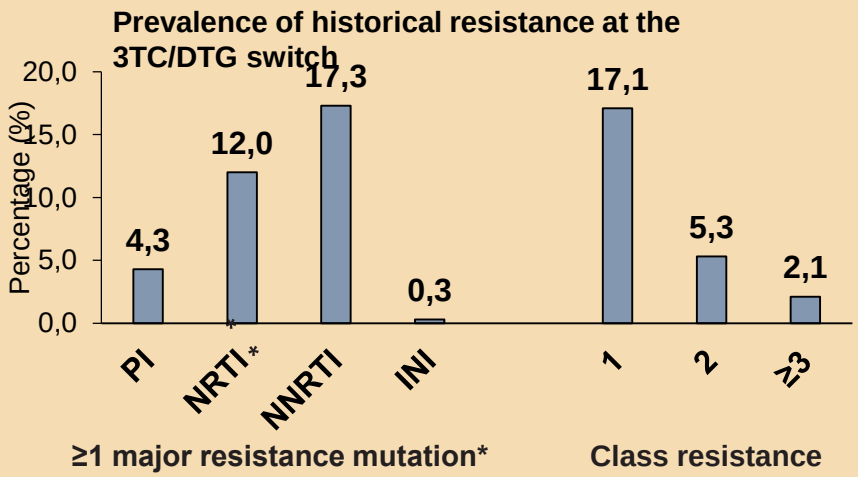
Viro-immunological characteristics

Variables	Overall (N=533)
HIV-1 subtype B, n (%)	392 (73.5)
Viremia Zenith (log$_{10}$ copies/mL), median (IQR)	5.1 (4.5-5.6)
Target not detected at switch, n (%)	233 (43.7)
Nadir CD4 cell count (cell/mm^3), median (IQR)	266 (133-384)
Baseline CD4 cell count (cell/mm^3), median (IQR)	691 (514-883)
At least one failure before switch, n (%)	209 (39.2)
INI-failure before switch, n (%)	18 (3.4)

Therapeutic characteristics

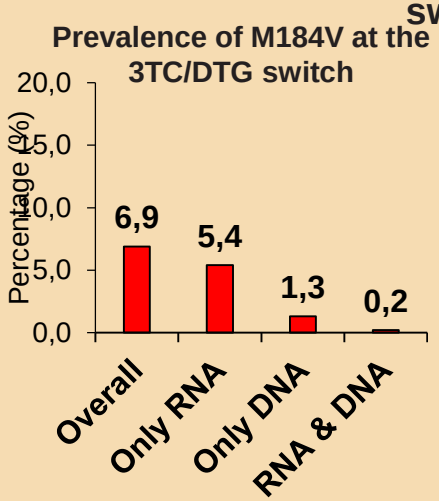
Variables	Overall (N=533)
Years under cART, median (IQR)	8 (4-15)
N° of previous regimens experienced, median (IQR)	3 (2-5)
N° of ARVs experienced, median (IQR)	
NRTIs	3 (2-4)
NNRTIs	1 (0-1)
PIs	2 (0-3)
INIs	1 (0-1)
Entry Inhibitors	0 (0-0)
Previous 3TC/FTC exposure, n (%)	301 (56.5)
Previous first generation INI-exposure, n (%)	166 (31.1)
Previous DTG exposure, n (%)	145 (27.2)

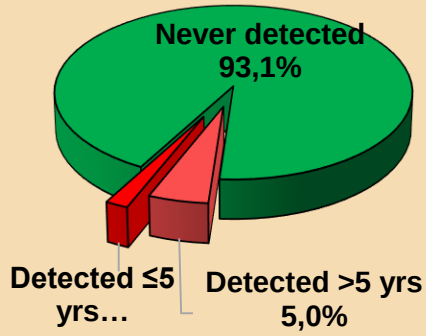
Historical resistance at the 3TC/DTG switch



* Mutations detected in all previous GRTs according to Stanford Resistance list 2019; ** Excluding M184V

Overview of past M184V detected before 3TC/DTG switch





*Median (IQR) time of last detection of M184V before

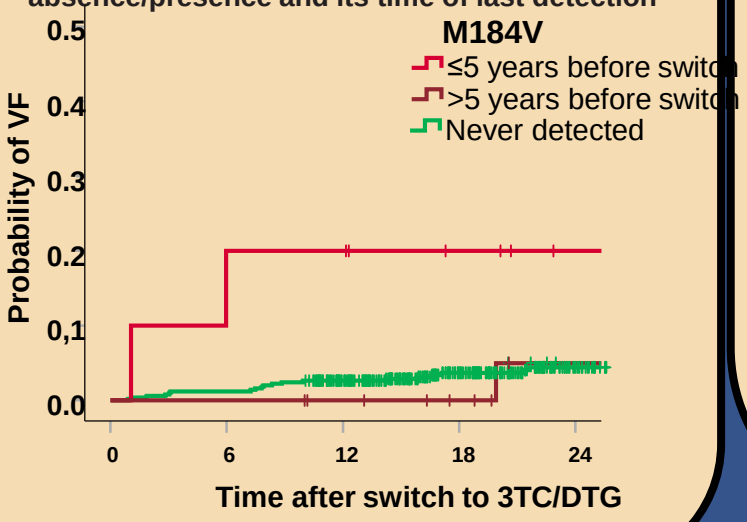
Probability of VF after 3TC/DTG switch

Overall probability at 1 year: 2.8%
Overall probaility at 2 years: 4.8%

No significant difference in the probability of VF was found according to the presence/absence of M184V (1 yr: 5.4% vs 2.6%; 2 yrs: 9.2% vs 4.4%; p=0.345).

A significant higher probability of VF was found in individuals with M184V detected ≤5 yrs before switch compared to those with M184V detected >5 yrs and those without M184V (Figure).

Kaplan-Meier estimates of VF according to M184V absence/presence and its time of last detection



Probability of viral blips after 3TC/DTG switch

Overall probability at 1 year: 3.6%
Overall probaility at 2 years: 7.3%

No statistical association of M184V with the probability of blips (p=0.321), neither after considering the time of last M184V detection (p=0.596).

Factors associated with VF after 3TC/DTG switch

Factors significantly associated with virological failure at uni-multivariable Cox regression analyses

Variables	Hazard ratio (HR, 95% C.I.) to experience VF			
	Crude HR	P value	Adjusted HR	P value
Risk factor, n (%)				
Homosexual	1		1	
Heterosexual	**4.8 (1.8-13.1)**	**0.002**	**3.8 (1.1-13.3)**	**0.034**
Drug abuse	2.2 (0.5-9.1)	0.290	0.9 (0.1-5.4)	0.886
Sexual	2.2 (0.3-18.6)	0.479	2.3 (0.3-21.2)	0.458
Viremia Zenit (copies/mL), n (%)				
<100,000	1		1	
100,000-500,000	2.8 (0.9-8.1)	0.063	3.3 (1.0-11.1)	0.050
>500,000	**4.1 (1.4-12.0)**	**0.010**	**3.6 (1.1-12.0)**	**0.041**
Cumulative class resistance before switch, n (%)				
None	1		1	
1	1.6 (0.6-4.4)	0.366	1.3 (0.4-3.9)	0.635
2	3 (0.8-10.3)	0.089	5.1 (0.9-28-6)	0.065
≥3	**7.1 (2-24.7)**	**0.002**	**23.0 (3.1-168.5)**	**0.002**
Past M184V according to detection time, n (%)				
Never detected	1		1	
Detected ≤5 years before switch	**5.6 (1.3-23.7)**	**0.020**	1.9 (0.3-14.6)	0.518
Detected >5 years before switch	0.7 (0.1-5.6)	0.778	**0.1 (0.0-1.2)**	**0.040**

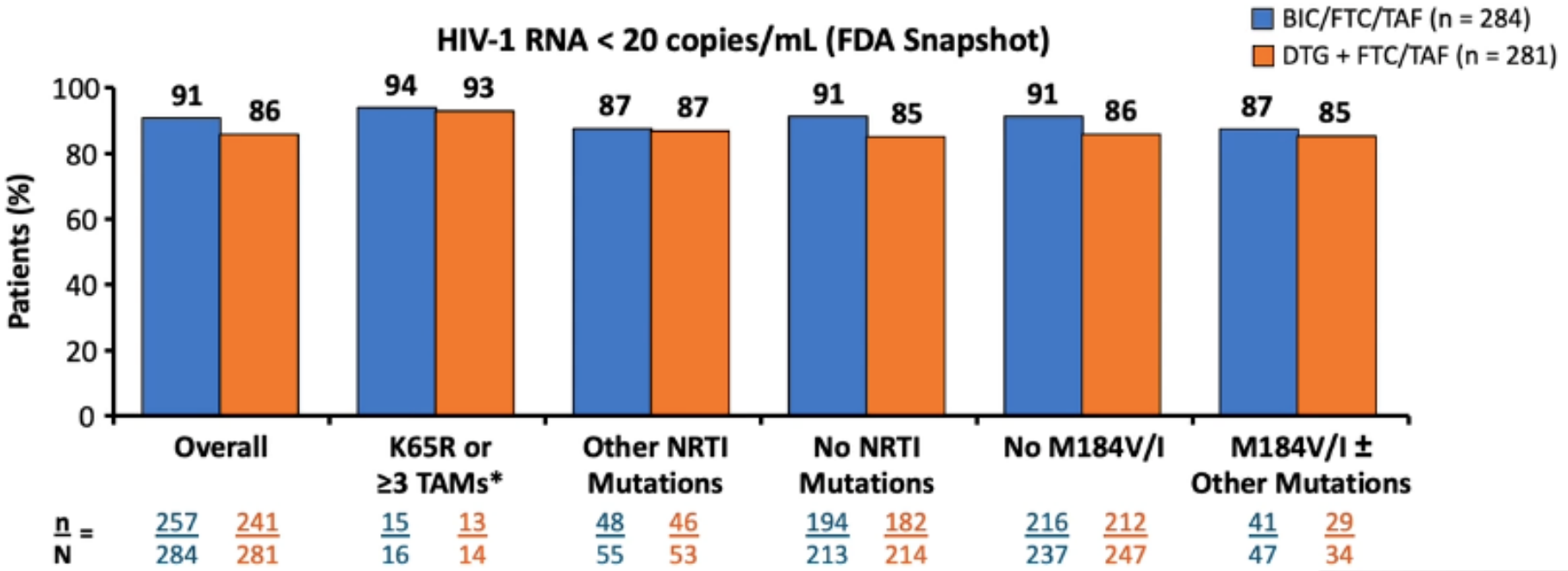
Factors associated with blips after 3TC/DTG switch

By Cox analysis, to be drug abuser was positevely associated with viral blips, while having viremia target not detected at switch was negatively associated.

Resistance at failure

Genotypic resistance test was available for 4/22 individuals who failed 3TC/DTG; no resistance to INIs and NRTIs was found.

STUDY 380-4030: SENSITIVITY ANALYSIS FOR LOW-LEVEL VIREMIA



* Includes K65R/E/N, or ≥3 TAMs that include M41L or L210W, or T69 insertion.

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Traitements ARV: nouveaux médicaments

FDA/EMA RECENT APPROVALS
(2019 - generic names)

Ibalizumab (EMA, Sept 2019)

The first mAb against HIV-1 to receive EMA/FDA approval therapy

Fostemsavir

Gp 120 attachement inhibitor (first-in-class)

Dapivirine (EMA approved)

Non-nucleosidic retro-transcriptase inhibitor (PrEP)

Dolutegravir tablets for oral suspension

Integrase Inhibitor Approved from 3 kg or 4 weeks of age

Cabotegravir/ rilpivirine injectable formulation

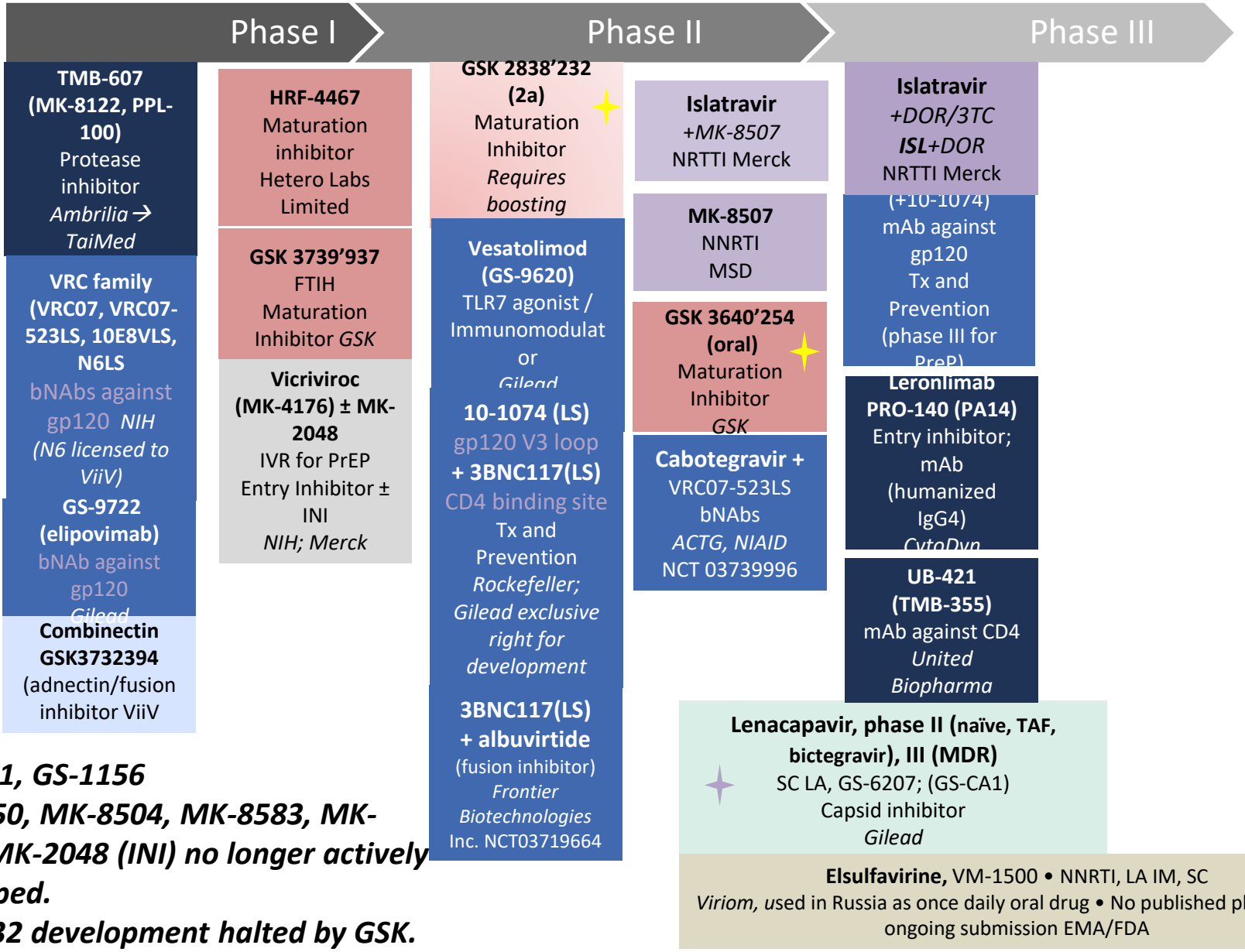
INI / NNRTIs LA once monthly Maintenance, *15'742 USD/Patients (Canada)*

Cabotegravir Oral

Integrase Inhibitor Oral formulation used for lead-in

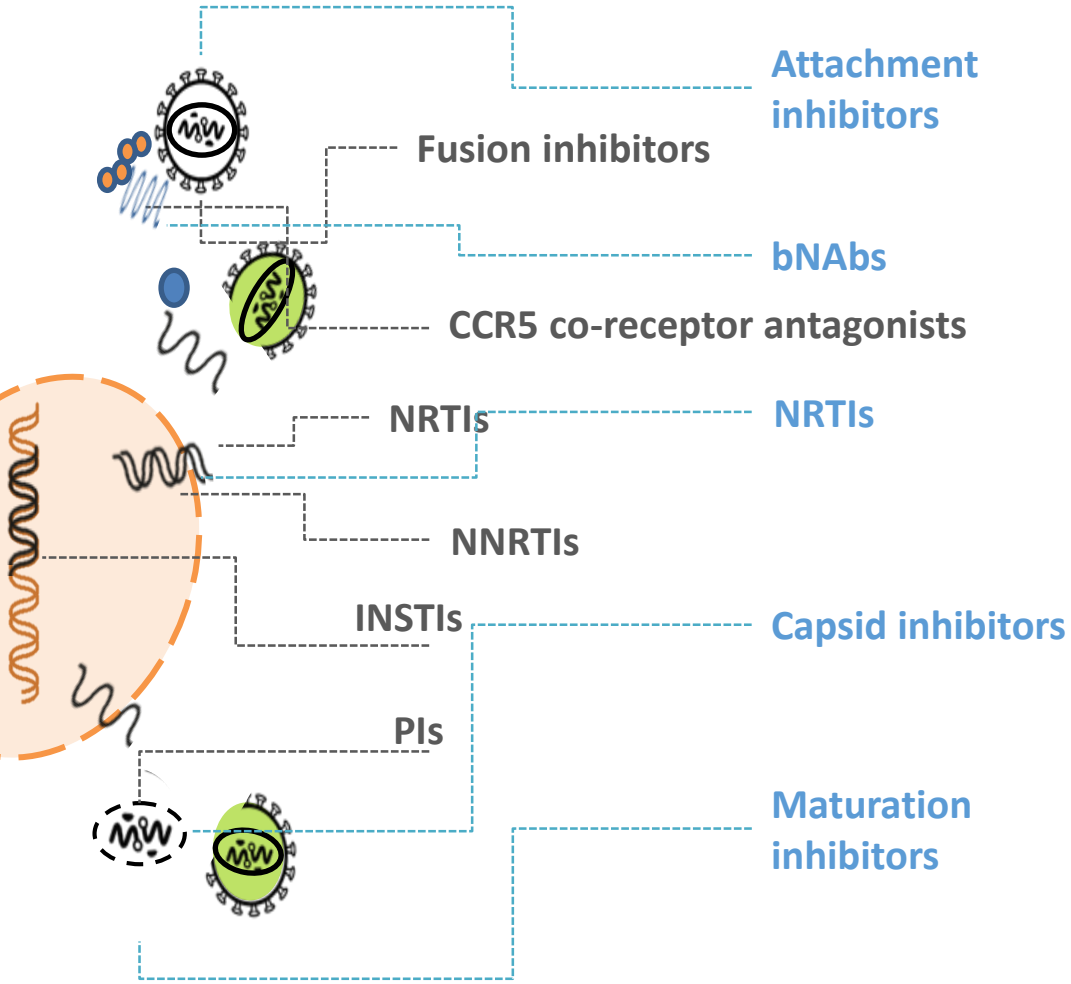
FDA website: «Cabenuva and Vocabria were granted Fast Track and Priority Review designation by the FDA»

2021 (active) ADULT TREATMENT CLINICAL PIPELINE



GS-9131, GS-1156
MK 4250, MK-8504, MK-8583, MK-8558, MK-2048 (INI) no longer actively developed.
GSK '232 development halted by GSK.

HIV PIPELINE (summary)

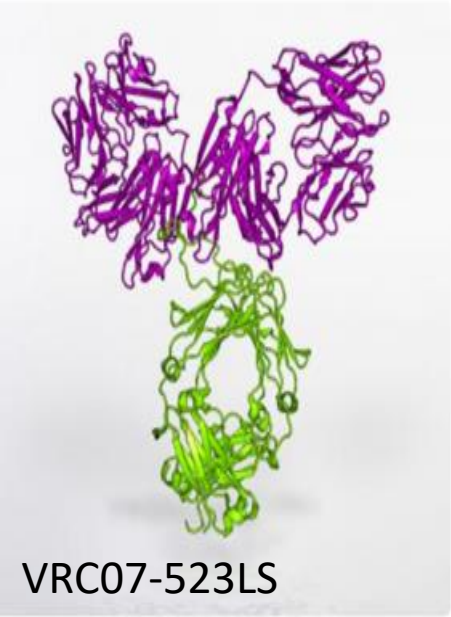


- Fewer large companies are bringing new HIV drugs to market with a strong focus on selected drugs (ISL, Merck, LEN, Gilead)
- Most molecules cover both ***treatment and prevention with LA properties***
- There are some overlap with the cure strategies (particularely with biologicals) – Gilead focuses on cure strategies (TLR-7 agonist and bNAbs)
- Dual LA combinations as treatment ***strategies*** are tested early in development stages
  - *The choice of partner matter*
  - bNAbs + ARVs (albuvirtide or cabotegravir) both in phase II trials

Figure adapted by Pedro Cahn, from Rambout A, et al. Nat Rev Genet 2004;5:52–61

Hôpitaux Universitaires Genève

BROAD SPECTRUM ANTIBODIES (bNAb) IN COMBINATION WITH ARVs

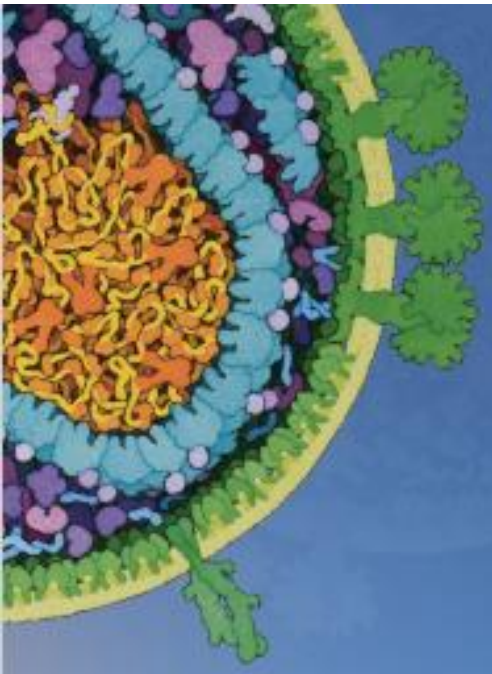


The VRC07-523LS broadly neutralizing antibody (bNAb) is based on a naturally occurring bNAb called VRC01, pictured here in a protein structure diagram.

1. Phase II, three part, maintenance trial combining 3BNC117/LK and albuvirtide (fusion inhibitor, injectable, every 2-4 weeks) (NCT03719664)
   - ✓ Albuvirtide approved in China in 2018 based on 48-week data of the TALENT study in second-line regimens, combined with LPV/r
2. Phase II maintenance trial in the US combining iv VRC07-523LS Q8 weeks and cabotegravir LA Q4W (NCT03739996)[2].
   - ✓ Participants will switch from standard ART and undergo a 46-week period of intermittent administration of the 2 molecules (before reinstituting their oral ART).

Albuvirtide is authorized in China

1. Wu et al, Lancet HIV posted 8th January, 2019 (TALENT Study) 2.
https://www.niaid.nih.gov/news-events/antibody-and-drug-combo-trial-long-acting-hiv-treatment



SCIENCE SPOTLIGHT™

WEEK 96 ANALYSIS OF VIRAL BLIPS FROM A PHASE 2B TRIAL OF ISLATRAVIR AND DORAVIRINE

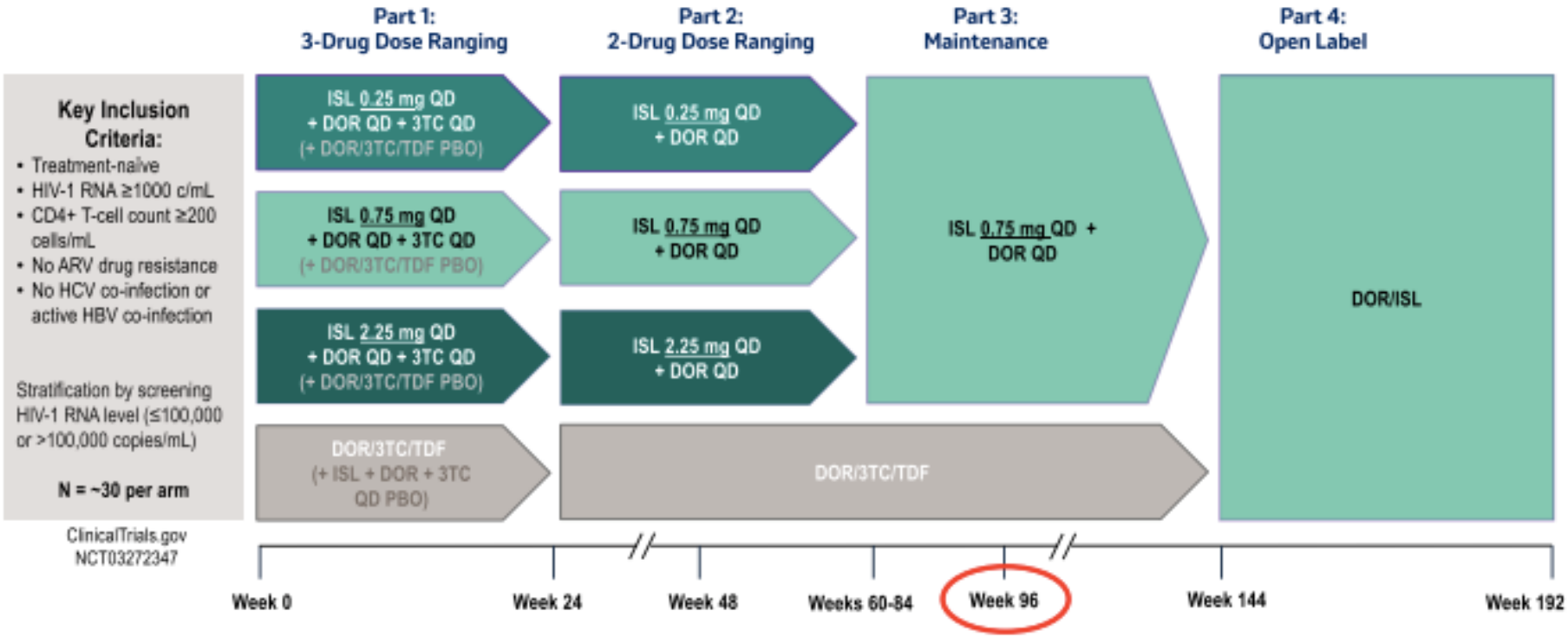
C. Orkin[1]; J.-M. Molina[2]; Y. Yazdanpanah[3]; C. Chahin Anania[4]; J. Eron[5]; S.O. Klopfer[6]; A Grandhi[6]; K. Eves[6]; D. Hepler[6]; C. Hwang[6]; T. Correll[6]

[1]Queen Mary University of London, London, UK; [2]Saint-Louis Hospital and University, Department of Infectious Diseases, Paris, France; [3]Bichat Hospital, Paris, France; [4]Hospital Hernán Henríquez Aravena de Temuco, Temuco, Chile; [5]Division of Infectious Diseases, University of North Carolina, Chapel Hill, NC, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA

Disclosure: Recipient of grants (to institution), speakers bureau honoraria, advisory boards honoraria and travel sponsorship from: ViiV, GSK, MSD, Janssen and Gilead

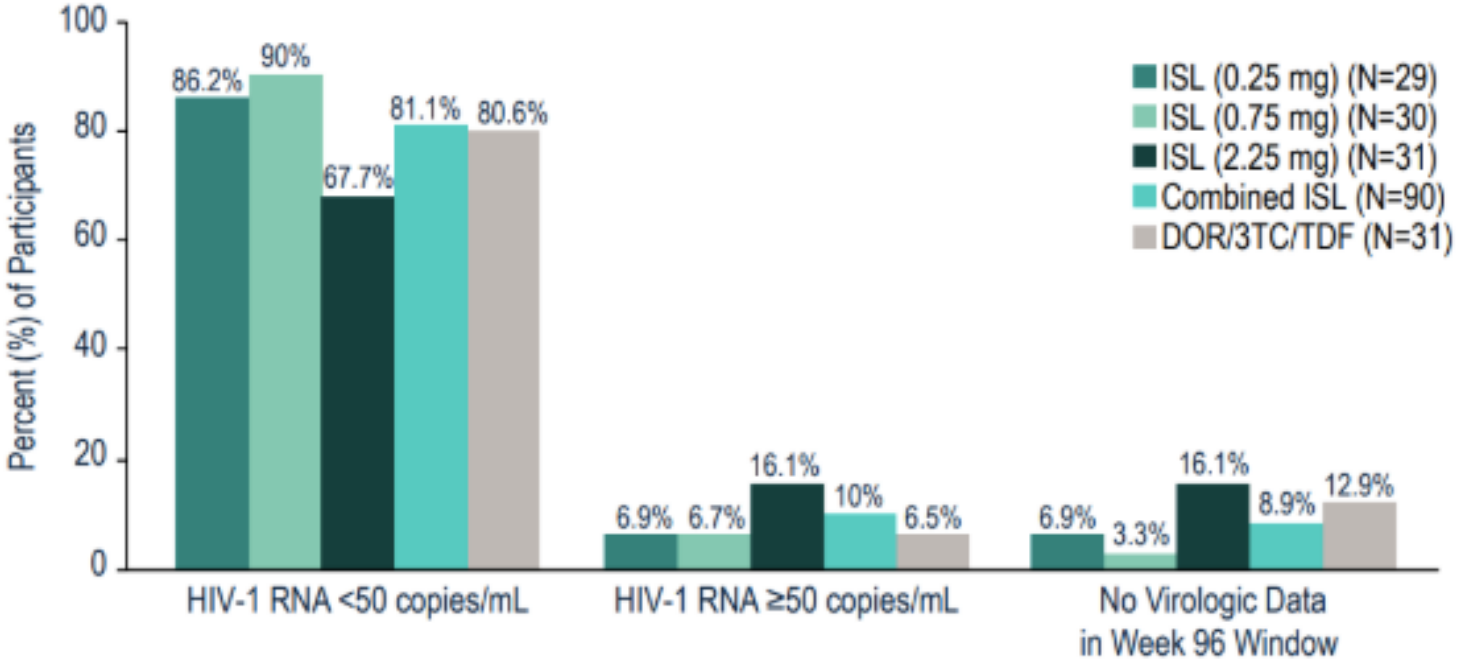
CROI 2021

Protocol 011: Phase 2 Dose Ranging Trial of ISL+DOR



After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.

Virologic outcomes at week 96[1] (FDA Snapshot Approach)



1. Molina J-M et al. Islatravir in Combination With Doravirine Maintains HIV-1 Viral Suppression Through 96 Weeks . Presented Drug Therapy Glasgow 2020.

Summary of viral blips for participants who entered Part 2 of the trial

Time Period	Parameter	ISL 0.25 mg + DOR + 3TC QD		ISL 0.75 mg + DOR + 3TC QD		ISL 2.25 mg + DOR + 3TC QD		Combined ISL + DOR + 3TC QD		DOR/3TC/TDF	
Part 2 through week 96 (ISL groups on 2-drug Regimen)	N	29		30		27		86		28	
	Number of Participants with Blips	3	10.3 %	1	3.3 %	2	7.4 %	6	7.0 %	4	14.3%
	Number of Distinct Blip Episodes	4		1		2		7		4	

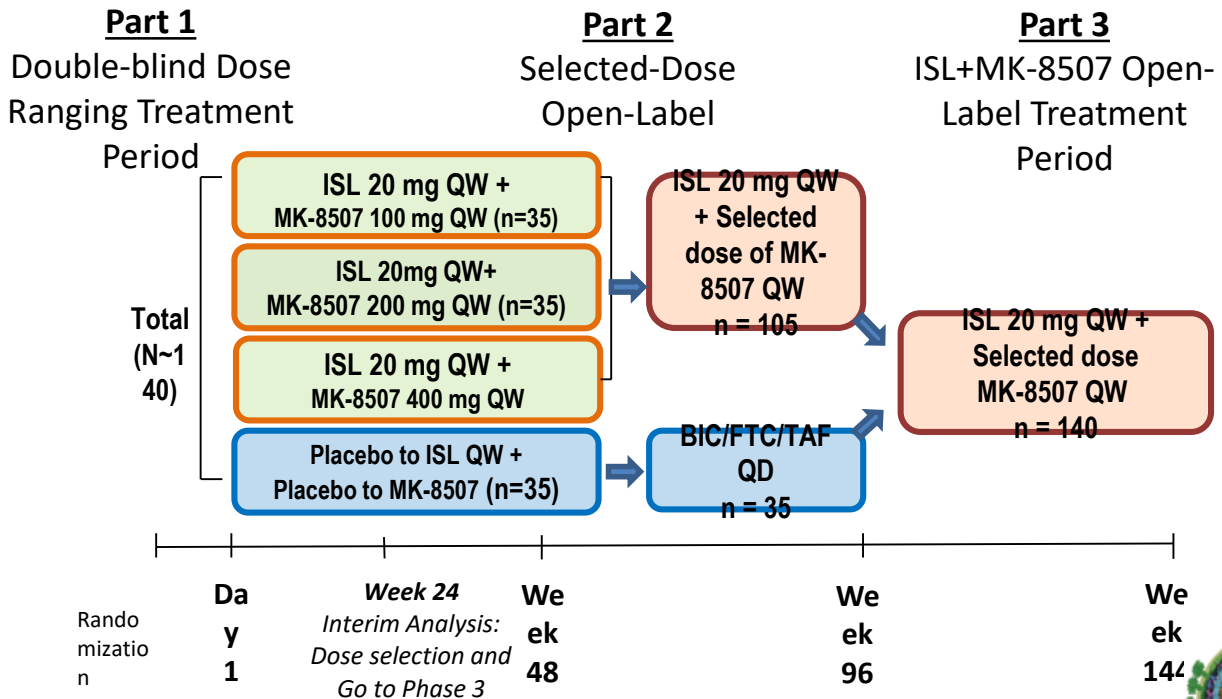
- In ISL groups, HIV-1 RNA was <200 copies/ml VL during all blip episodes
- In DOR/3TC/TDF group, one of four blip episodes was HIV-1 RNA ≥ 200 copies/ml and in the other 3 episodes HIV-1 RNA was <200 copies/mL
- No participant who experienced a viral blip subsequently experienced protocol defined virologic failure
- No participant met the criteria for resistance testing

Islatravir partners

Islatravir positioning – choosing the right partner

1. A daily dual therapy (doravirine)
2. An implant for PreP---- 12 months longe
3. An oral long-acting regimen when combined with MK-8507 (phase 2b)

NCT04564547

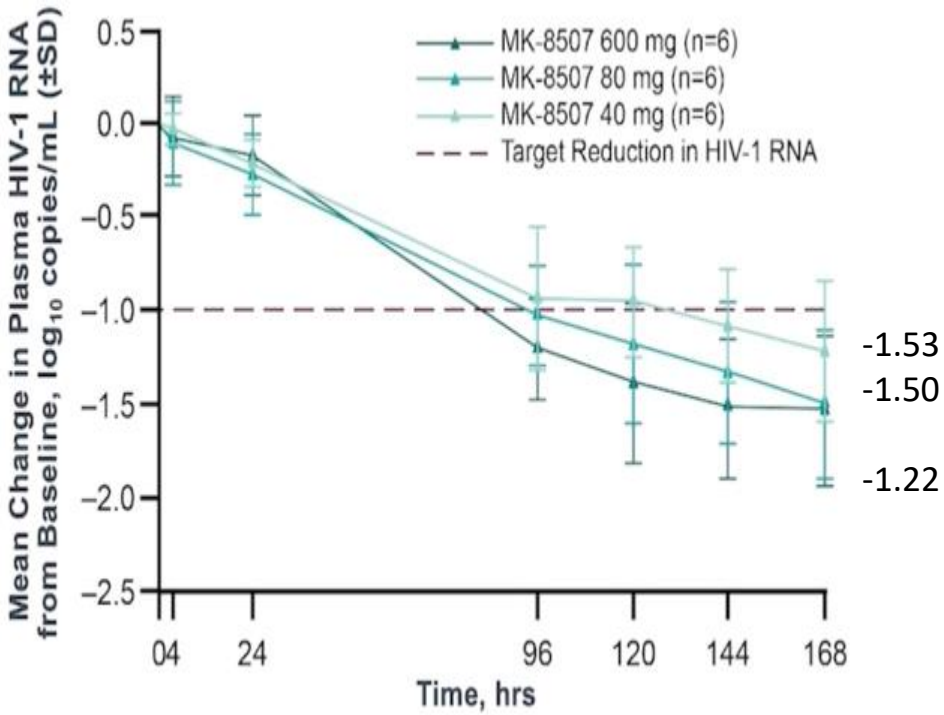


Friedman, et al., CROI 2016 Poster 437LB, Matthews RP et al, IAS 2017, abstract # TUPD Matthews R, IAS 2019, Abs. TUAC0401LB, Hillier. HIVR4P 2021. Abstr OA04-05LB, Kandala

The new NNRTI, MK-8507

A single dose reduced HIV-RNA for at least one week – half life 59-65 hours

- 18 individuals with no ARV experience (all male and white, with an average age of 34) were divided into three groups of six who were given a single dose of MK-8507 (300mg, 80 mg and 40 mg) .
- The two larger doses of MK-8507 produced a similar drop in viral load of about a 1.5 logs.
- After 14 days, one of the three participants who did not start conventional ART developed a single drug resistance mutation, F227C (high-level resistance to doravirine and other NNRTIs, *hyper*-susceptibility to islatravir)
- Merck announced that the 80mg dose will be taken forward to weekly dosing studies in combination with islatravir.



CAPSID INHIBITORS: Lenacapavir (formerly GS-6207)

First-in-class

- Multiple targets in the replication cycle: capsid core assembly, capsid core disassembly, nuclear translocation – activity not impaired by resistance mutations of known ARVs. Developed for both prevention and treatment.
- Administered orally as a lead-in dose followed by

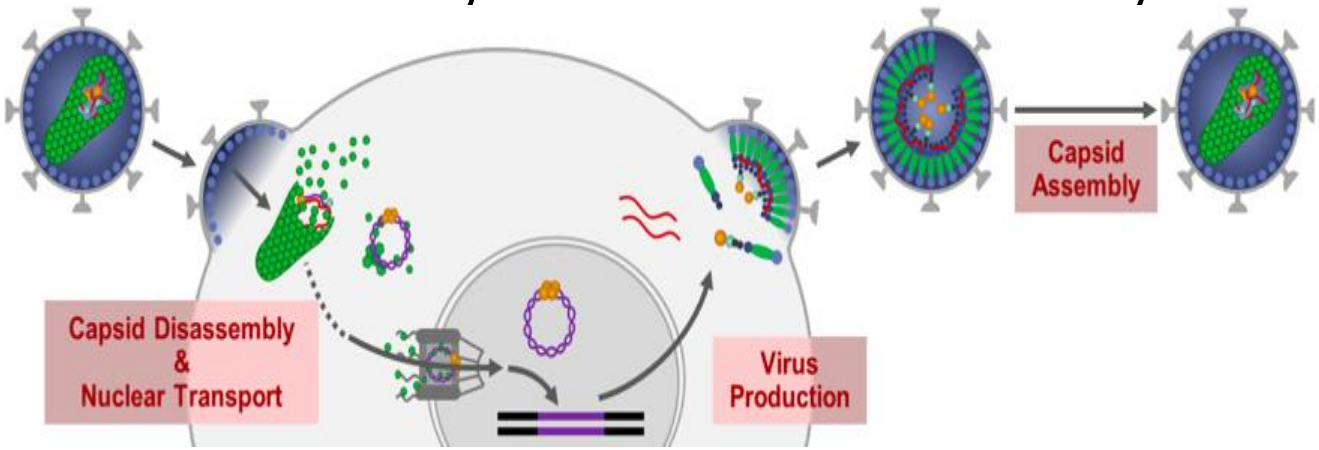
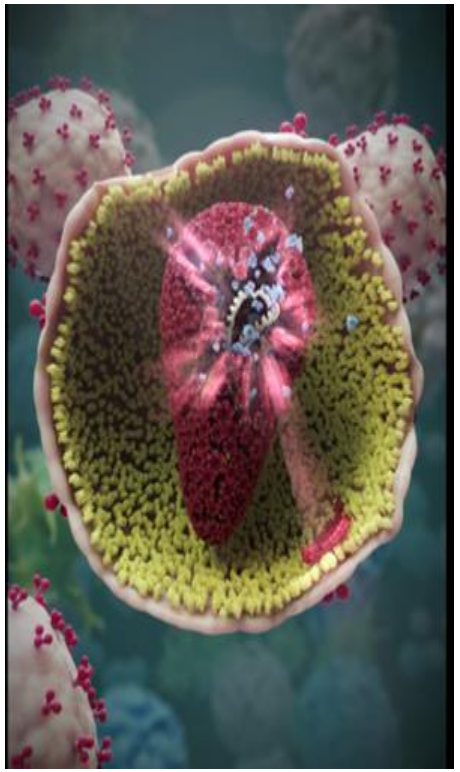


Photo credit: Gilead

Capsid: cone-shaped structural core within the HIV virion



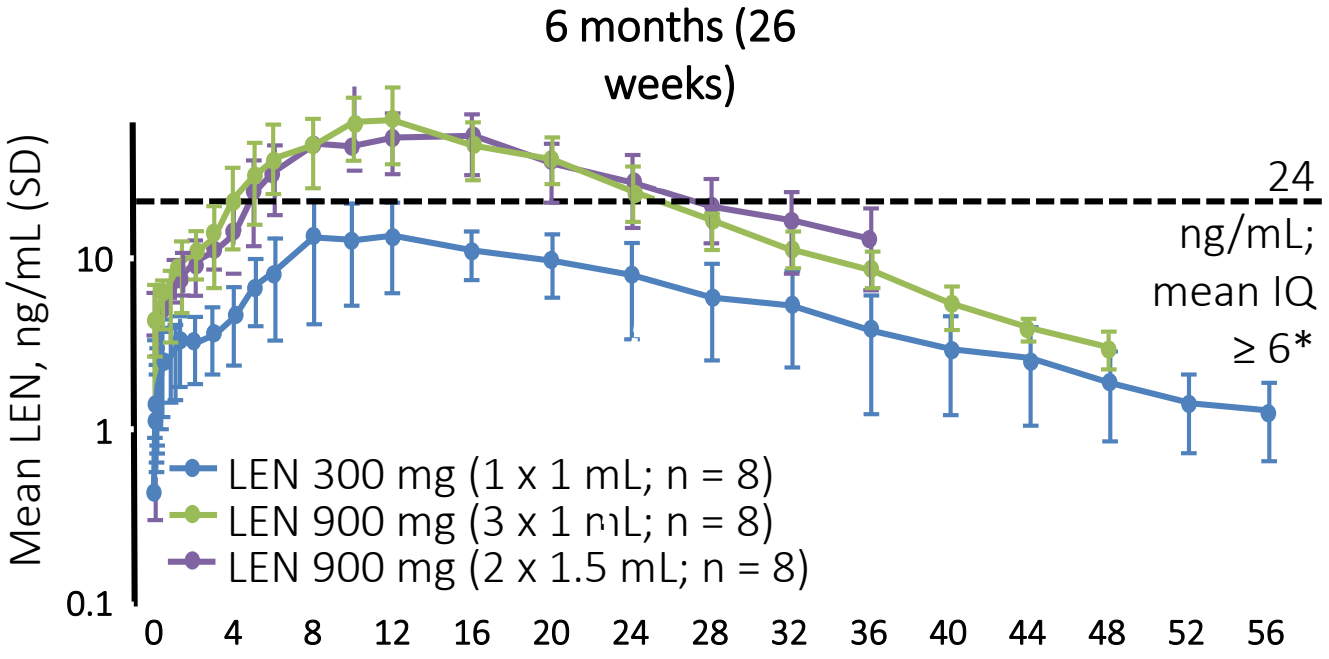
Publico.pt

1. Zheng J, et al. IDWeek 2018
2. Phase 1: Sager J, et al. CROI 2019. Abstract # 141,
3. Phase 1b: Daar E, CROI 2020, Abstract # 469

LENACAPAVIR (GS-6207) Pharmacokinetic profile

Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants (N = 30). Supports 6 monthly dosing , maintained target concentrations for 26 weeks

Mean LEN Single-Dose Plasma Concentration-Time Profiles



*IQ: ratio of LEN plasma concentration to IC_{50}.

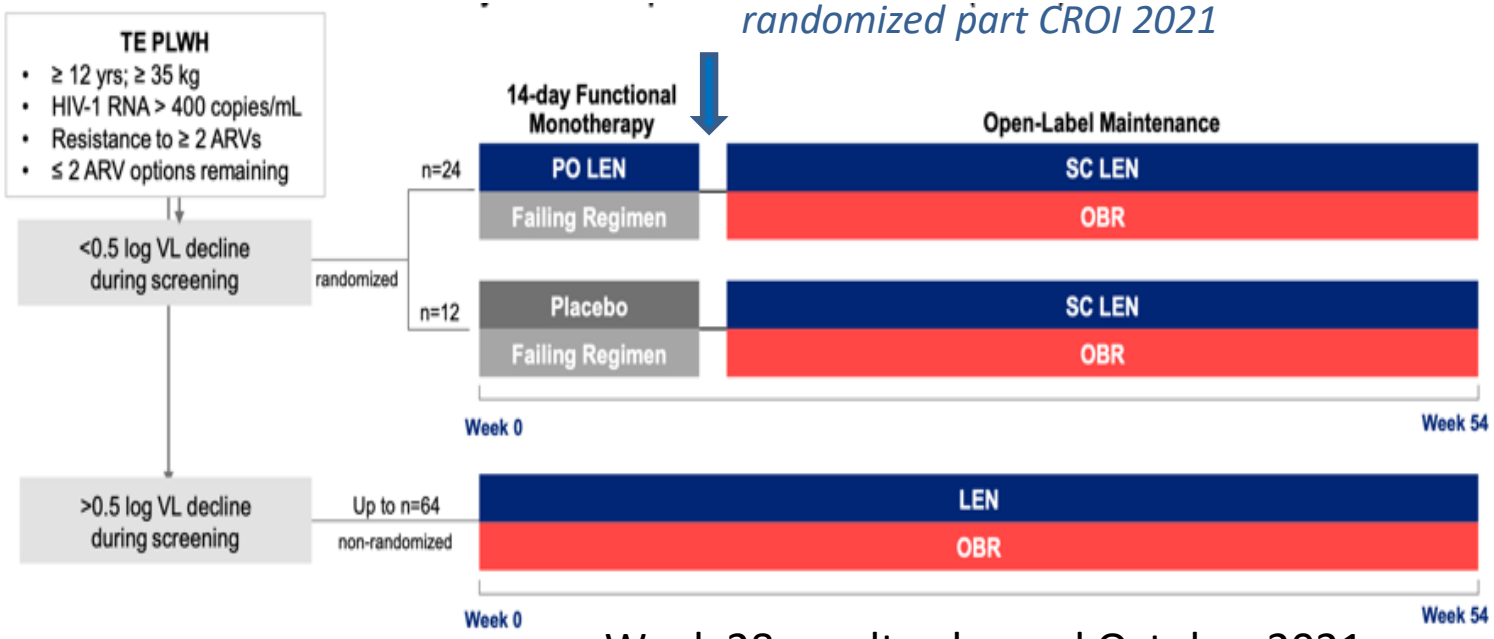
Begley. AIDS 2020. Abstr PEB0265.

LENACAPAVIR (GS-6207) (c'd)

Drug positioning

- Treatment of Heavily Treatment-experienced PLW
- CAPELLA phase 2/3 ClinicalTrials.gov URL: https://clinicaltrials.gov/ct2/show/NCT04150068

Primary endpoint of the randomized part CROI 2021



Week 28 results planned October 2021

Segal-Maurer S (Margot N) et al, Abstract # 127 CROI 2021,
VanderVeen L, (Callebaut C) et al, Abstract # 128, CROI 2021

CROI Conference on Retroviruses and Opportunistic Infections

LENACAPAVIR (GS-6207) (c'd)

Drug positioning

- Treatment of Heavily Treatment-experienced PLW
  - CAPELLA NCT04150068 : Gilead issued a press release on November 18th, 2020 to announce that lenacapavir achieves primary endpoint in a phase 2/3 study (% minus 0-5 log HIV-RNA after 14 days of monotherapy, 88% vs 17%)
    - Pubmed? A COVID-19 (side) effect?

- Treatment naïve patients (phase 2, n=175)
  - CALIBRATE NCT04143594 (active, not recruiting) – US sites, Puerto Rico and Dominican Republic – results (primary endpoint) planned October 2021
  - No HBV, no CD4 below 200 cells/mm3
  - Induction (TAF/FTC+LEN) and Maintenance (oral TAF or oral BIC + sc LEN)

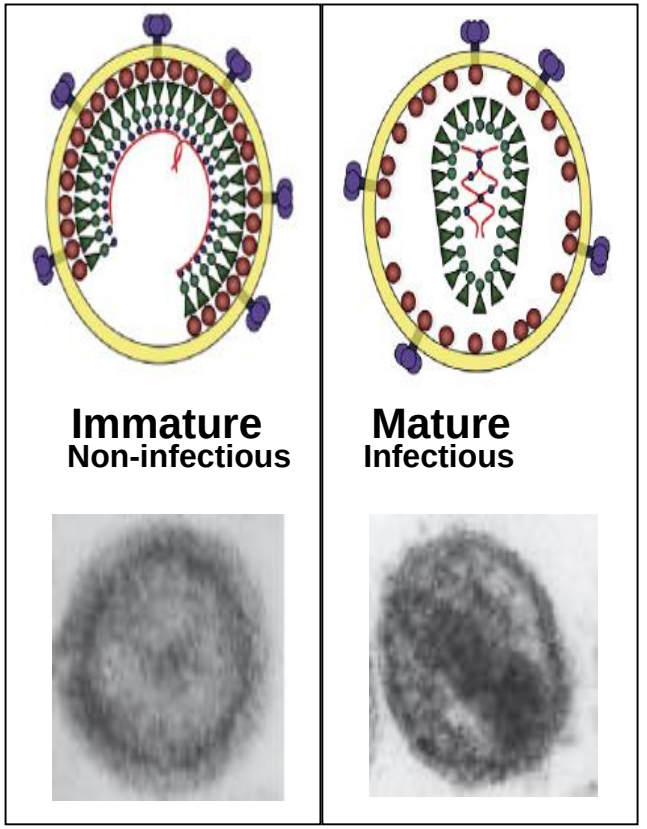
CROI 2021: Segal-Maurer S et al, Abstract # 127, VanderVeen L, et al, Abstract # 128;*Begley et al, Abstract # 1024,* ***Jogiraju V,*** *Abstract # 1315*

CROI
Conference on Retroviruses and Opportunistic Infections

MATURATION INHIBITORS – GSK ‘254 and GSK ‘937

New mode of action

- HIV-maturation inhibitors act at a late stage of the replication cycle.
- Gag polyprotein is the main structural protein of HIV-1; HIV-1 protease cleaves Gag in a stepwise fashion into six pieces
- MI’s inhibit the last protease cleavage between the capsid and SP1 subunit.
- Non-infectious, immature HIV-1 particles are then released.
- No cross-resistance to other types of HIV drugs
- Subjects infected with viruses containing gag polymorphisms may fail – as a consequence, new generation of MI are being developed.



MATURATION INHIBITORS – GSK ‘254 and GSK ’937

New mode of action

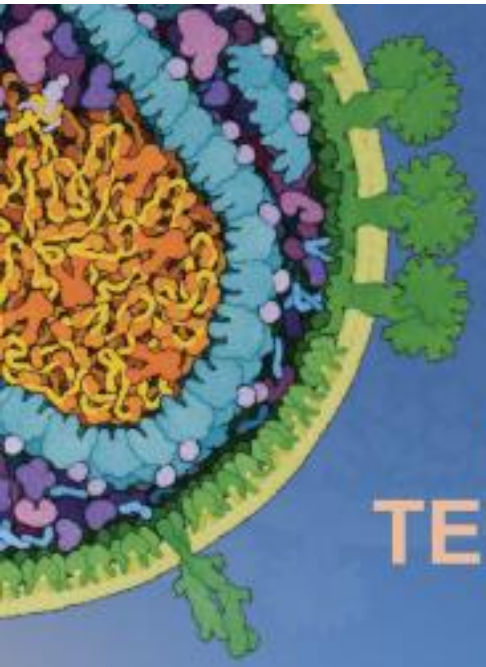
- **GSK ‘254** phase 2a adaptative monotherapy study presented at this conference – supports phase 2b progression Q4 2020[1,2]
  - Antiviral effect, safety, tolerability and PK of once-daily ‘254 MI in 24 treatment naïve patients (94% men, mean age 31)
  - Two parts (10 and 200 mg in part 1, 40, 80 and 140 in part 2)
  - 4/6 participants in the 200-mg group developed RAMs on D11 (monotherapy duration longer in part 1)
  - SAE: congestive cardiomyopathy, anal abscess
  - Dose-response relationship
- **GSK ‘937** (structurally related to ’254) has a potential for LA – First-Time-in Human initiated in 2020 (NCT04493684)
- **GSK’232 phase 2a (boosted by cobicistat)[3,4] -** development halted by GSK

1.CROI 2021 Jeffrey JL et al, 2.Spinner C et al (phase 2a) abstract # 126

3. Johnson M et al, Pharmacol Res Perspect. 2018; e00408, De Jesus E et al,

LIKELY POSITIONING OF NEW DRUG

INDICATION	MOLECULES NAME
Treatment-naive	Islatravir (ISL), doravirine/ISL (lenacapavir, phase 2)
When HIV-RNA is suppressed (switch regimens)	Cabotegravir/rilpivirine LA, bNAbs, islatravir, isltravir/MK doravirine/islatravir/MK-8507
MDR (Heavily Treatment Experienced)	Fostamsavir, ibalizumab, lenecapavir, maturation inhibitors



SCIENCE SPOTLIGHT™

REDUCED SUSCEPTIBILITY TO TEMSAVIR IS NOT LINKED TO IBA OR MVC RESISTANCE

Burt Rose,[1] Margaret Gartland,[2] Eugene Stewart,[3] Mark Cockett,[1] Peter Ackerman,[1] Max Lataillade,[1] Cyril Llamoso,[1] Mark Krystal[1]

[1]ViiV Healthcare, Branford, CT, USA; [2]ViiV Healthcare, Research Triangle Park, NC, USA; [3]GlaxoSmithKline, Philadelphia, PA, USA

Disclosure: Mark Krystal is an employee of ViiV Healthcare and holds stock in GlaxoSmithKline.

CROI 2015

Conclusions

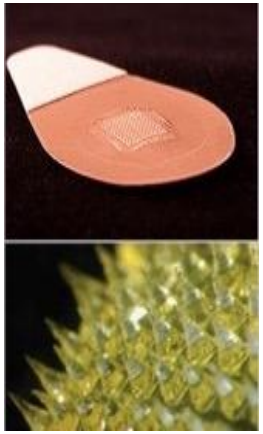
- Data from BRIGHTE and MOTIVATE strongly suggest that there is no correlation between IBA or MVC resistance and a meaningful reduction in TMR susceptibility
- From BRIGHTE:
  - In participants co-dosed with FTR and IBA who demonstrated reduced susceptibility to both agents, susceptibility to TMR could be restored without restoring IBA susceptibility
  - A failing regimen with MVC did not impact virologic success of functional FTR monotherapy at Day 8
- From MOTIVATE:
  - Susceptibility to TMR was not indicative of susceptibility to MVC
  - The envelope with reduced susceptibility to TMR contained an M426L polymorphism; when reverted to M426M, susceptibility to TMR was rescued while susceptibility to MVC was unchanged

Acknowledgments: This study was funded by ViiV Healthcare.

LOOKING ACROSS TECHNOLOGIES

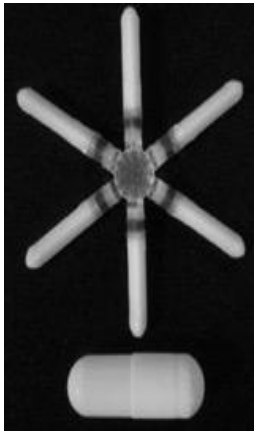
Long-acting injectables

Implants



Microarray patches

Vaginal rings

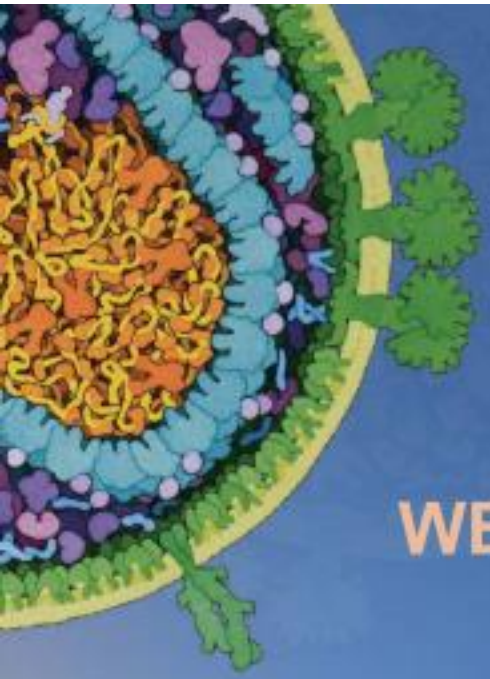


Lyndra gastric resident system

Oral LA: islatravir + MK-8507
New chemical entities: cabotegravir, MK-8591 (islatravir), GS-9131, GS 6207, VRC01
Oral drugs repositioned to become LA: rilpivirine, TAF, TDF, elsufavirine, dapivirine

eCROI 2021

Traitements ARV: prise de poids



SCIENCE SPOTLIGHT™

WEIGHT GAIN AMONG PWH WHO SWITCH TO ART CONTAINING INSTIs OR TAF

Frank J. Palella Jr. MD

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Disclosure: Dr. Palella has been a consultant and/or on the Speakers' Bureau for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co. and ViiV. The other co-authors declare no conflicts of interest.

CROI 2021

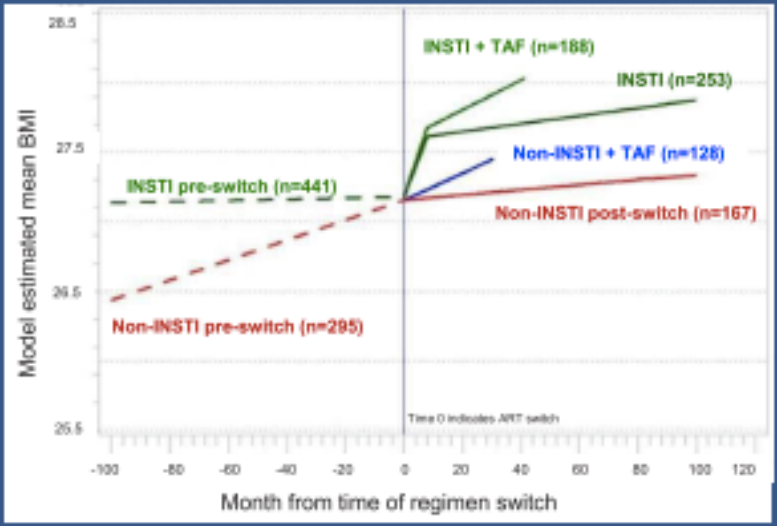
Results

Table 1. Cohort characteristics, including types of ART regimens received, the HIV Outpatient Study, 2007-2018 (N = 736).

CHARACTERISTICS	INSTI N (%)	NON-INSTI N (%)	P-VALUE
Total	441 (59.9)	295 (40.1)	
Age at ART switch			0.05
<50	189 (42.9)	148 (50.2)	
Median IQR	51.7 (45.3,58.0)	50.0 (43.0,56.5)	0.02
Sex at birth			0.64
Female	82 (18.6)	59 (20)	
Male	359 (81.4)	236 (80)	
Race and ethnicity			0.41
Non-Hispanic White	259 (58.7)	156 (52.9)	
Non-Hispanic Black	110 (24.9)	80 (27.1)	
Hispanic	54 (12.2)	46 (15.6)	
HIV Risk			0.19
MSM	292 (66.2)	176 (59.7)	
Heterosexual	90 (20.4)	66 (22.4)	
PWID	32 (7.3)	33 (11.2)	
Payer at ART switch			0.38
Private	295 (66.9)	185 (62.7)	
Public	130 (29.5)	101 (34.2)	
CD4 at ART switch			0.37
<200	19 (4.3)	6 (2)	
≥500	284 (64.4)	183 (62)	
BMI at ART switch			0.93
<25	175 (39.7)	113 (38.3)	
25-29.9	165 (37.4)	112 (38)	
30+	101 (22.9)	70 (23.7)	

CHARACTERISTICS	INSTI N (%)	NON-INSTI N (%)	P-VALUE
POST-SWITCH ART REGIMEN			
Mean Duration in years (95% CI)	2.5 (2.4, 2.7)	2.6 (2.4,2.9)	0.41
INSTI Type			
Dolutegravir	143 (32.4)	N/A	
Elvitegravir	112 (25.4)	N/A	
Raltegravir	178 (40.4)	N/A	
ART regimen contains protease inhibitor			<0.01
Yes	48 (10.9)	108 (36.6)	
ART regimen contains NNRTI			<0.001
Yes	43 (9.8)	173 (58.6)	
ART regimen contains NRTI			0.18
Yes	420 (95.2)	274 (92.9)	
PRE- SWITCH ART REGIMEN			
Mean Duration (95% CI)	5.4 (5.1,5.8)	5.8 (5.4,6.3)	0.13
ART regimen contains protease inhibitor			0.25
Yes	189 (42.9)	139 (47.1)	
ART regimen contains NNRTI			0.64
Yes	238 (54)	154 (52.2)	
ART regimen contains NRTI			0.31
Yes	429 (97.3)	283 (95.9)	
ART regimen contains TAF			
Yes	188 (42.6)	128 (43.4)	0.84
Change in weight (kg) during pre-ART regimen (mean 95%CI)	**2.0 (1.1,2.8)**	**2.2 (1.3,3.1)**	**0.73**

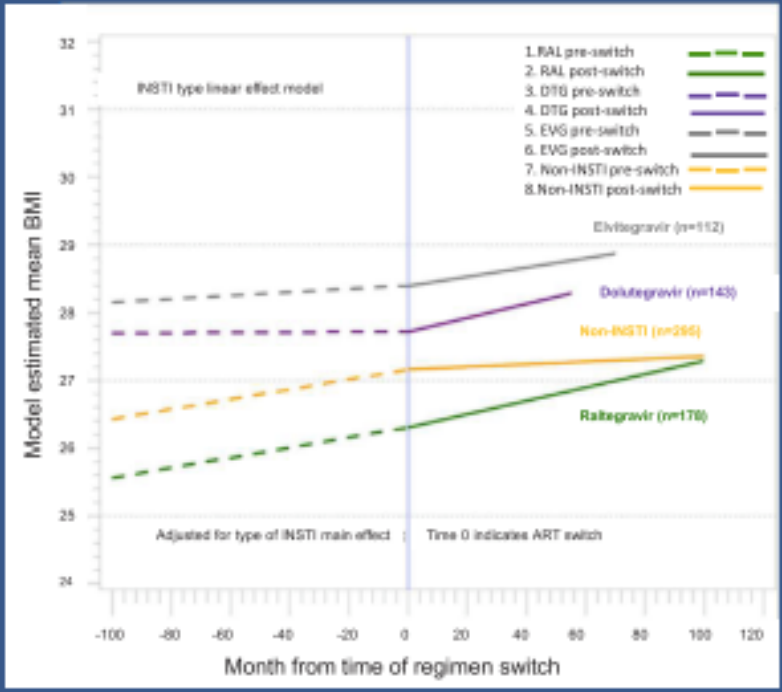
Figure 1. Predicted BMI trajectories for persons who switched ART, by INSTI and TAF use, the HIV Outpatient Study, 2007-2018 (N = 736).



Effect	Slope (± STD Error) Slope represents BMI gain/month on medication	P-value
INSTI pre-switch	0.0005 (±0.0005)	0.36
Non-INSTI pre-switch	0.0073 (±0.0006)	<.001
INSTI+TAF (months 0-8)	0.0620 (±0.0065)	<.001
INSTI+TAF (months 8+)	0.0108 (±0.0048)	0.02
INSTI (months 0-8)	0.0541 (±0.0059)	<.001
INSTI (months 8+)	0.0029 (±0.0015)	0.05
Non-INSTI +TAF	0.0098 (±0.0045)	0.03
Non-INSTI	0.0019 (±0.0012)	0.12

- Switching to INSTI based ART was associated with more rapid weight (BMI slope) gain during the eight months immediately following INSTI initiation than switching to non-INSTI ART regimens, regardless of whether the new regimen contained TAF
- Overall, receiving TAF was associated with more rapid weight gain post-ART switch than not switching to TAF-containing ART
- After the first 8 months of receiving INSTI-based ART:
  - weight change assumed a trajectory similar to persons not receiving INSTI-based ART
  - weight change among persons on TAF remained greater than non-TAF recipients
- Among persons who switched to INSTI-based ART that included TAF:
  - proportion of weight gain observed during the first 8 months after ART switch that was attributable to INSTI was 87%, after 8 months 27%
  - proportion of weight gain during the first 8 months after ART switch attributable to TAF was 13%, after 8 months was 73%
- Among persons who switched to non-INSTI-based ART that included TAF:
  - proportion of weight gain observed both during and after the first 8 months after ART switch that was attributable to TAF was 84% , indicating a linear trend in weight gain for persons receiving TAF without INSTI
- Adjustment for age, gender, race and baseline BMI at ART switch did not change our main inferences.

Figure 2. BMI trajectories from linear model for persons who switched cART, by INSTI drug used, the HIV Outpatient Study, 2007-2018 (N = 736).



Trajectory	Slope	STDErr	P-value
1.RAL pre-switch	0.00746	0.00108	<0.001
2.DTG pre-switch	0.00022	0.00075	0.77
3.EVG pre-switch	0.00243	0.00101	0.02
4.Pre-non-INSTI	0.00732	0.00064	<0.001
5.RAL post-switch	0.00989	0.00126	<0.001
6.DTG post-switch	0.01045	0.00302	<0.001
7.EVG post-switch	0.00694	0.00413	0.09
8.Post non-INSTI	0.00197	0.00124	0.11
9.RAL vs DTG post-switch	-0.00056	0.00327	0.86
10.RAL vs EVG post-switch	0.00295	0.00432	0.49
11.DTG vs EVG post-switch	0.00351	0.00512	0.49
12.INSTI vs non-INSTI post-switch	0.00712	0.00215	<0.001

1-8 P-values reflect slopes significantly different than zero.

Among persons who switched to INSTI-based ART, weight (BMI slope) increased post switch, but there were no significant differences by INSTI types (p >0.49 for all pairwise comparisons), though the dolutegravir slope was steepest.

Conclusions

- Among virally suppressed persons who switched ART, both INSTI and TAF use were independently associated with weight gain.
- During the first 8 months post-switch, the rate of weight gain was greatest and was mostly associated with INSTI use; after that, continued gradual weight gain was primarily associated with TAF use.
- No significant differences in weight gain were apparent by INSTI type.
- These data help define the proportional contribution, magnitude, and duration of effect upon weight gain of INSTI and TAF use.

COAUTHORS: Hou Q[2], Li J[3], Mahnken J[2], Carlson K[2], Durham M[3], Ward D[4], Fuhrer J[5], Tedaldi E[6], Novak R[7], Buchacz K[3]

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[6] Lewis Katz School of Medicine at Temple University, Philadelphia, PA
[7] University of Illinois College of Medicine at Chicago, Chicago, IL.

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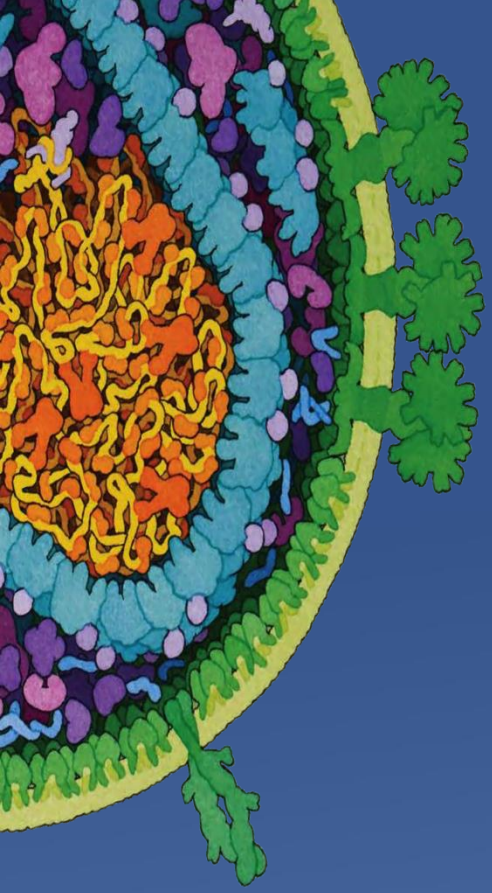


PREDICTED 10-YEAR RISKS OF CARDIOVASCULAR DISEASE AND DIABETES IN THE ADVANCE TRIAL

Laura Hindley MPH

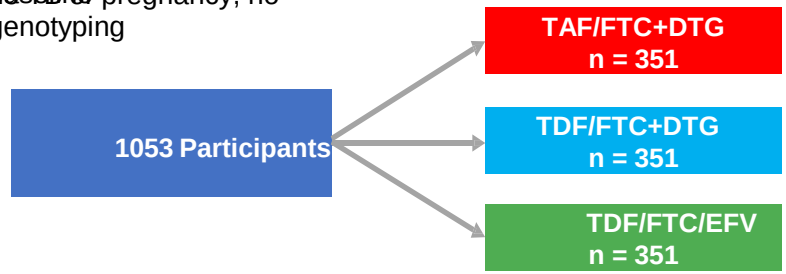
Imperial College School of Public Health
London, United Kingdom

CROI 2021

Methods

ADVANCE trial design (2017 – 22)

Inclusion criteria: Treatment-naïve, HIV-1 RNA level > 500 copies/mL, baseline TB or pregnancy, no genotyping



Study visits: Baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96 then every 24 weeks to Week 192.

Sample characteristics: 99% black, 56% female, 62% South African

Risk prediction analysis

- Bodyweight and laboratory measures from Week 144 were used to calculate the 10-year risk of CVD and T2D using the **QRISK**[1], **Framingham**[2] (non-laboratory) and **QDiabetes**[3] risk algorithms
- Participants ≥30 years old at baseline included in analysis
- *Most recent laboratory measure since Week 96 used when Week 144 measure was unavailable

[1] Hippisley-Cox et al. 2017. doi:10.1136/bmj.j2099. [2]D'Agostino et al. 2008. doi:10.1161/CIRCULATIONAHA.107.699579. [3]Hippisley-Cox et al. 2017 doi:10.1136/bmj.j5019

10-year risk of developing: **myocardial infarction/stroke** or **type II diabetes**

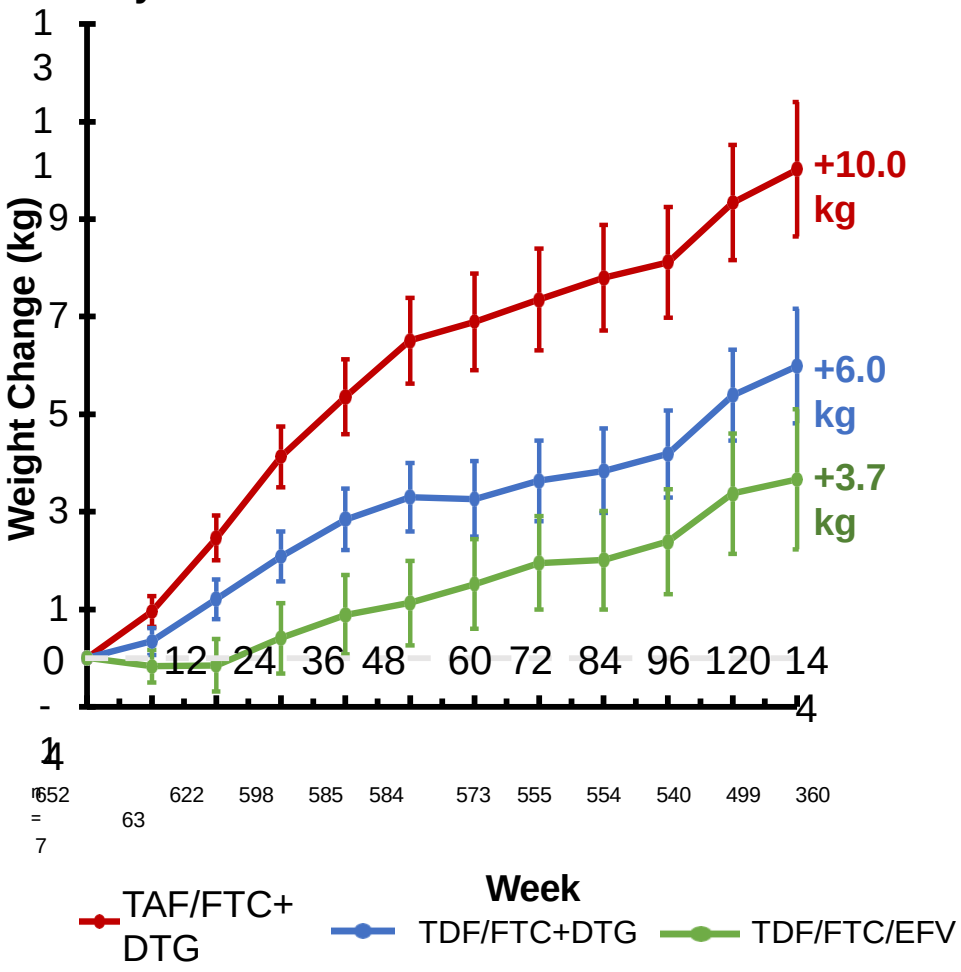
Risk equation Variables	QRISK3-2018	Framingham (non-laboratory)	QDiabetes-2018
Age (validated population)	✓ (25-84)	✓ (≥30)	✓ (25-84)
Gender	✓	✓	✓
Smoking status	✓	✓	✓
Ethnicity	✓	×	✓
Personal history of CVD	✓	×	✓
Family history of CVD (X)	✓	×	×
Family history of diabetes (X)	×	×	✓
Treatment for hypertension	✓	✓	✓
Prescribed steroids	✓	×	✓
Prescribed statins	×	×	✓
Cholesterol ratio (Total cholesterol / HDL)	✓	×	×
Fasting blood glucose (mmol/L)	×	×	✓
Haemoglobin A1C (X)	×	×	✓
Systolic blood pressure (mmHg)	✓	✓	✓
Body mass index (kg/m²)	✓	✓	✓
Other	*	×	*

*Variables marked with **(X)** were not available from the ADVANCE trial database*

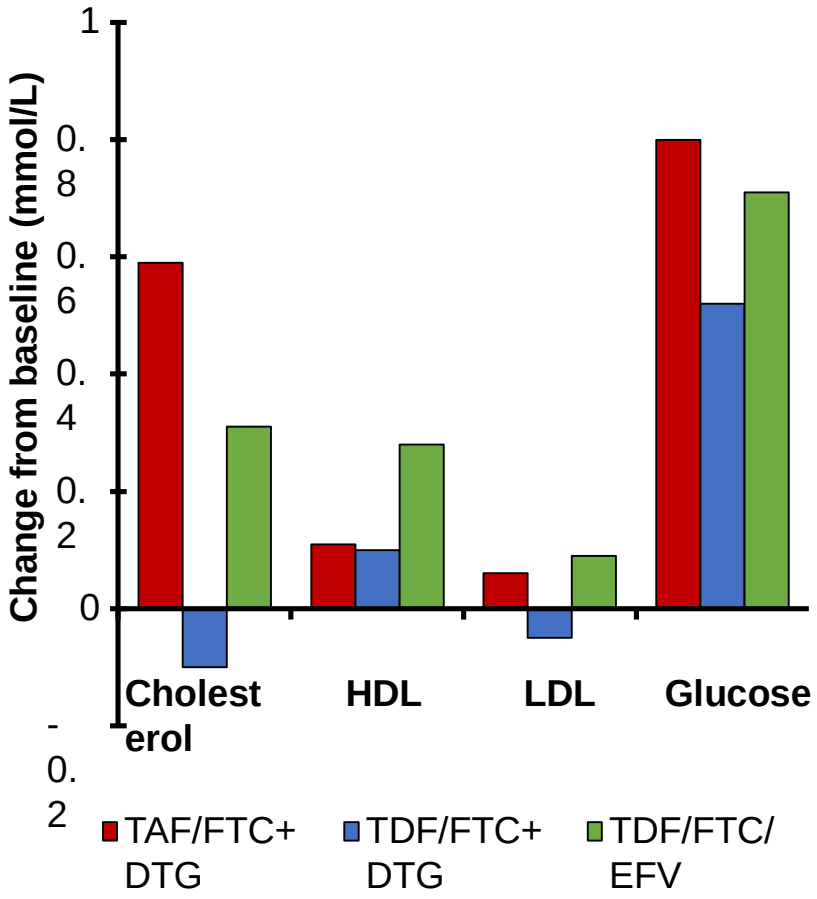
*Other variables included in QRISK: standard deviation of at least two recent SBP readings (mmHg), erectile dysfunction, atypical antipsychotic medication, history of severe mental illness, systemic lupus erythematosus, rheumatoid arthritis, migraines, atrial fibrillation, stage 3-5 chronic kidney disease. *Other variables included in QDiabetes: atypical antipsychotic medication, severe mental illness, gestational diabetes and polycystic ovary syndrome.

Results (1/2)

Weight gain to week 144, participants ≥ 30 years*

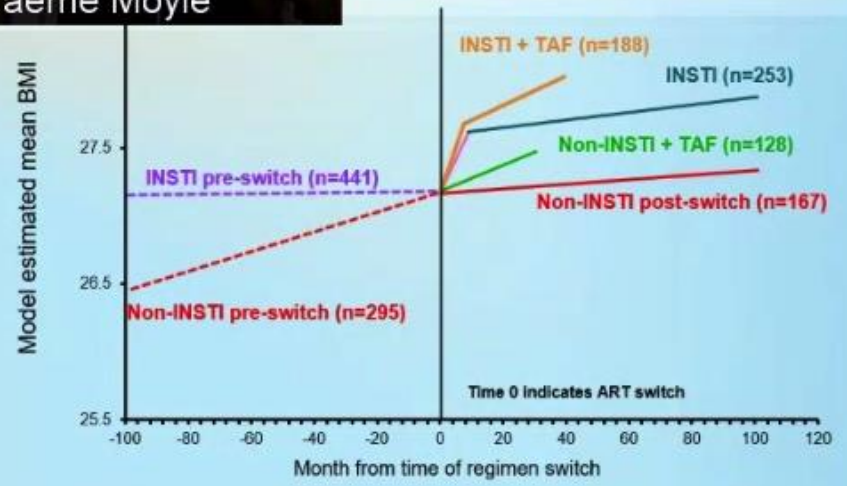


Changes in lab parameters to week 144, participants ≥ 30 years



HOPS cohort

Trajectories for Persons Who Switched ART, by INSTI and TAF use, the HIV Outpatient Study, 2007-2018 (N = 736)



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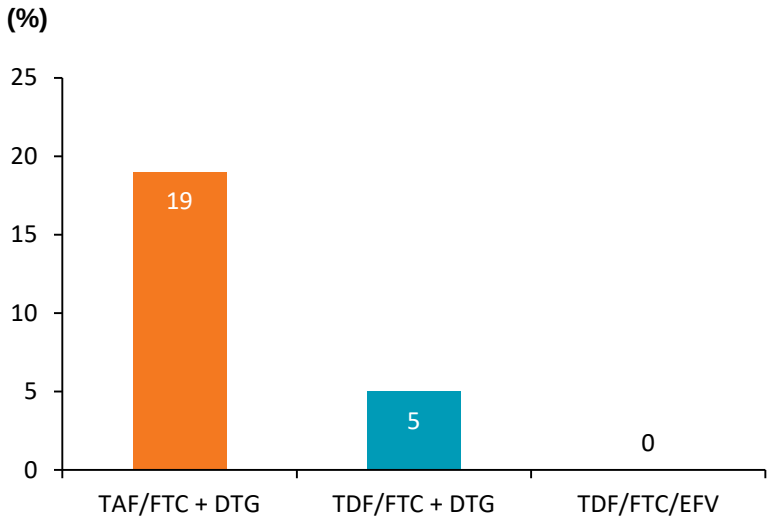
  - weight change among persons on TAF remained greater than non-TAF recipients
- Adjustment for age, gender, race and baseline BMI at ART switch did not change our main inferences

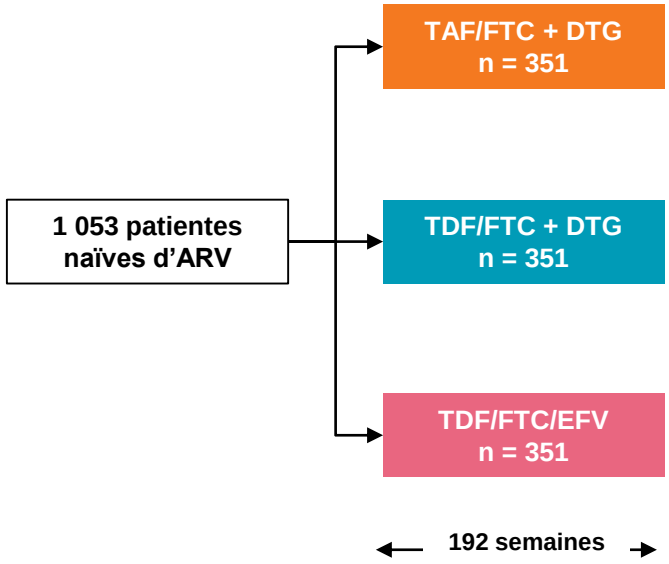
Femmes, grossesse et pédiatrie

Risque pédiatrique à long terme dans l'étude ADVANCE

- Revue des données de la littérature sur l'impact de l'obésité maternelle puis modélisation pour prédire le risque attendu dans l'étude ADVANCE chez les chez les femmes obèses ou non avant la grossesse

Obésité associée au traitement chez les femmes avec IMC prégestationnel normal dans ADVANCE





Visites : inclusion, semaines 4, 12, 24, 36, 48, 60, 72, 84 et 96 puis toutes les 24 semaines

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Femmes, grossesse et pédiatrie

Risque pédiatrique à long terme dans l'étude ADVANCE

- Augmentation du risque maternel et fœtal en cas d'obésité prégestationnelle
- Analyse selon le risque prédit :
  - Sous DTC+FTC/TAF :
    - 15 % de cas supplémentaires d'issues défavorables de la grossesse
    - 28 % de cas supplémentaires d'évènements indésirables pour l'enfant
  - Sous DTG+FTC/TDF
    - 4 % de cas supplémentaires d'issues défavorables de la grossesse
    - 7 % de cas supplémentaires d'évènements indésirables pour l'enfant

Issue défavorable	RR	IC_{95}	P
Hypertension gravidique	3,68	2,97 – 4,55	< 0,00001
Diabète gestationnel	4,31	3,18 – 5,85	< 0,00001
Pré éclampsie	4,06	3,09 – 5,33	< 0,00001
Hémorragie du post partum	1,23	1,01 – 1,50	p = 0,04
Césarienne	1,64	1,55 – 1,73	< 0,00001
Poids élevé pour l'âge gestationnel	2,04	1,65 – 2,52	< 0,00001
Macrosomie	2,48	2,10 – 2,93	< 0,00001
Surpoids et obésité enfant	3,75	2,41 – 5,86	< 0,001
Facteurs de risque cardiométaboliques enfant	2,59	1,93 – 3,48	< 0,00001
Troubles respiratoires enfant (asthme)	1,66	1,14 – 2,43	p = 0,009

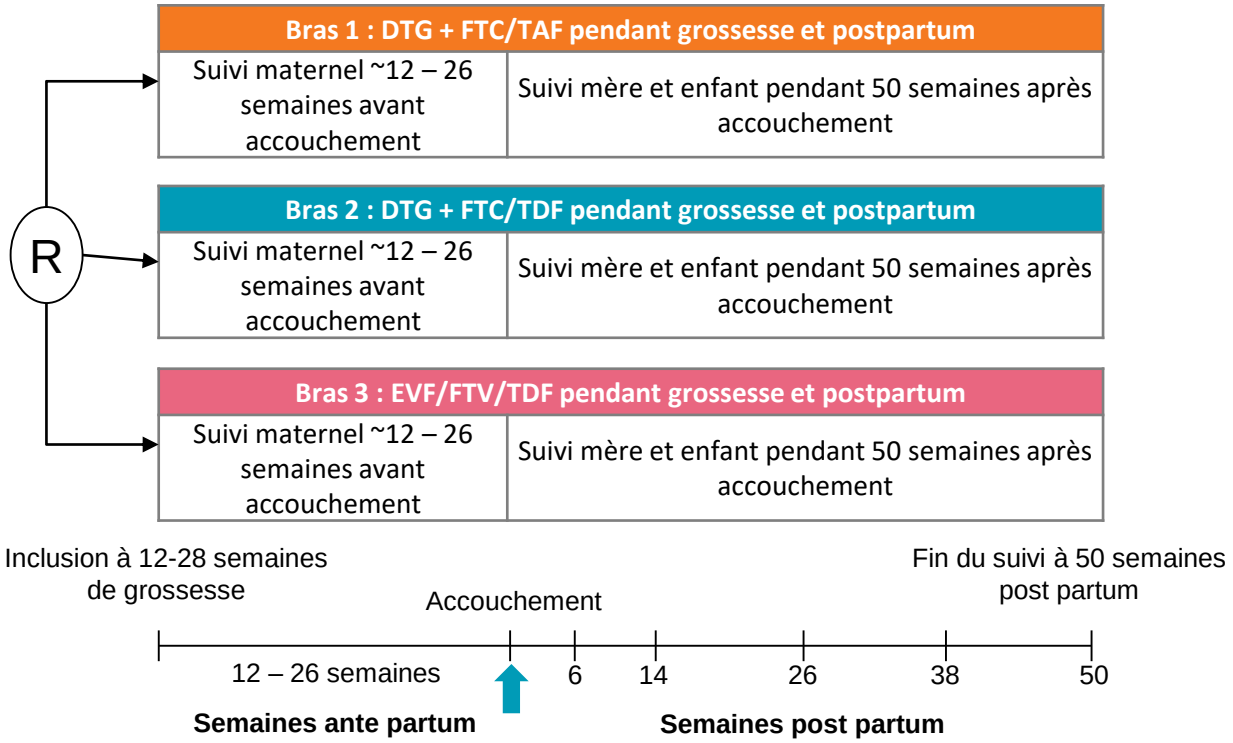
→ **L'obésité prégestationnelle induite par les ARV p[illegible] fœtales; les combinaisons à base de DTG+FTC/TA[illegible] grossesse**

CROI 2021 - D'après Baxevanidi E et al., abstr. 572, actualisé

Femmes, grossesse et pédiatrie

Lien entre prise de poids (PP) pendant la grossesse et issue défavorable dans IMPAACT 2010

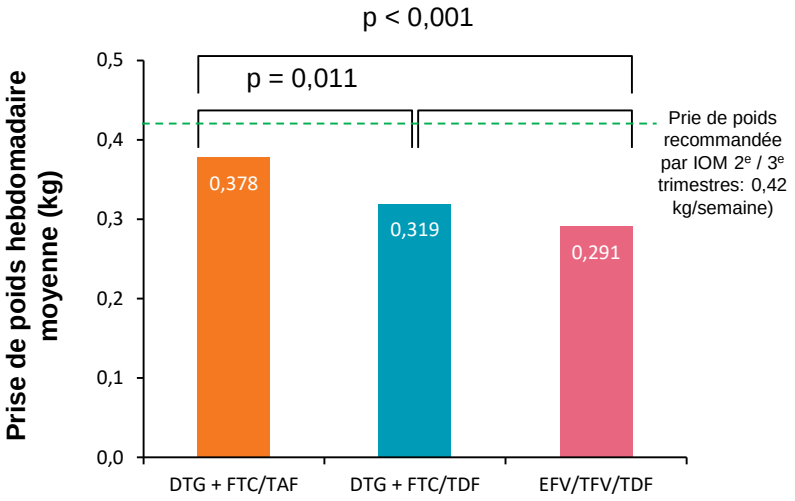
- Inclusion femmes à 14-28 semaines de gestation, naïves d'ARV ; critères principaux : suppression virale (CV < 200 copies/ml à l'accouchement) et EIs grade ≥ 3 chez la mère ou l'enfant jusqu'à la semaine 50
- Suivi médian avant accouchement : 17,4 semaines
- Caractéristiques à l'inclusion :
  - Âge médian 26,6 ans
  - Inclusion en Afrique : 88 %
  - Âge gestationnel : 21,9 semaines
  - CD4 médiane 466 cellules/mm^3
  - ARN VIH médiane 903 copies/mL
  - Poids moyen 66,2 ± 15,2 kg



CROI 2021 - D'après Hoffman R et al., abstr. 176, actualisé

Femmes, grossesse et pédiatrie

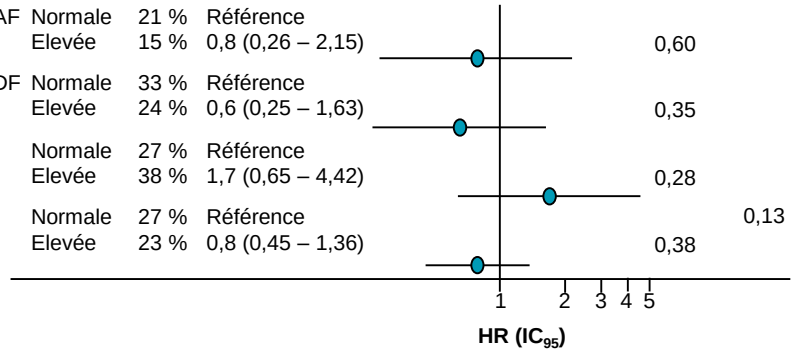
Lien entre prise de poids (PP) pendant la grossesse et issue défavorable dans IMPAACT 2010



- **Faible PP plus fréquente sous EFV/FTC/TDF et mois fréquente sous DTG+FTC/TAF**
- **PP faible (mais pas PP élevée) associée à issue défavorable**
- **PP sous DTG+FTC/TAF proche de celle recommandée par IOM**
- **Plus faible taux d'issues défavorables sous DTG+FTC/TAF pourrait être lié à PP plus élevée**

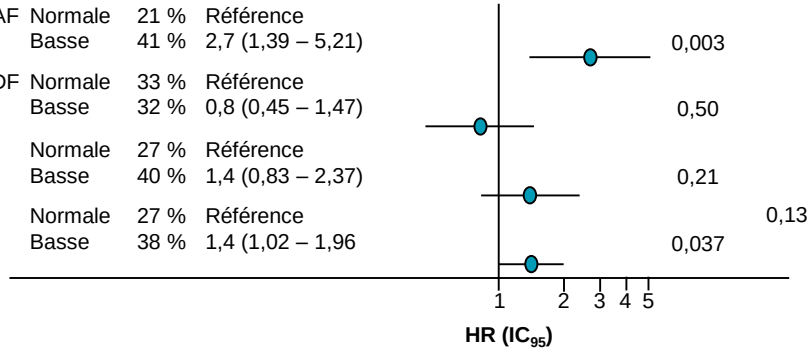
PP élevée vs. normale

Groupe de traitement	PP	Proportion avec évènement	HR (IC_{95})	Interaction poids/bras p
DTG + FTC/TAF	Normale	21 %	Référence	
	Elevée	15 %	0,8 (0,26 – 2,15)	0,60
DTG + FTC/TDF	Normale	33 %	Référence	
	Elevée	24 %	0,6 (0,25 – 1,63)	0,35
EFV/FTC/TDF	Normale	27 %	Référence	
	Elevée	38 %	1,7 (0,65 – 4,42)	0,28
Total	Normale	27 %	Référence	0,13
	Elevée	23 %	0,8 (0,45 – 1,36)	0,38



PP basse vs. normale

Groupe de traitement	PP	Proportion avec évènement	HR (IC_{95})	Interaction poids/bras p
DTG + FTC/TAF	Normale	21 %	Référence	
	Basse	41 %	2,7 (1,39 – 5,21)	0,003
DTG + FTC/TDF	Normale	33 %	Référence	
	Basse	32 %	0,8 (0,45 – 1,47)	0,50
EFV/FTC/TDF	Normale	27 %	Référence	
	Basse	40 %	1,4 (0,83 – 2,37)	0,21
Total	Normale	27 %	Référence	0,13
	Basse	38 %	1,4 (1,02 – 1,96	0,037



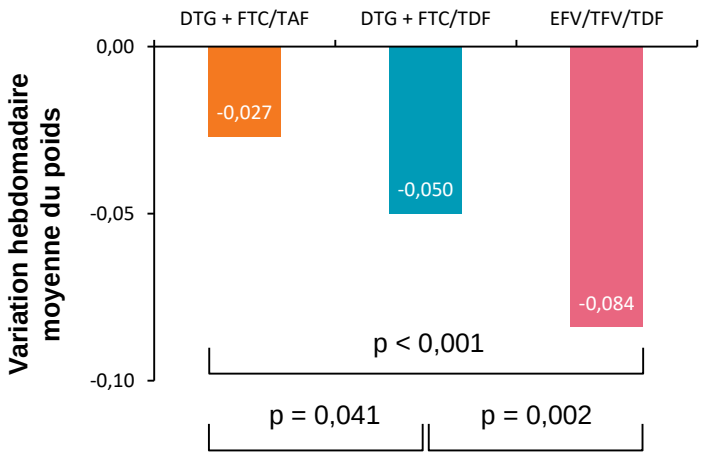
CROI 2021 - D'après Hoffman R et al., abstr. 176, actualisé

Femmes, grossesse et pédiatrie

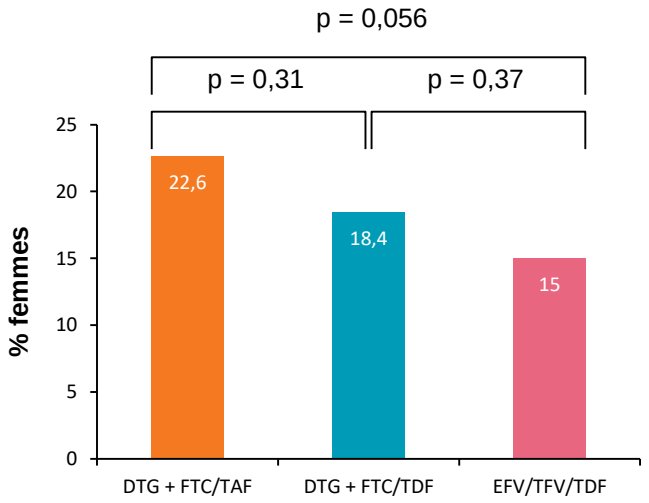
Résultats d'efficacité et tolérance de IMPAACT 2010

- Suppression virale maternelle à la semaine 50 : 96,3 % dans les bras DTG combinés vs. 96,4% dans le bras EFV/FTC/TDF (différence non statistiquement significative)
- Echec virologique
  - DTG+FTC/TAF : 4,1 %
  - DTG+FTC/TDF : 5,1 %
  - EFV/FTC/TDF : 10,4 % (p = 0,012 vs. DTG+FTC/TAF, autres comparaisons non statistiquement significatives)

Variation hebdomadaire moyenne du poids maternel
De l'inclusion à S 50 post partum



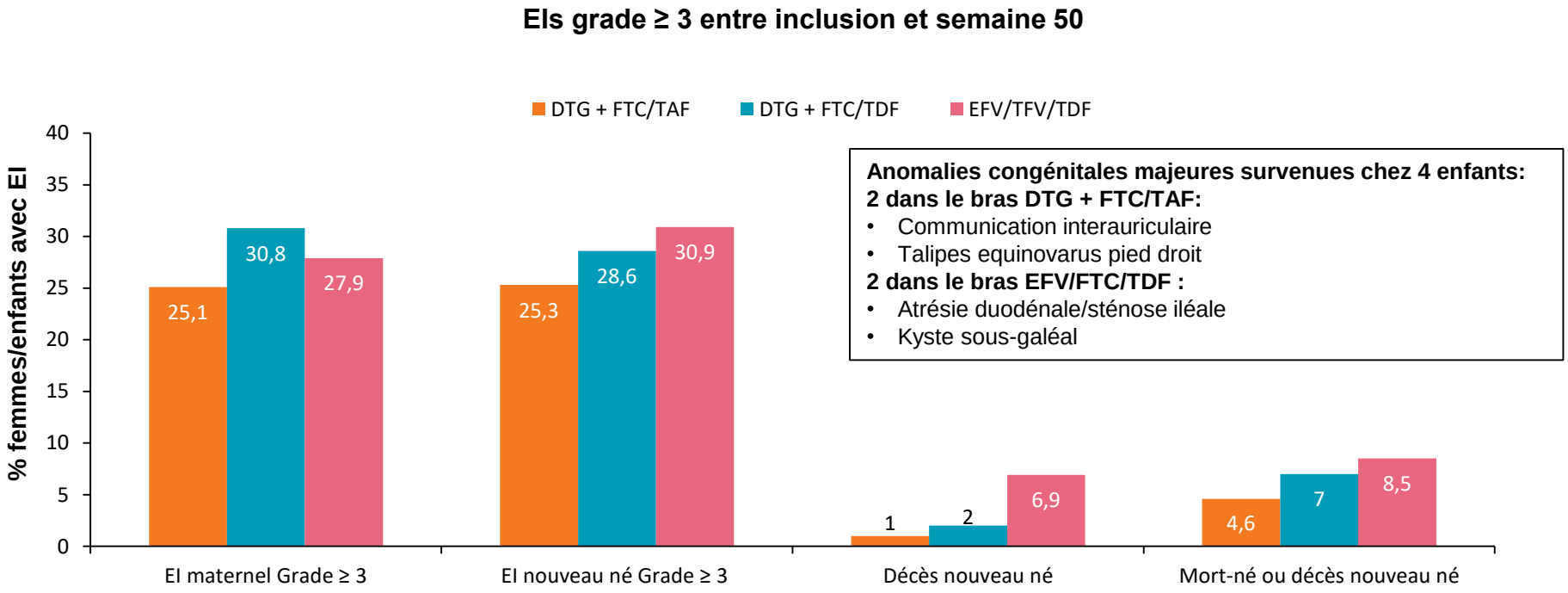
Obésité maternelle à S 50
(IMC ≥ 30 kg/m²)



CROI 2021 - D'après Chinula L et al., abstr. 177, actualisé

Femmes, grossesse et pédiatrie

Résultats d'efficacité et tolérance de IMPAACT 2010



→ **Suppression virologique similaire dans les 3 bras mais plus d'échecs virologiques dans le bras EFV**

→ **Taux d'évènements indésirables grade ≥3 maternels et infantiles similaires dans les 3 bras mais plus de décès infantiles dans le bras EFV**

CROI 2021 - D'après Chinula L et al., abstr. 177, actualisé