State of the ART of ARV Therapy

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- Trustee, British HIV Association (BHIVA) and member of the BHIVA Guidelines Writing group

Overview

- **Current Treatment Guidelines**
  - When to start
  - How quickly should ART be started?
  - What to start
- **The future of ART**
  - New treatment paradigms
    - 2 drug regimens
    - Injectables
  - Pipeline

International ART Guidelines

International Antiviral Society-USA Panel

- *https://jamanetwork.com/journals/jama/fullarticle/2688574*
- Last update: July 2018

European AIDS Clinical Society Guidelines (EACS)

- http://www.eacsociety.org/files/guidelines v9.1-english.pdf
- Last update: October 2018

DHHS Panel Guidelines (USA)

- https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0
- Last update: July 2019

World Health Organization (WHO)

- https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/
- Last update: July 2019

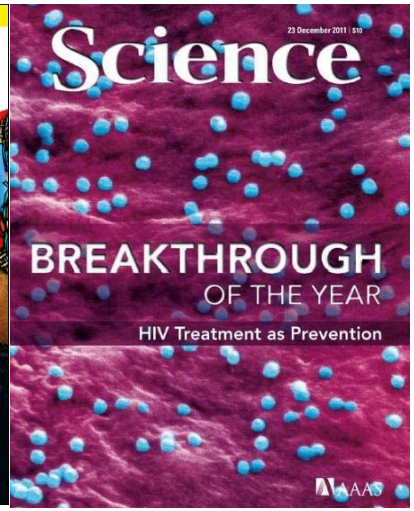
WHEN TO START

When to start

IAS-USA[1]	Initiate ART as soon as possible after HIV diagnosis. Rapid start (including same day) unless patient not ready to commit.
DHHS[2]	ART recommended for all regardless of CD4 T lymphocyte count. Therapy should be initiated as soon as possible.
WHO[3]	Start ART in all regardless of WHO clinical stage or CD4. Prioritise severe/advance clinical disease (WHO stage 3 or 4) and adults with CD4 ≤350
EACS[4]	ART should always be recommended irrespective of the CD4 count. Immediate (same day ART) should be considered in certain situations.

1. Saag M et al, JAMA, 2018
2. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/10/initiation-of-antiretroviral-therapy
3. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf ;
4. http://www.eacsociety.org/files/guidelines_9.1-english.pdf

Treatment as prevention



PARTNER

HPTN 052

96% reduced transmissions initially

93% reduction in final analysis:

- 8 transmissions in ART arm
  - 4 virological failures
  - 4 prior to suppression

PARTNER 2

> 75,000 CLSI in 758 MSM serodifferent couples where HIV+ partner on suppressive ART (VL<200)

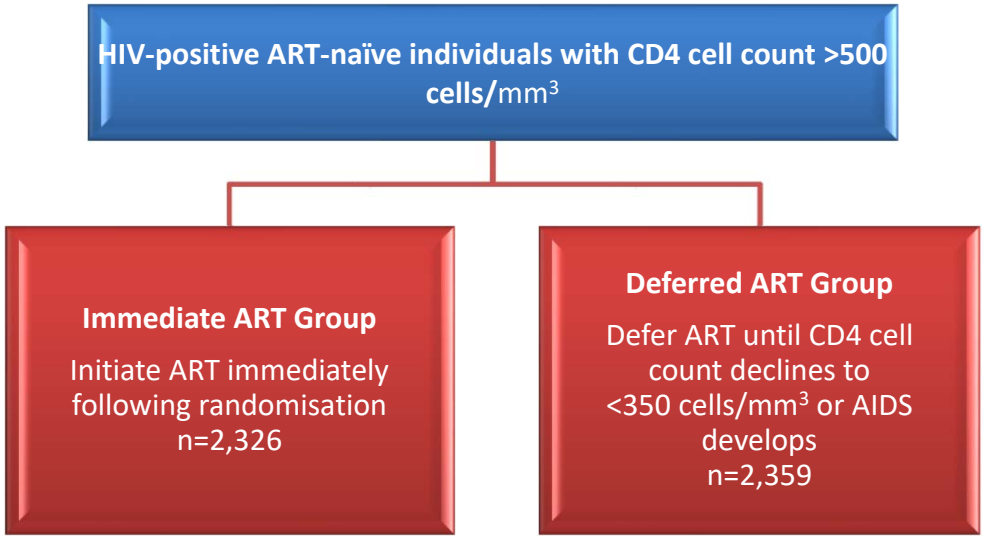
= **ZERO transmissions**

1. Cohen MS *et al*. N Engl J Med. 2011; 2. Cohen MS *et al.* NEJM 2016; 375: 830-839;
3. Rodger A et al. Lancet 2019; 393: 2428-2438

Strategic Timing of Antiretroviral Treatment (START) Trial

START

- International RCT of immediate vs deferred ART
- The primary composite endpoint = a serious AIDS event, serious non-AIDS event, or death from any cause



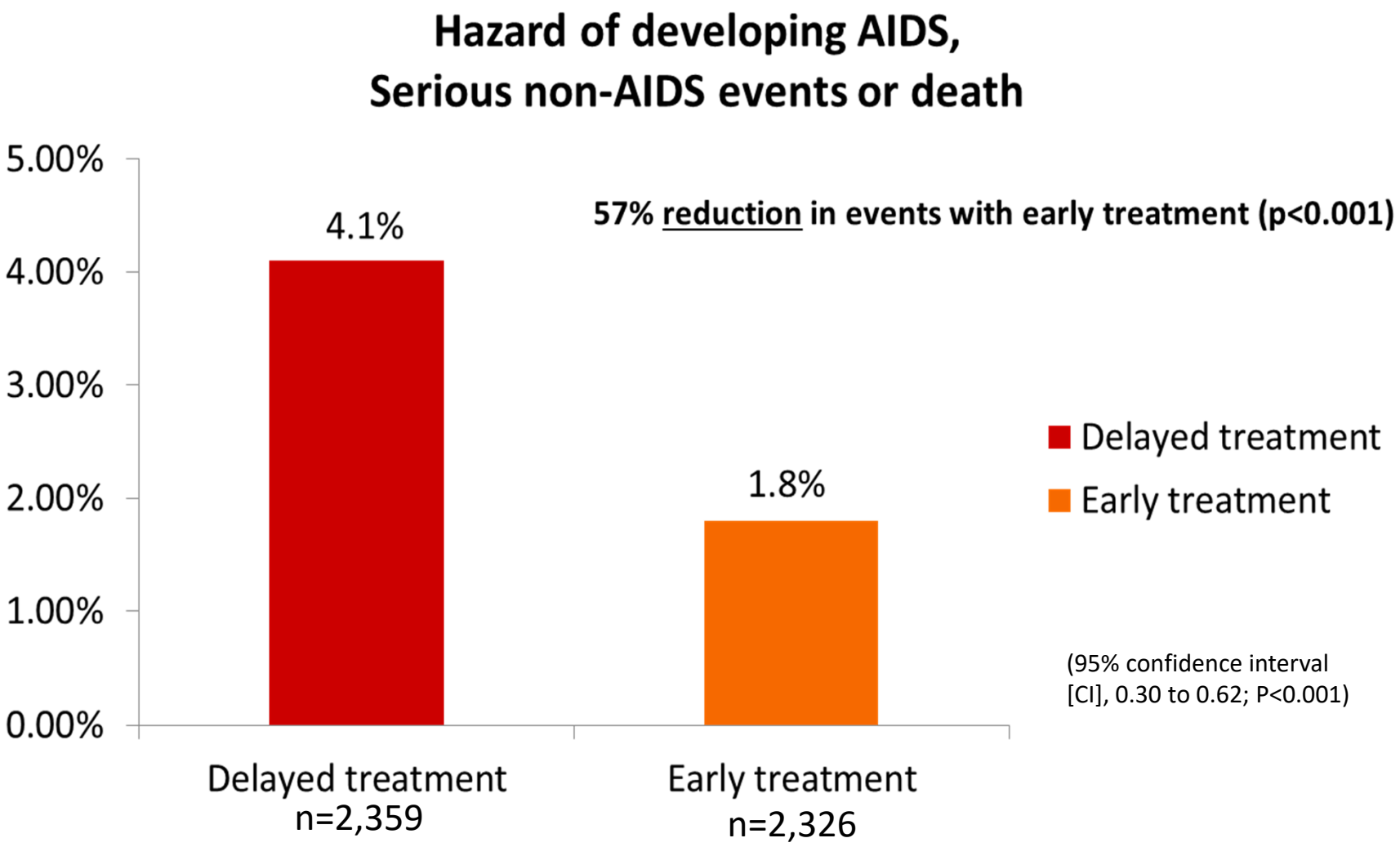
Characteristic	N=4,685
Age (year)*	36 (29, 44)
Female, n (%)	1257 (27)
Race, n (%)	
White	2086 (45)
Black	1,410 (30)
Time since HIV diagnosis (year)*	1.0 (0.4, 3.1)
CD4 cell count (cells/mm^3)*	651 (584–765)
Baseline HIV-RNA (copies/mL)*	12,759 (3,019–43,391)
TDF usage	89% in both groups

* Median (IQR)

- On 15 May 2015, at a planned interim review, DSMB recommended participants in the deferred arm not already on ART should be offered ART and follow-up should continue with all subjects on therapy. LFU (last contact >10/12) 4% immediate & 5% deferred

Lundgren D, et al. NEJM 2015

START: Primary results



Lundgren D, et al. NEJM 2015

HOW QUICKLY SHOULD ART BE STARTED?

Rapid ART

Why?

- Reduce risk of clinical progression
- Improve engagement and retention in care
- Shorter time to treatment means less anxiety, more trust
- Treatment as prevention

Why not?

- Deferral of ART if symptoms/signs of a significant OI
- Unable to 'tailor' ART (TDR, Hepatitis B, renal insufficiency)
- Less time to address barriers to ART and adherence
- LTFU* pre-ART doesn't risk resistance; LTFU* after ART may do so

*LTFU: loss to follow up

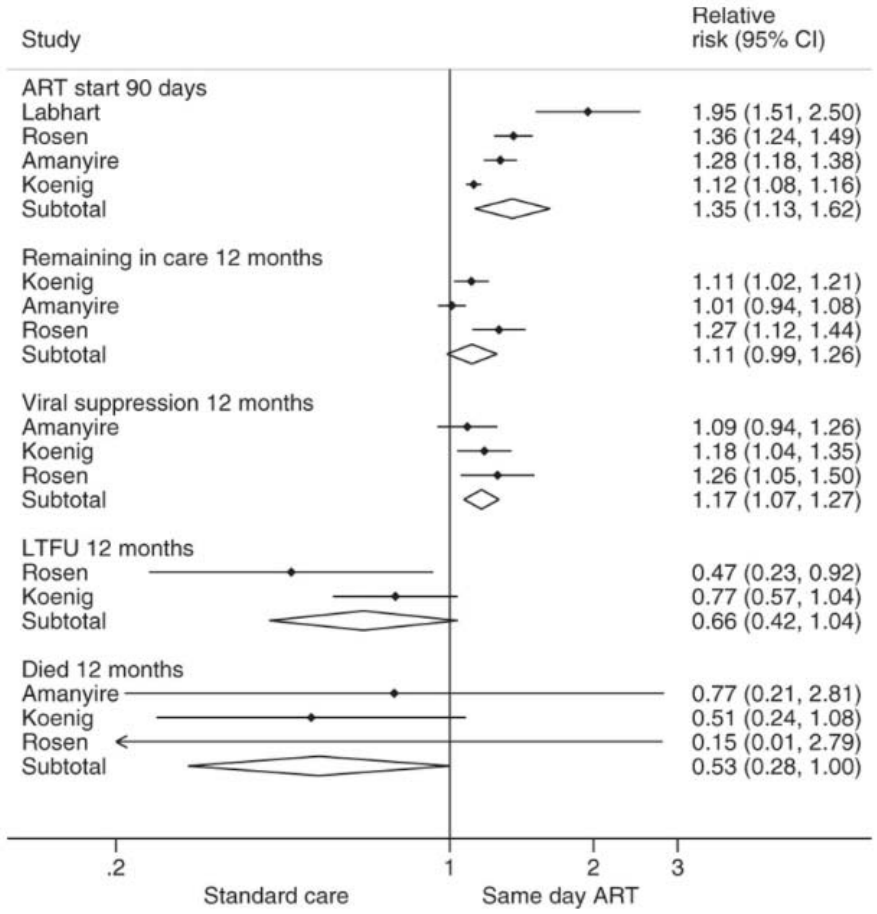
WHO Guidelines July 2017

- "Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment."
  - *"Rapid" defined as within 7 days*

- "ART initiation should be offered on the same day to people who are ready to start."

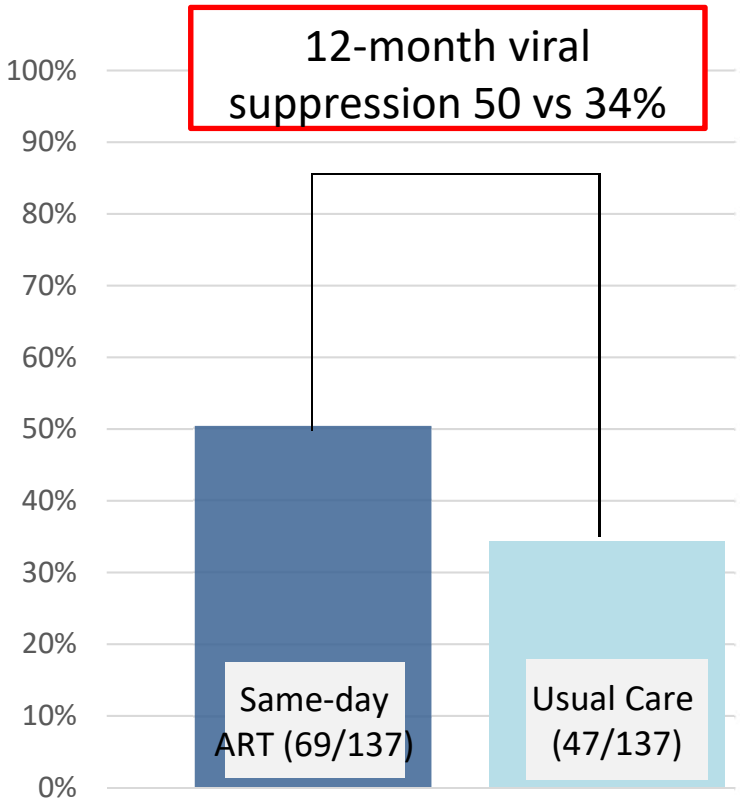
- Goal: To improve linkage to care and reduce LTFU

Four RCTs that Impacted the WHO Guidelines for Rapid ART

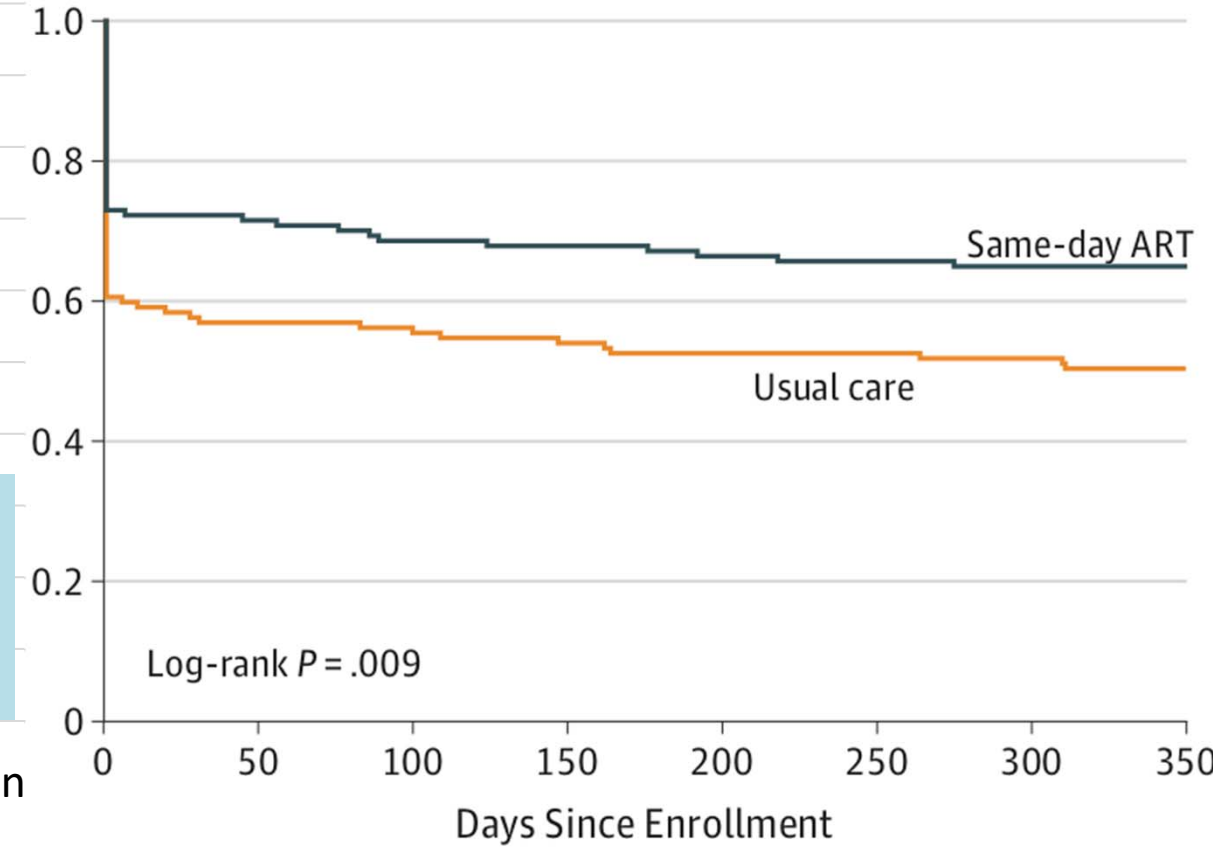


Ford N *et al*. AIDS 2018; **32**: 17-23

CASCADE: SDART vc SOC in Home-based Testing in Lesotho



12-months viral suppression



12-months engagement in care

Labhardt ND *et al*. JAMA 2018; 319(11):1103-12

What about High-Income Countries?

- Cohort studies of Rapid ART initiation
- San Francisco General Hospital, RAPID model
  - Faster time to viral suppression
  - High rates of viral suppression

- Unclear if this improves engagement with care
- Considerations around readiness to start and infrastructure needed to deliver

Pilcher CD et al. JAIDS 2017; 74 (1): 44-51; Coffey S et al. AIDS 2019; 33 (5): 825-832

IAS-USA Guidelines 2018

- ART should be initiated as soon as possible after diagnosis … unless patient is not ready
- Structural barriers that delay receipt of ART should be removed to allow newly diagnosed patients to receive ART at the first clinic visit….
- Treatment may be started before test results are available (HIV-1 RNA, CD4 count, resistance testing, chemistries, hepatitis serologies)
- Recommended ART for Rapid Start:
  - Biktarvy (bictegravir/TAF/FTC)
  - Dolutegravir or boosted darunavir with TAF/TDF + FTC/3TC

Saag MS *et al*. JAMA 2018

WHAT TO START

Recommended and preferred regimens

GUIDELINES	NRTI BACKBONE	NNRTI	INSTI	PI
EACS (2018)[1]	TAF/FTC TDF/FTC ABC/3TC*	RPV**	**DTG** **RAL** **EVG**	DRV/c or /r
DHHS (2019)[2]	TAF/FTC TDF/FTC ABC/3TC*	–	**DTG** **BIC** **RAL**	–
IAS USA (2018)[3]	TAF/FTC ABC/3TC*	–	**DTG** **BIC**	–
WHO (2019)[4]	TDF/XTC		**DTG**	–

*Use recommended as backbone only if prescribed with DTG and HLA B5701 negative
**Use if HIV RNA < 100, 000 copies/mL

3TC, lamivudine; ABC, abacavir; BIC, bictarvy; c, cobicistat; DHHS, Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EVG, elvitegravir; FTC, emtricitabine; IAS USA, International Antiviral Society–USA; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; XTC, FTC or 3TC.

1.EACS Guidelines Version 9.1. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed August 2019;
2.DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed August 2019;
3.Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. *JAMA.* 2018;320(4):1-18.
4.WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/ Accessed August 2019.

INTEGRASE INHIBITORS

Why are INIs* first line?

*INI=integrase inhibitors

	Dolutegravir	Raltegravir	Elvitegravir/c	Bictegravir
Efficacy[1-6]	✓✓	✓	✓	✓
Once daily dosing	✓	✓	✓	✓
Available as a STR	✓		✓	✓
High genetic barrier[1-6]	✓			✓
Few drug interactions	✓	✓		✓
Tolerability		✓	✓	
Studies in women[7-9]	✓		✓	(✓)

1. SINGLE study: Walmsley S et al. *NEJM* 2013; 2. SPRING-2 study: Raffi F et al. *Lancet* 2013. 3. FLAMINGO study. Molina JM et al. *Lancet HIV* 2015; 4. GS-1490. Sax PE et al. *Lancet* 2017; 5. GS 1489: Gallant J et al. Lancet 2017; 6. GS 1490: Sax P et al. Lancet 2017; 7. ARIA study: Orrell C et al. *Lancet HIV* 2017; 8. WAVES study: Squires K et al. *Lancet HIV* 2016; 9. Kityo C, et al. CROI 2018. Boston, MA. Poster 500

Current challenges of INIs as third agent

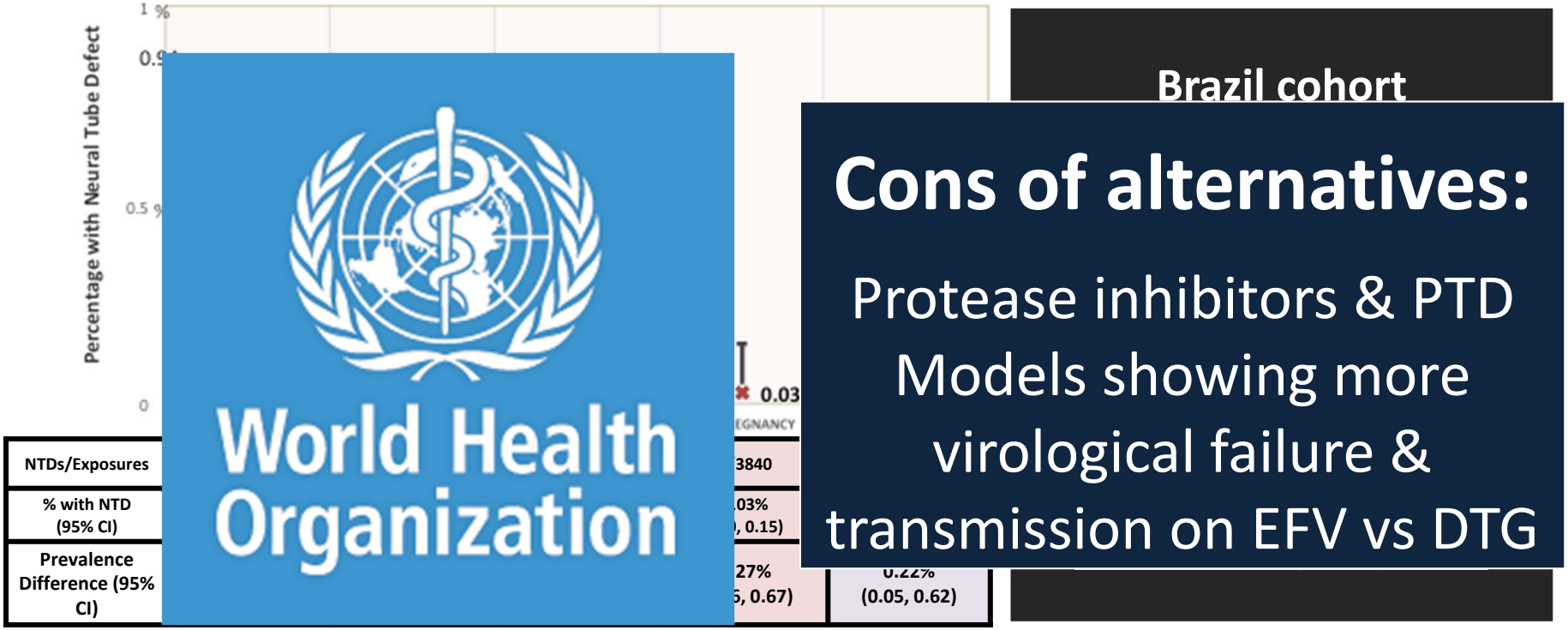
CNS AEs	Resistance	DDIs
Phase III FDA trials DTG[1] ▪Only SINGLE re… events (espe… **Six cohor…** **disconti…** ▪More D… than othe… **Opera cohor…** ▪ Similar CNS incid… for third agents **Wohl series[9]** ▪ Depression and sleep disturbances were significantly higher in DTG vs EVG, and DRV/r, but not RAL ▪ Suicidal ideation rates similar among INIs	**First-generation INI** …d EVG more resistance …on INI …loser to PI/r	**INI drug–drug interactions** ▪RAL/DTG chelation ▪EVG/c booster, so DDIs ▪BIC: UGT1A1 and Cyp3 A4 metabolism (cannot be used with rifampicin)

Concerns regarding neural tube defects in infants born to women who conceived whilst taking DTG

Weight gain???

1. Viswanathan P, *et al.* CROI 2017, Seattle, WA, United States; poster #372; 2. Quercia R, *et al.* HIV Glasgow 2016, Glasgow, United Kingdom; poster #210; 3. Hoffmann C, et al. *HIV Med* 2017;18:56–63; 4. Padilla M, *et al.* International Workshop on Comorbidities and ADRs in HIV 2016, New York, NY, United States; 5. Lepik KJ, *et al.* IAS 2015, Vancouver, Canada; abstract #TUPEB256; 6. Hsu R, *et al.* CROI 2017, Seattle, WA, United States; poster #664; 7. Llibre JM, *et al.* CROI 2017, Seattle, WA, United States; poster #651; 8. Baldin G, *et al.* HIV Glasgow 2016, Glasgow, United Kingdom; poster #P106; 9. Wohl D, *et al.* ID Week 2017; San Diego, CA, United States; abstract #664.

Pre-conception dolutegravir & NTDs

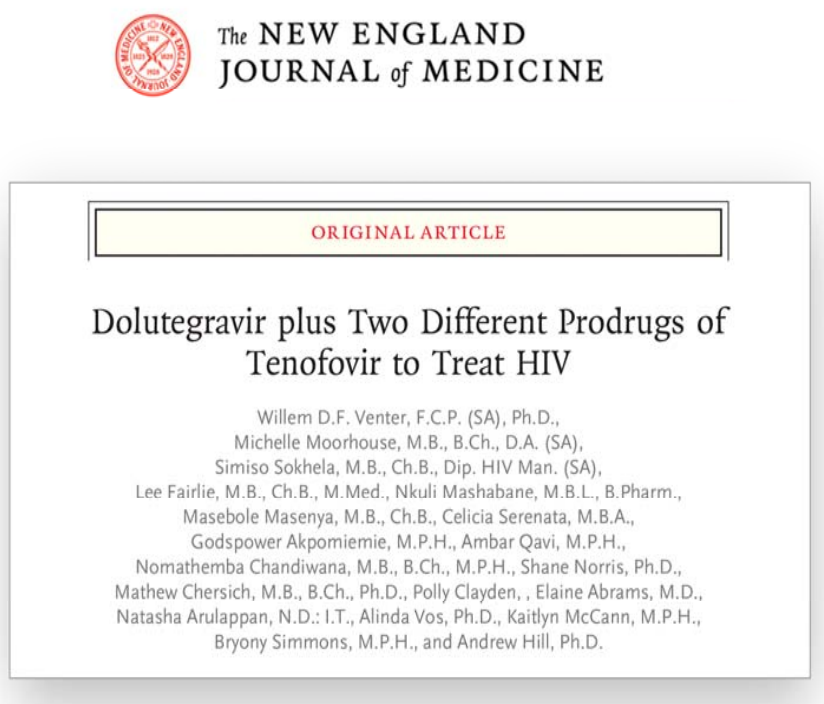


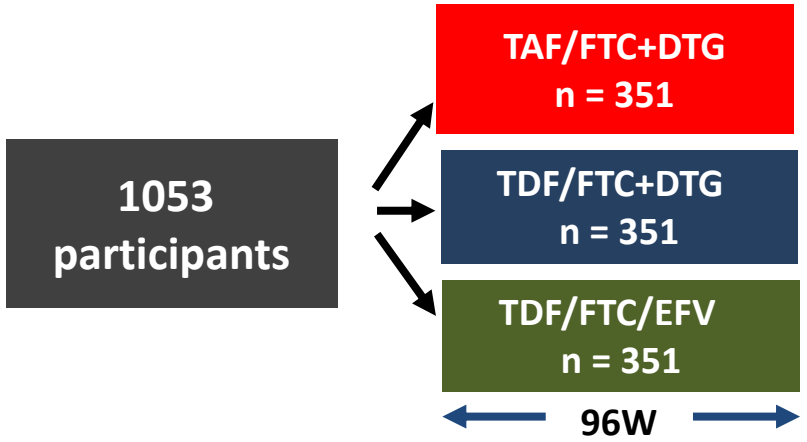
[1]Zash R. IAS 2019 Mexico. Abstract TUSY0102; NEJM 2019

[2]Pereira G et al. IAS 2019 Mexico. Abstract MOAX0104LB

[3]WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/ Accessed August 2019.

ADVANCE, 1st line trial in South Africa

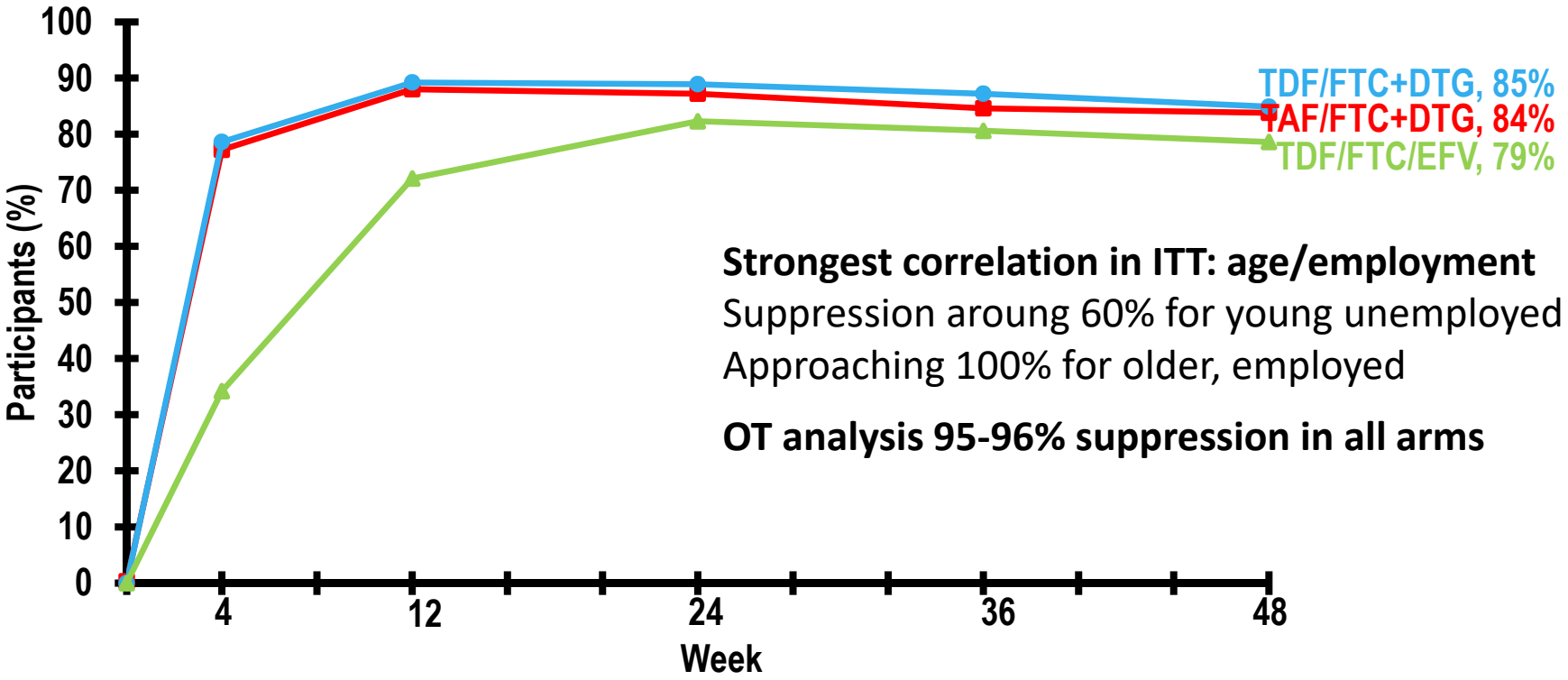




- 60% female, ≈100% Black
- Drawn from a group representing a quarter of the global epidemic

Venter WF et al. IAS 2019. Mexico. Abstract WEAB0405LB; NEJM July 2019

Proportion with VL<50 (ITT)



Strongest correlation in ITT: age/employment
Suppression aroung 60% for young unemployed
Approaching 100% for older, employed

OT analysis 95-96% suppression in all arms

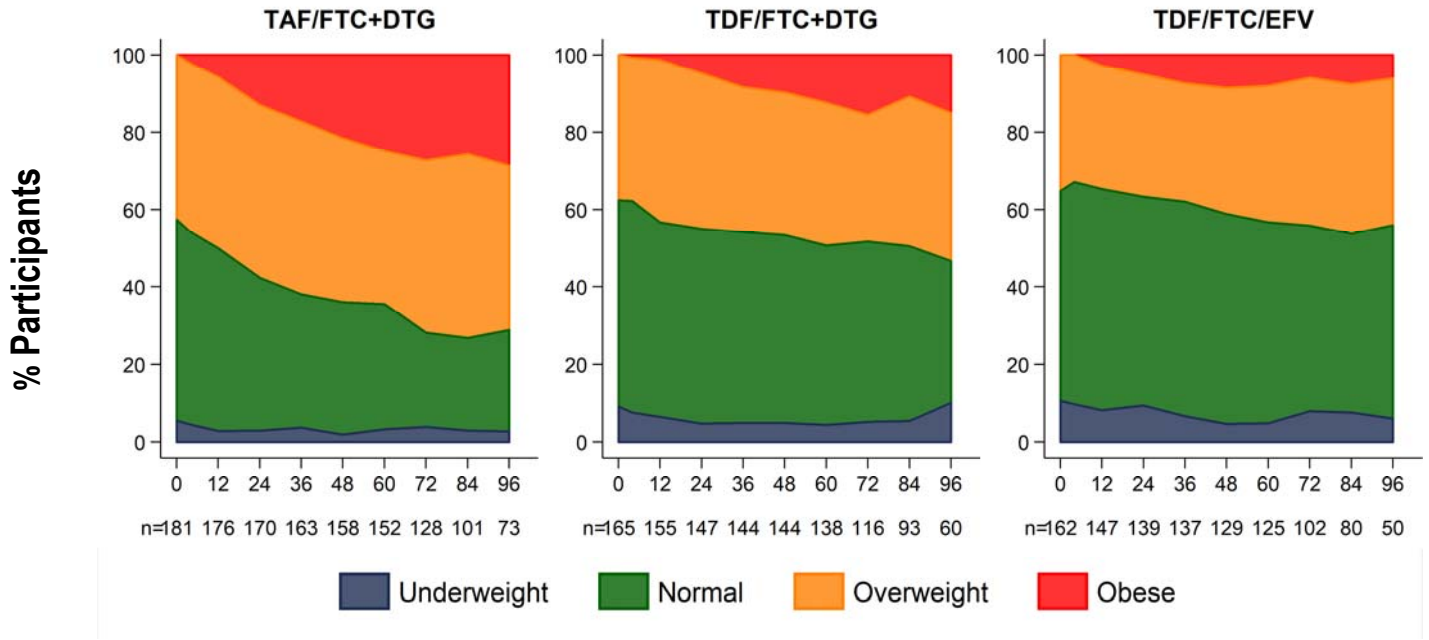
Weight

- **ADVANCE[1] 96 weeks (baseline BMI 22 in men, 27 in women)**
  - **TAF/F/DTG** vs **TDF/F/DTG** vs **TDF/FTC/EFV**
  - Men **+5kg**, **+4kg**, **+1kg** (DEXA: similar fat/lean mass gain)
  - Women **+10kg**, **+5kg**, **+3kg** (DEXA: fat>lean mass gain)
- **NAMSAL[2] 48 weeks (baseline BMI 23)**
  - Significantly more weight/BMI gain & emergent obesity on TDF/3TC + DTG vs TDF/3TC/EFV 400

Hill A et al. IAS 2019 Mexico. Abstract MOAX0102LB

ADVANCE: BMI category over time: women

(obese at baseline excluded)



NNRTIS

NNRTIs

GUIDELINES	NRTI BACKBONE	NNRTI	INSTI	PI
EACS (2018)	TAF/FTC TDF/FTC ABC/3TC	RPV	DTG RAL EVG	DRV/c or /r
DHHS (2019)	TAF/FTC TDF/FTC ABC/3TC	–	DTG BIC RAL EVG/c	–
IAS USA (2018)	TAF/FTC ABC/3TC	–	DTG BIC	–
WHO (2019)	TDF/XTC		DTG	–

- Less effective at high viral load (>100K) and low baseline CD4 count (<200)
- Restricted use with PPIs and H2 blockers

NNRTIs

DHHS (2019)

'recommended in certain clinical situations'

- **Rilpivirine + TDF/FTC or TAF/FTC**
  - Well tolerated; available as a small single tablet regimen (STR)
  - Non-inferior to EFV in ECHO/THRIVE[1]
  - Superior to EFV at VL<100K in STaR[2]
  - Favourable lipid profile in STaR[2]
  - Less effective at high viral load (>100K) and low baseline CD4 count (<200)[1]

- **Doravirine**
  - Available as a single pill (Pifeltro®) or as an STR with TDF/3TC (Delstrigo®)
  - Non-inferior to EFV[3] and DRV/r[4] (no VL or CD4 concern)
  - Better tolerated in terms of CNS AE (EFV)[3] and lipids (EFV[3] and DRV/r[4])
  - Fewer potential drug interactions compared with EFV or RPV

[1]Cohen CJ et al. JAIDS 2012; [2]Cohen CJ et al. AIDS 2014; [3] Orkin C et al. CID 2019; [4]Molina JM et al. Lancet HIV 2018

Will EFV remain in guidelines?

- Newer drugs superior:
  - DTG at primary endpoint in SINGLE[1]
  - RAL after long enough follow-up in STARTMRK[2]
  - RPV in subgroup analysis of StAR (VL<100K)[3]
- Tolerability issues (CNS/lipids)
- ACTG suicidality analysis[4]

[1]Walmsley S et al. NEJM 2013; [2]Rockstroh JK et al. JAIDS 2013; [3]Cohen CJ et al. AIDS 2014;
[4]Mollan KR et al. Ann Intern Med 2014

Will EFV remain in guidelines?

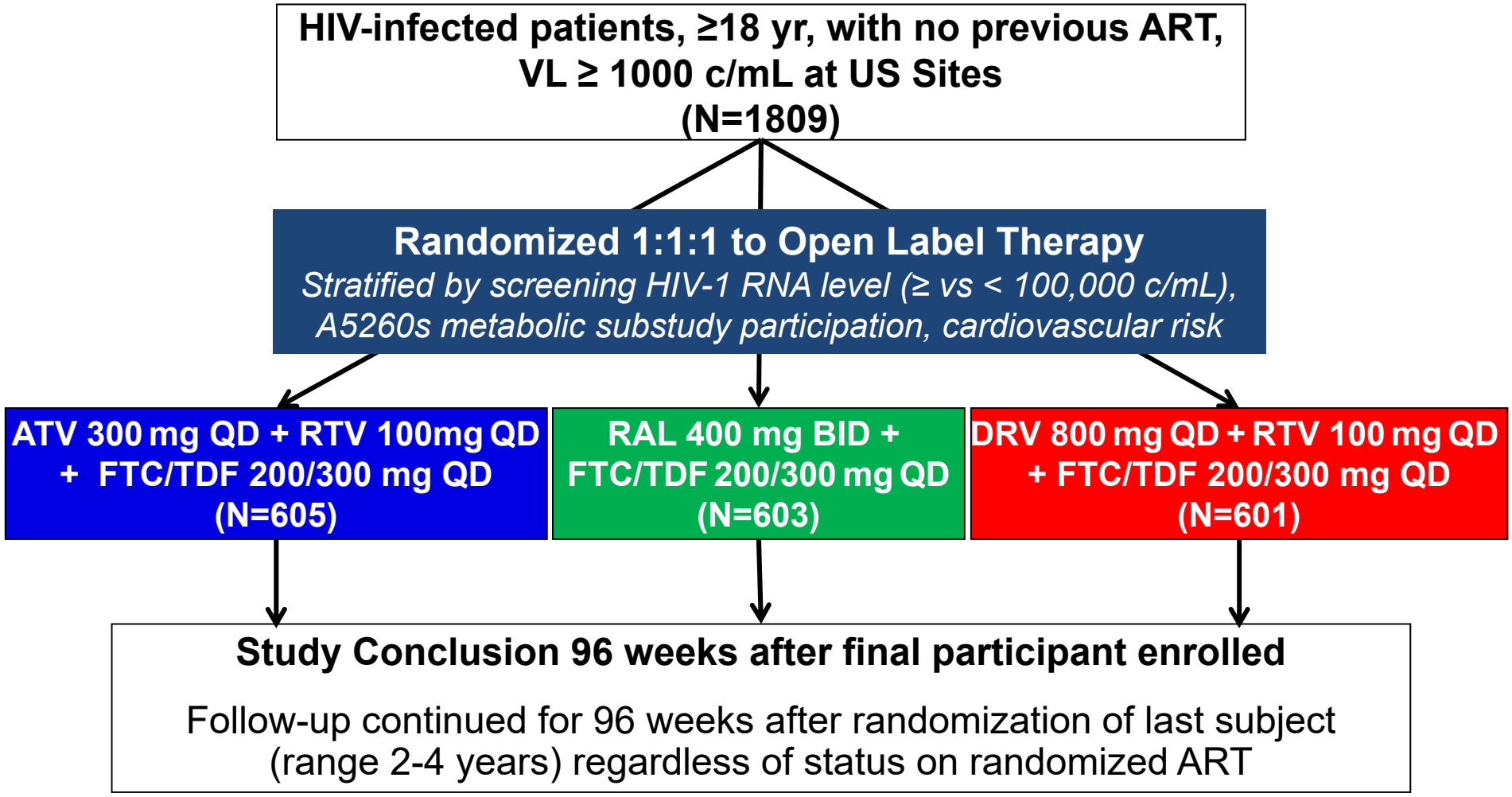
- Newer drugs superior:
  - DTG at primary endpoint in SINGLE
  - RAL after long enough follow-up in STARTMRK
  - RPV in subgroup analysis of StAR (VL<100K)
- Tolerability issues (CNS/lipids)
- ACTG suicidality analysis
- **BUT** long track record
- Considered safe in women trying to conceive
- Can be used with rifamycins in patients with TB
- ?concerns re weight gain with DTG in LMIC

BOOSTED PROTEASE INHIBITORS

Boosted Protease inhibitors

- Many guidelines have downgraded ATV/r
- Based mainly on ACTG 5257…..

A5257 Study Design



Lennox JL *et al.* Annals of Int Med 2014; 161(7): 461-471

ACTG 5257: failures

Virologic failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	3.4%	-0.7%, 7.4%	Equivalent
DRV/r vs RAL	5.6%	1.3%, 9.9%	Equivalent
ATV/r vs DRV/r	-2.2%	-6.7%, 2.3%	Equivalent

Tolerability failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	13%	9.4%, 16%	RAL superior
DRV/r vs RAL	3.6%	1.4%, 5.8%	Equivalent
ATV/r vs DRV/r	9.2%	5.5%, 13%	DRV/r superior

Cumulative failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	15%	10%, 20%	RAL superior
DRV/r vs RAL	7.5%	3.2%, 12%	RAL superior
ATV/r vs DRV/r	7.5%	2.3%, 13%	DRV/r superior

ACTG 5257: toxicity discontinuation

	ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Any toxicity discontinuation	95 (16%)	8 (1%)	32 (5%)
Gastrointestinal toxicity	25	2	14
Jaundice/hyperbilirubinemia	47	0	0
Other hepatic toxicity	4	1	5
Skin toxicity	7	2	5
Metabolic toxicity	6	0	2
Renal toxicity (all nephrolithiasis)	4	0	0
Abnormal chem/haeme (excl. LFTs)	0	0	2
Other toxicity	2	3	4

Lennox JL *et al.* Annals of Int Med 2014; 161(7): 461-471

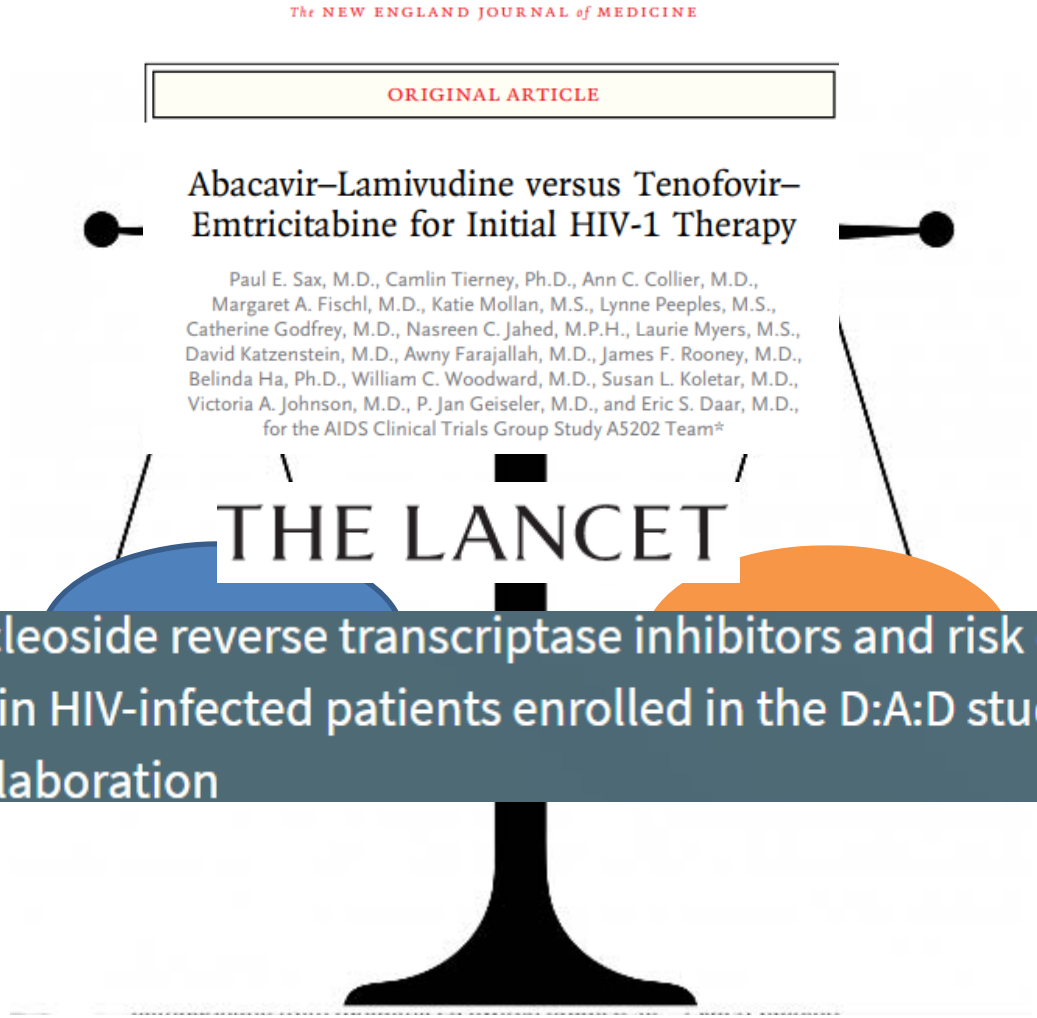
DRV/cobi/FTC/TAF: First PI-based STR

- Once daily single-tablet regimen approved by FDA in July 2018
  - For treatment-naïve patients
  - For patients with virological suppression for >6 months with no resistance to DRV or TDF
- Take with food
- Multiple potential drug-drug interactions

Symtuza SmPC. Available from: http://www.medicines.org.uk/emc/medicine/34148. Updated September 2017. Accessed October 2017

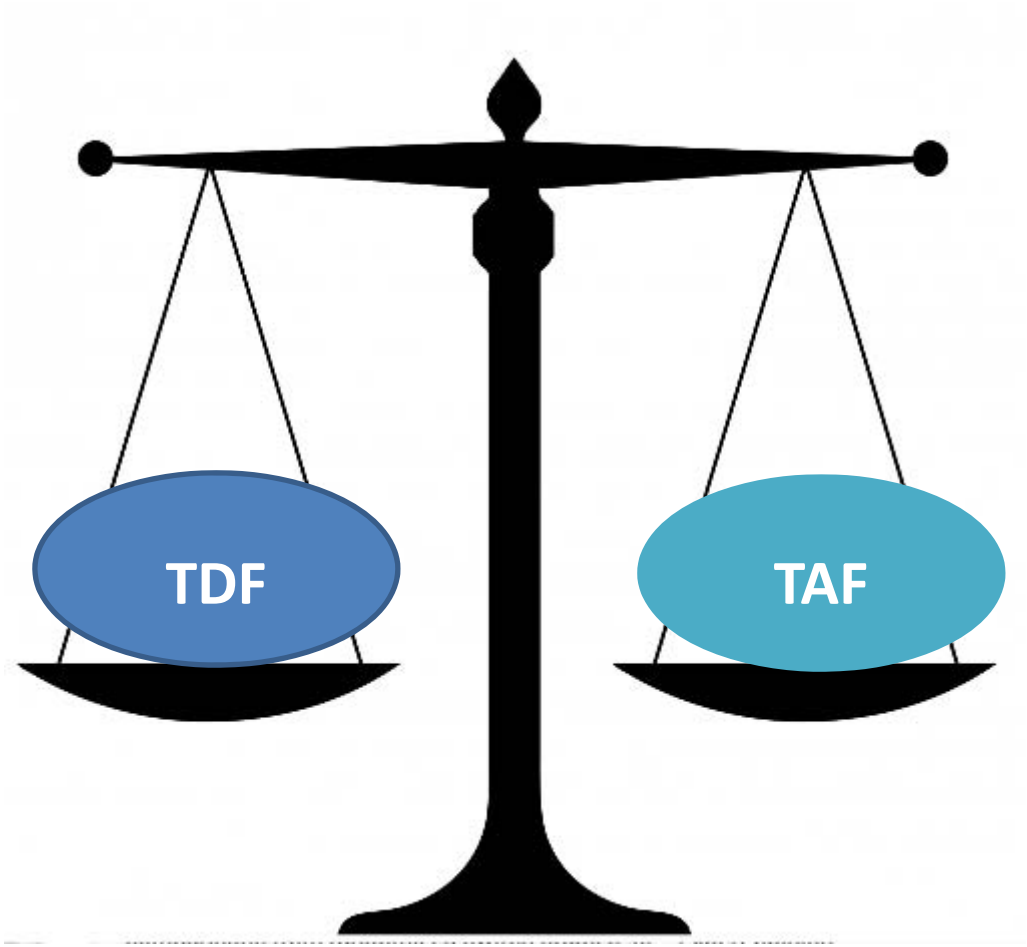
NRTI BACKBONE

NRTI: Tenofovir-DF vs Abacavir

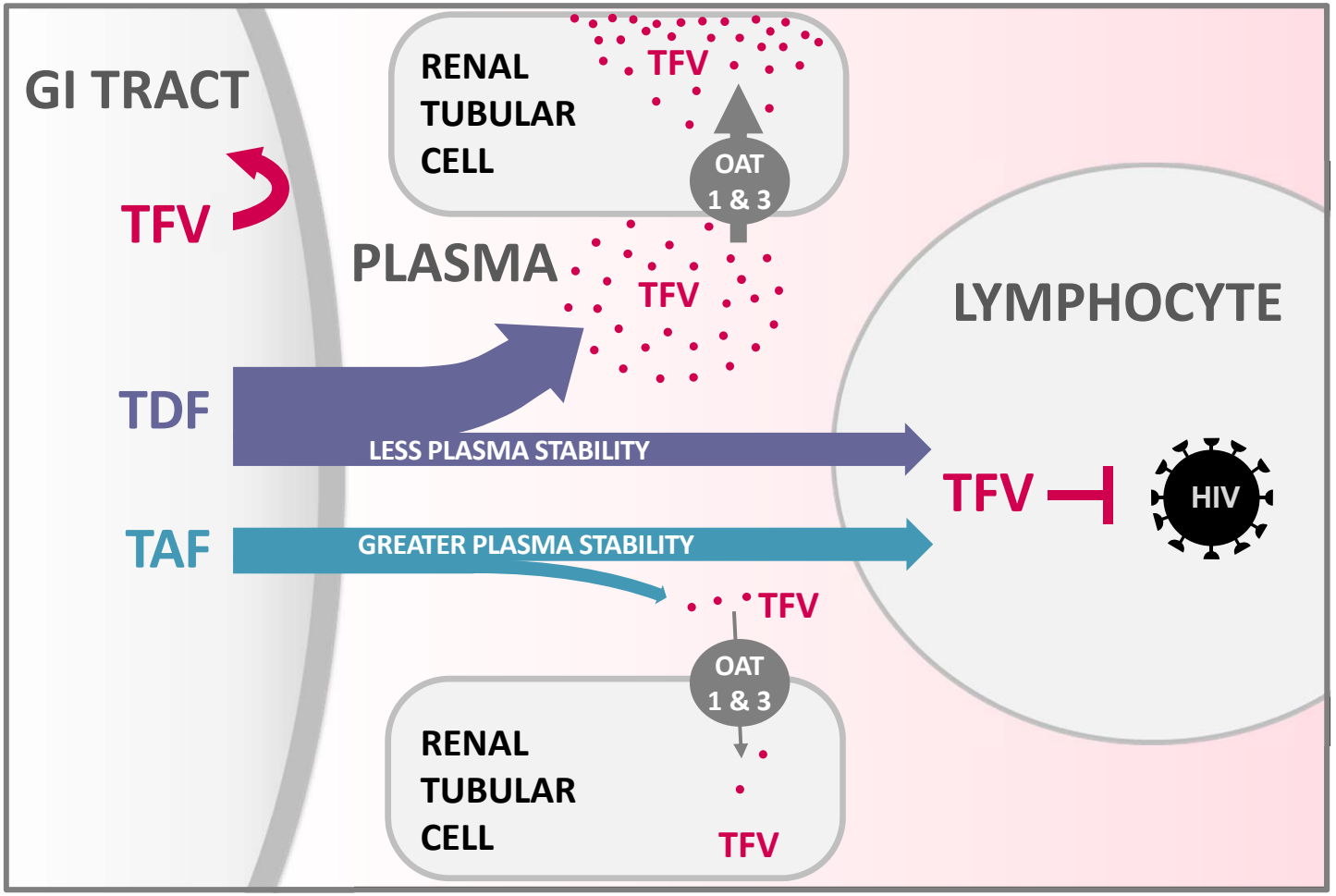


Sax PE, et al. NEJM 2009; 361:2230-2240
Sabin C *et al.* Lancet 2008; 371(9622): 1417-26

NRTI: Tenofovir-DF vs Tenofovir-AF



Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide



TAF 25 mg results in 80-90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

1. Sax P, et al. Lancet 2014 2. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5.

Clinical Trials Supporting FTC/TAF Use

Study	Pt Population	Treatment
GS-104/111[1]	Treatment naive (N = 1733)	Pts randomized to EVG/COBI/FTC/TAF* *or* EVG/COBI/FTC/TDF
GS-109[2]	Virologically suppressed on TDF-based regimen (N = 1436)	Pts switched to EVG/COBI/FTC/TAF* *or* remained on TDF-based regimen
GS-1089[3]	Virologically suppressed on FTC/TDF + third ARV (N = 663)	Pts switched to FTC/TAF† + continued third ARV *or* remained on FTC/TDF + third ARV
GS-112[4]	Virologically suppressed on varied regimens; stable $eGFR_{CG}$ 30-69 mL/min (N = 242)	Pts switched to EVG/COBI/FTC/TAF*

* EVG/cobi/FTC/TAF dosing: 150/150//200/10 mg.
†FTC/TAF dosing: 200/10 mg with boosted PIs; 200/25 mg with unboosted third drug as per SmPC

1. Sax PE, et al. Lancet. 2015;385:2606-2615. 2. Mills A, et al. Lancet Infect Dis. 2016;16:43-52. 3. Gallant JE, et al. Lancet HIV. 2016;3:e158-e165. 4. Pozniak A, et al. J Acquir Immune Defic Syndr. 2016;71:530-537.

Overall Week 144: Renal Events Leading to Discontinuation

Reason for Treatment Discontinuation	E/C/F/TAF n	E/C/F/TDF n
Total Renal Event Discontinuations	**0**	**12**
Creatinine increased and GFR decreased	0	1
Reduced GFR	0	1
Fanconi syndrome + glycosuria	0	1
Nephropathy	0	1
Proteinuria	0	1
Renal failure	0	2
Renal tubular disorder	0	3
Creatinine increased + bone density decreased	0	1
Bladder spasm	0	1

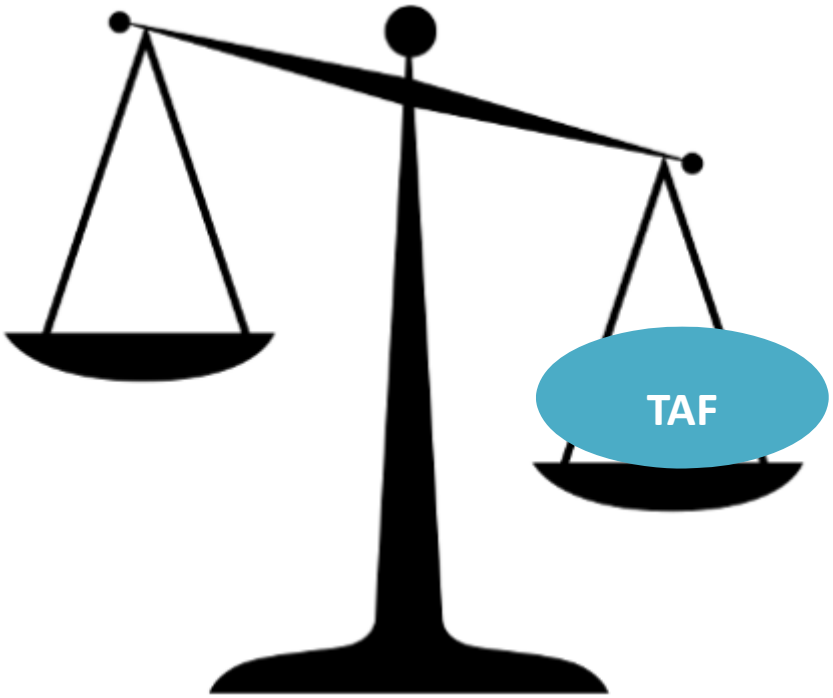
- On the E/C/F/TAF arm through 144 weeks there were
  - No cases of renal tubulopathy (including Fanconi Syndrome) vs. 2 for E/C/F/TDF
  - No discontinuations due to renal AE vs. 12 for E/C/F/TDF ($p<0.001$)

Ward, D. et al. HIV and Aging 2016. Washington, DC. #33

TDF vs TAF

- Renal
  - TAF has greatest safety benefits in patients at high risk of ren… …n co-morbidities) or with est… …e
  - Patients wi… …isease show less marked im… …function
- Bone
  - Individuals … …al density or high fracture risk are most likely to benefit from TAF over TDF

TAF vs no TAF?



THE FUTURE OF ART

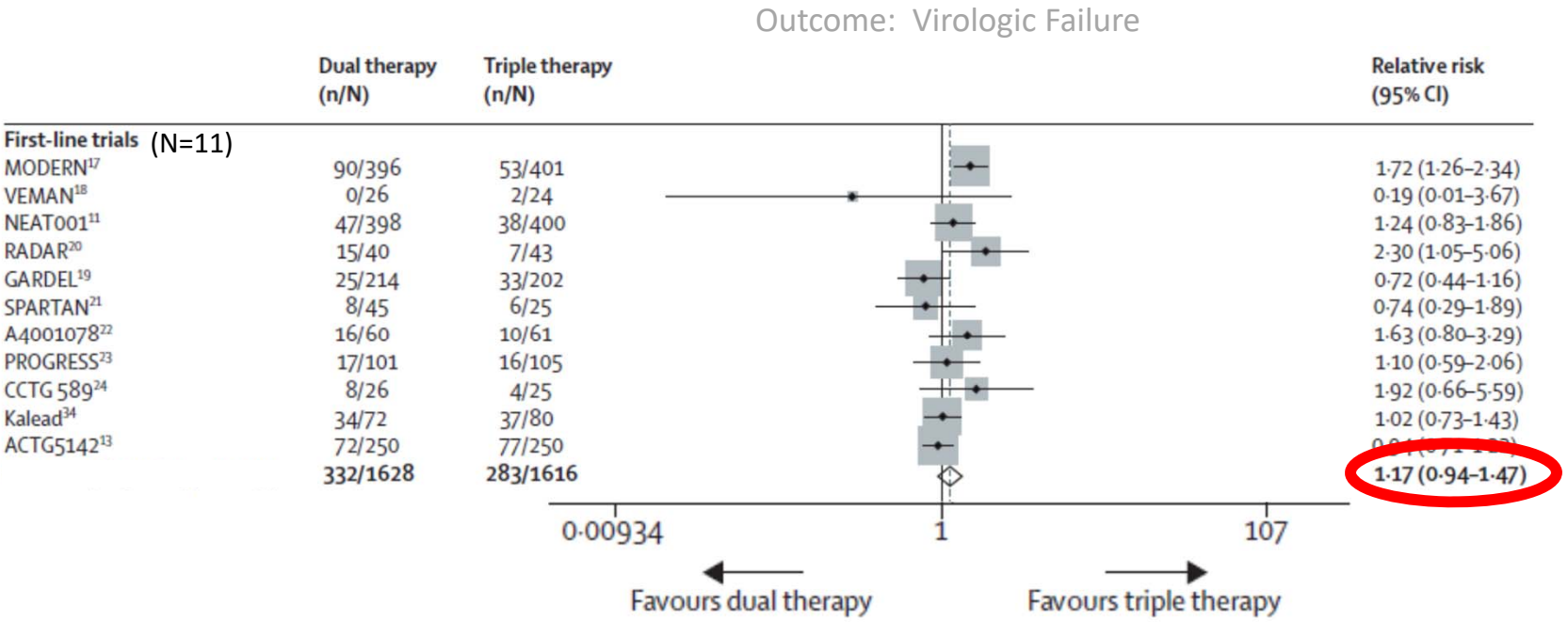
The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline**

The future of ART

- Decreasing ART exposure
  - Decreasing drug dose
  - Decreasing dosing frequency
  - **Decreasing numbers of drugs***
- Different ART formulations
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- Pipeline*

Meta-Analysis: 2-drug Initial ART Regimens (2008-15)



For baseline HIV RNA >100,000: RR 1.24 (95% CI: 1.03, 1.49)
For resistance mutations: RR 2.04 (95% CI: 1.23, 3.39)

Achhra *et al*. Lancet HIV 2016;3:e351-e360.

Why revisit 2DR?

- More efficacious, high barrier regimens
  - Including unboosted
- Increasing concern about NRTI toxicities
- ?Lower costs
- Less drug exposure
  - Ageing, multimorbidity, polypharmacy

2 drug regimen (2DR)-naïve studies DTG +3TC

PADDLE[1] (n=20)

- ART-naïve VL 5-100K
- All suppressed VL<50 by week 8
- 18/20 (96%) suppressed through week 96
  - 1 had VL 99→246→61 with no RT mutations, then resuppressed
  - 1 had adverse event (suicide) between weeks 24 and 36

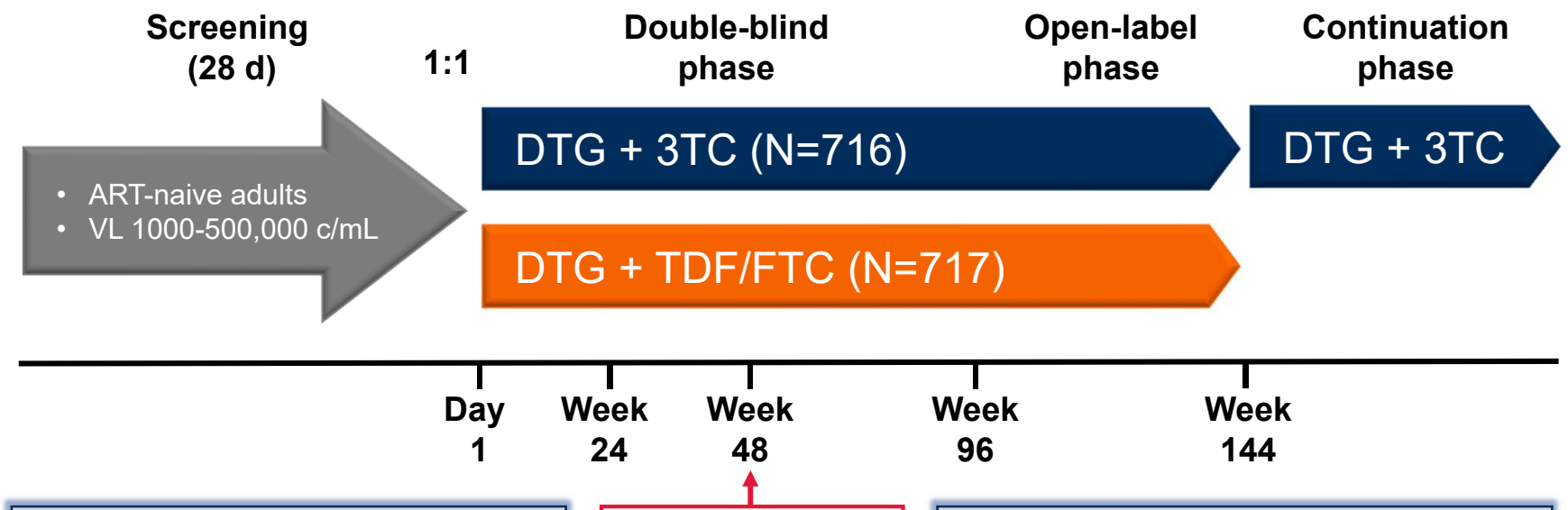
ACTG 5353[2] (n=120)

- Single-arm study DTG + 3TC
- >100,000 c/mL vs <100,000 c/mL randomization
- 90% <50 at week 24
- Three PDVFs
- n=1 [emergent M184V, R263R/K]

[1]Cahn P et al. JIAS 2017;20:1-7
[2]Taiwo BO et al. CID 2018;66:1689

GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Eligibility criteria
- ≤10 days of prior ART
- No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E snapshot)[a]

Countries

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

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3).

[a]–10% noninferiority margin for individual studies.

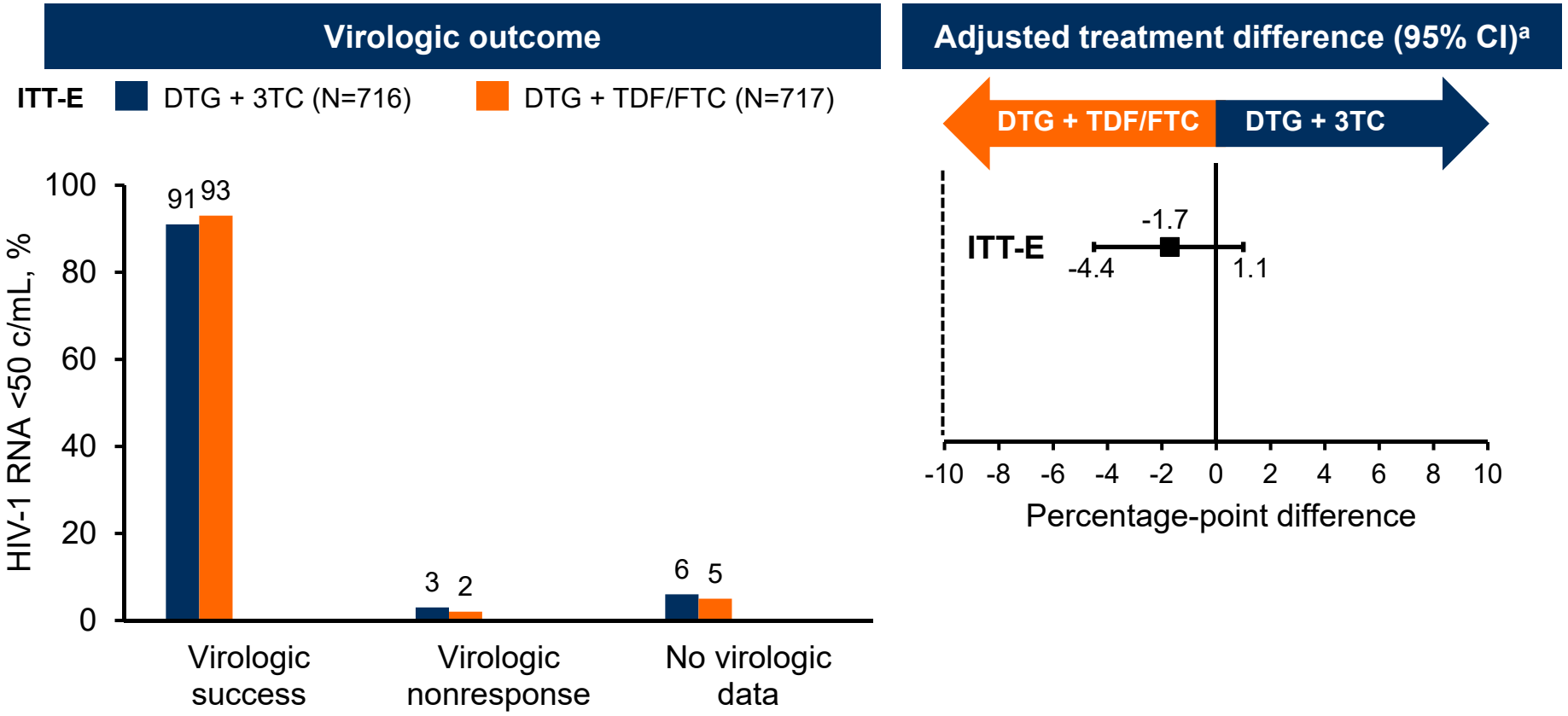
Cahn P et al. AIDS 2018; Amsterdam. Abstract TUAB0106LB

Demographic and Baseline Characteristics

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	63 (9)	55 (8)

[a]2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL

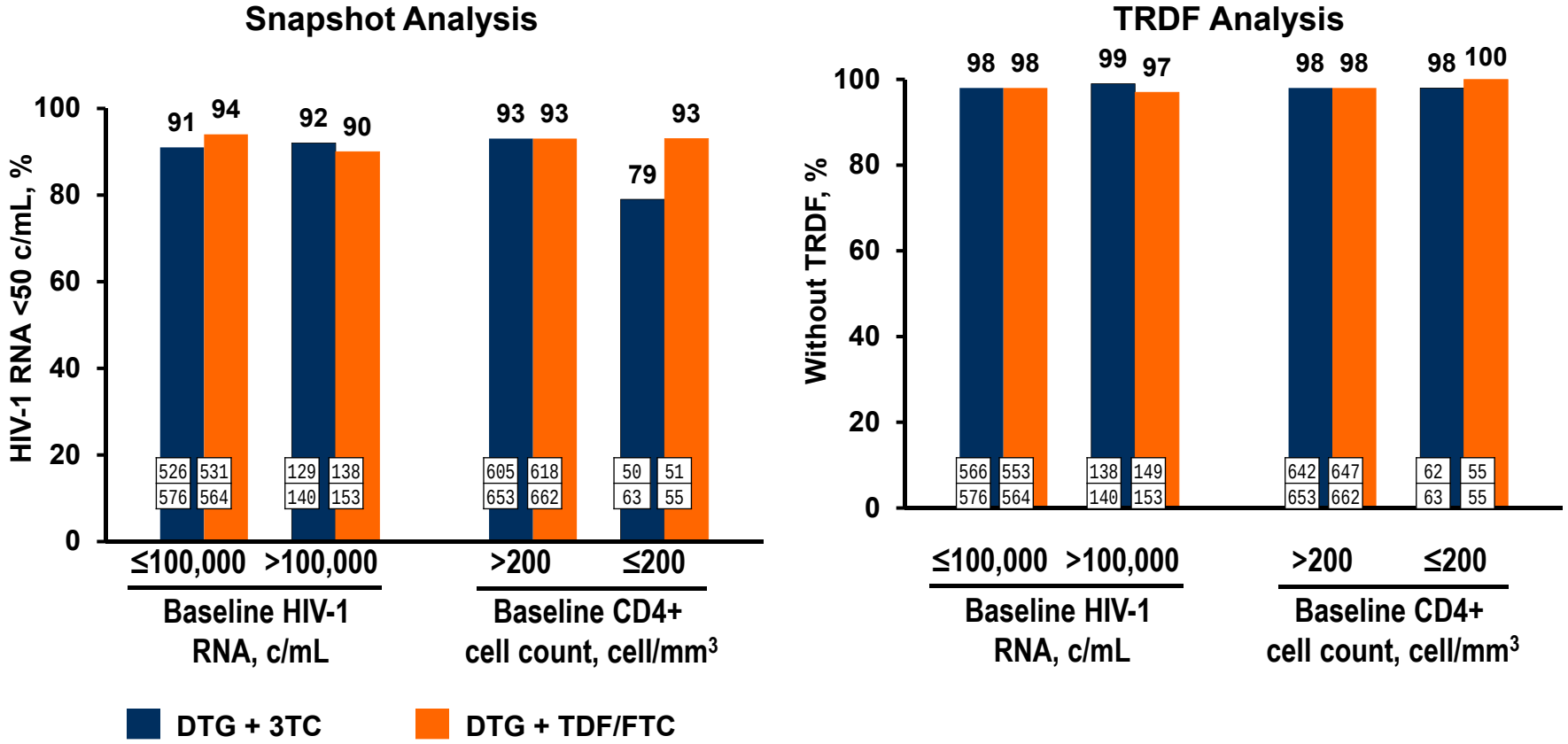
Pooled Snapshot Outcomes at Week 48: ITT-E Population



[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL), CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).

Cahn P et al. AIDS 2018; Amsterdam. Abstract TUAB0106LB

Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis



- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
- Treatment related discontinuation = failure (TRDF) population accounts for confirmed virologic withdrawal (CVW), withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria
- DTG + 3TC CD4 <200 Snapshot non-response (n=13): **1 CVW**, 3 with VL >50 in window **(2 of 3 re-suppressed),** 2 discontinued due to AE (TB, Chagas disease), 2 protocol violations, 2 lost to follow-up, 1 withdrew consent, 1 withdrew to start HCV treatment, 1 change in ART (incarcerated)
- DTG + TDF/FTC < 200 Snapshot non-response (n=4):1 investigator discretion, 1 withdrew consent, 1 lost to follow-up, 1 VL >50 (re-suppressed)

Cahn P et al. AIDS 2018; Amsterdam. Abstract TUAB0106LB

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

Variable, n (%)	GEMINI 1		GEMINI 2		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

.

Cahn P et al. AIDS 2018; Amsterdam. Abstract TUAB0106LB

Adverse Events: Pooled ITT-E Population

n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	543 (76)	579 (81)
AE occurring in ≥5% of participants in either group		
Headache	71 (10)	75 (10)
Diarrhea	68 (9)	77 (11)
Nasopharyngitis	55 (8)	78 (11)
Upper respiratory tract infection	56 (8)	44 (6)
Nausea	27 (4)	53 (7)
Insomnia	27 (4)	45 (6)
Pharyngitis	36 (5)	32 (4)
Back pain	35 (5)	31 (4)
Drug-related AE	126 (18)	169 (24)
Grade 2-4 AE occurring in ≥1% of participants	42 (6)	47 (7)
Headache	8 (1)	8 (1)
AE leading to withdrawal from the study	15 (2)	16 (2)
Neuropsychiatric AEs leading to withdrawal	6 (<1)	4 (<1)
Any serious AE[a]	50 (7)	55 (8)

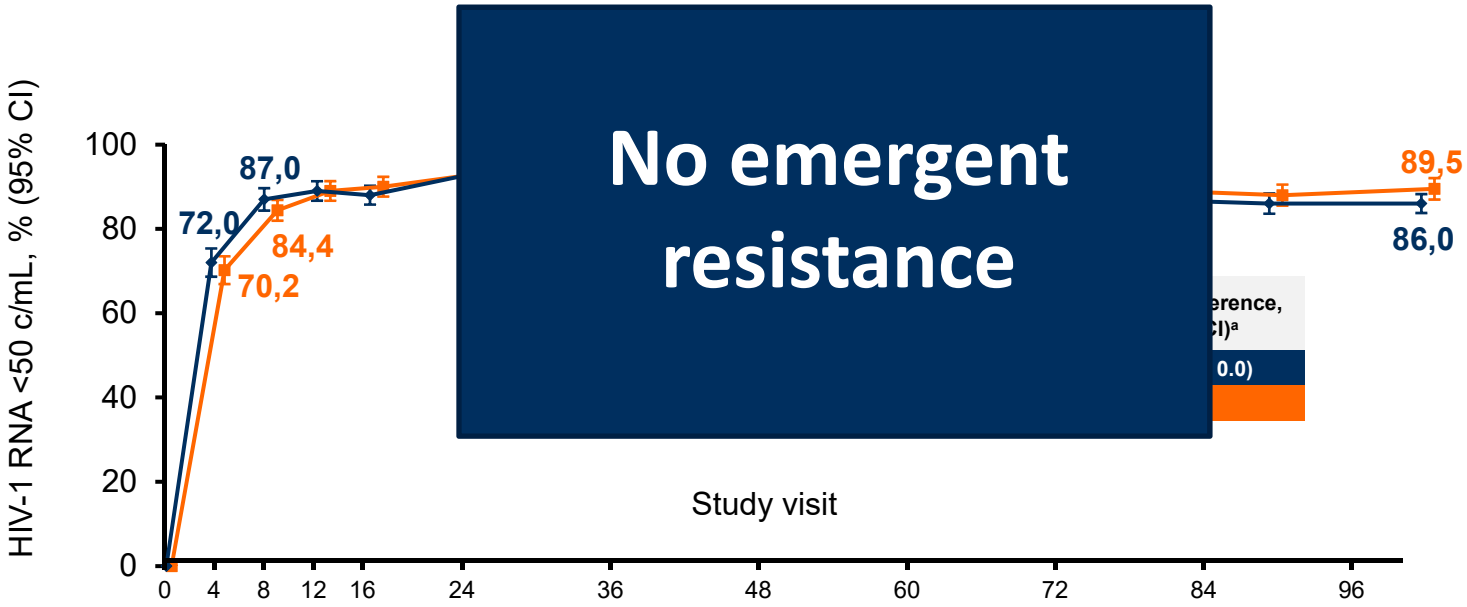
[a]2 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1) in the GEMINI-2 study; both were in the DTG + 3TC group and were considered unrelated to the study drug regimen.

Conclusions

- GEMINI-1 and-2 results demonstrate non-inferior virologic efficacy for the 2DR DTG + 3TC versus the 3DR DTG + TDF/FTC at Week 48
- Both DTG + 3TC and DTG + TDF/FTC were associated with low rates of confirmed virologic withdrawals through Week 48
  - No treatment-emergent INSTI or NRTI mutations were observed among participants who met CVW criteria
- Overall safety and tolerability profile at Week 48 was comparable between the 2 regimens
  - Fewer drug-related AEs with DTG + 3TC
  - Change in renal and bone biomarkers significantly favors DTG + 3TC

GEMINI: DTG+3TC non-inferior to DTG+TDF/FTC

Snapshot VL<50 c/mL at W96



Non-inferiority criteria were met for GEMINI-1, GEMINI-2, and the pooled analysis[b]

Implications for clinical practice

- Strategy may reduce potential toxicities and cost but who are the best candidates for dual therapy?
- ?applicability in resource limited settings (Hep B)
- Role of dual therapy in more complex situations is unclear
  - High VL (?and CD4<200)
  - Comorbidities including TB
  - Pregnancy
  - Same day ART initiation (no VL/no resistance)

Emerging 2-drug ART Regimens in treatment-naïve individuals

ANDES[1] (n=145)

- DRV/r + 3TC vs DRV/r + TDF/3TC (open label)
- 93% VL<50 at wk48
- One PDVF on DRV/r + TDF/3TC
- 2DR non-inferior to 3DR

ISLATRAVIR (MK-8591) + Doravirine[2]

- Phase 2 study: doravirine + 3TC + islatravir (0.25, 0.75 or 2.25mg) vs doravirine/TDF/3TC for 24 weeks, then drop 3TC in islatravir arms
- Good viral suppression to W48

[1]Figueroa MI et al. CROI 2018. Boston, MA. Poster #489
[2]Molina JM et al. IAS 2019. Mexico. Abstract WEAB0402LB

Current Guidelines

DHHS (2019)

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

Regimens to Consider … re Not Optimal:

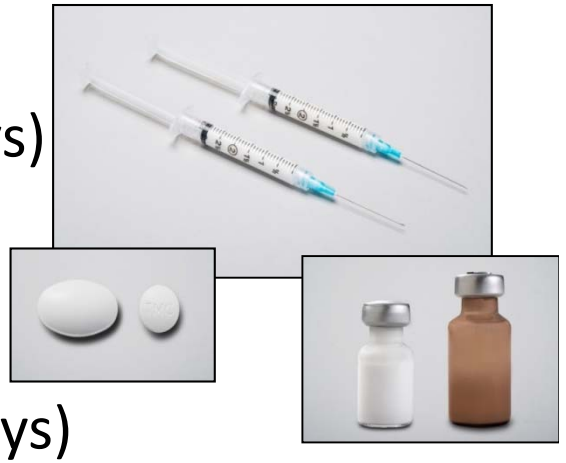
- DTG plus 3TC (BI…
- DRV/r plus RAL E… CD4 cell count >200 cells/mm^3
- DRV/r once daily…

The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline***

Long-acting injectables

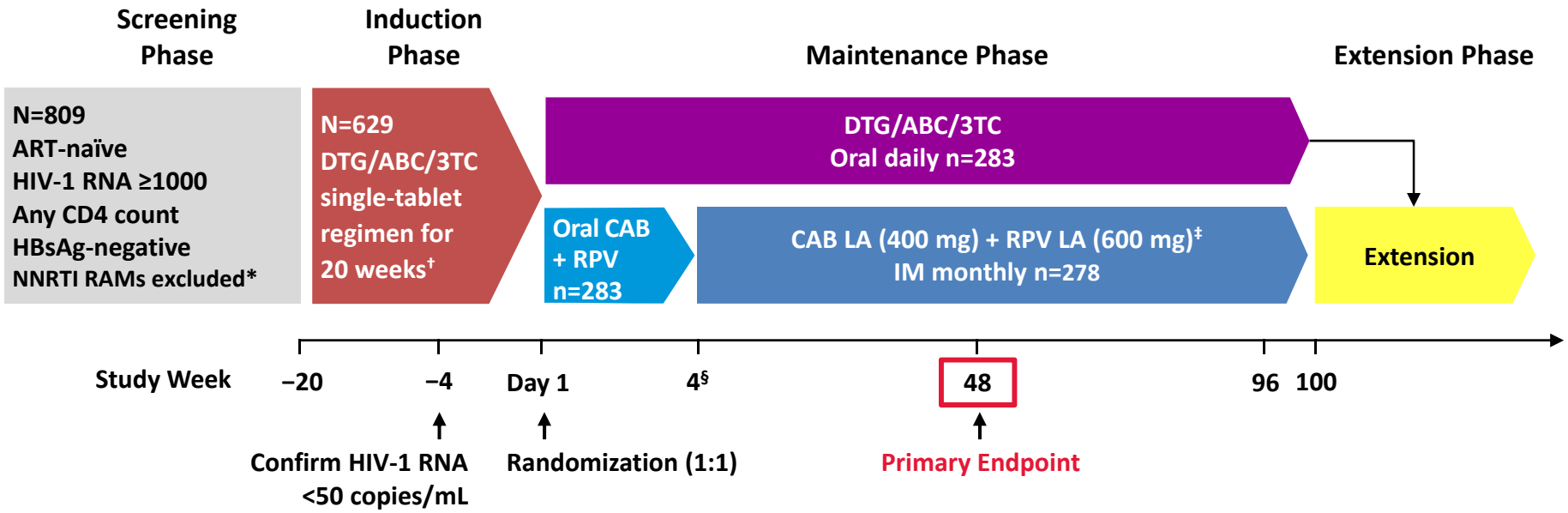
- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - Oral 30mg tablet ($t_{1/2}$ ~ 40 hours)
  - IM LA injection 200 mg/ml ($t_{1/2}$~20-40 days)
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25mg tablet ($t_{1/2}$ ~ 50 hours)
  - IM LA injection 300mg /ml ($t_{1/2}$ ~ 30-90 days)



- LATTE-2: CAB LA + RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years[1]
- Two phase 3 studies (ATLAS[2] and FLAIR) have reached their primary endpoints at 48 weeks

[1]Margolis D et al. HIV Glasgow 2018
[2]Swindells S et al. CROI 2019; Seattle, WA, Abstract 1475

FLAIR: Randomised Open-label Study in ART-Naïve Adults



3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; IM, intramuscular; HBsAg, hepatitis B surface antigen; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine.

*NNRTI RAMS but not K103N were exclusionary; †DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive (n=30 as last regimen during induction: n=2 discontinued during induction, n=14 randomized to CAB LA + RPV LA, n=14 randomized to DTG/ABC/3TC arm and continued on DTG plus 2 alternative non-ABC NRTIs in Maintenance Phase); ‡Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up; §Participants received initial loading doses of CAB LA 600 mg and RPV LA 900 mg at Week 4. Beginning Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections every 4 weeks.

Orkin C et al. CROI 2019; Seattle, WA, Abstract 3947

FLAIR Objectives and Endpoints

Objective

- Establish noninferior antiviral activity of monthly IM CAB LA + RPV LA vs continuing DTG/ABC/3TC

Primary endpoint

- Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48 using the FDA Snapshot algorithm
  - 6% noninferiority margin on difference between groups

Selected secondary endpoints

- HIV-1 RNA <50 copies/mL at Week 48 (Snapshot)*
- Safety and tolerability
- Viral resistance associated with CVF†
- Patient-reported outcomes‡

Selected exploratory endpoint

- Participant-reported preferences of the LA regimen§

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; FDA, Food and Drug Administration; IM, intramuscular; LA, long-acting; RPV, rilpivirine.

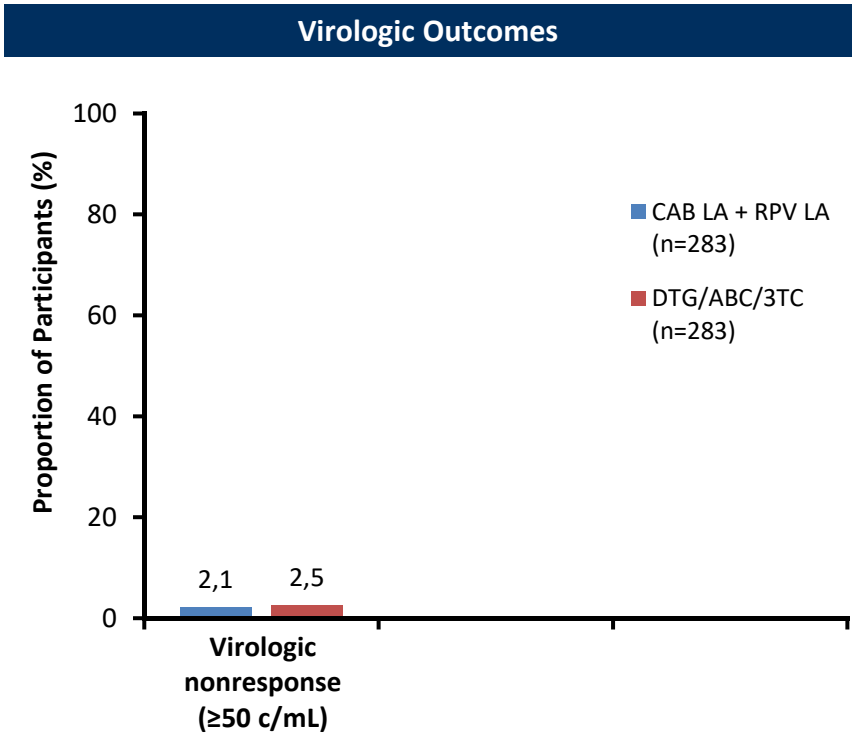
*Predefined key secondary endpoint; †Defined as 2 consecutive HIV-1 RNA measurements ≥200 copies/mL; ‡HIVTSQc, HIV Treatment Satisfaction Questionnaire (Change version); §Single-item question for participant-reported preference on the LA and daily oral regimen.

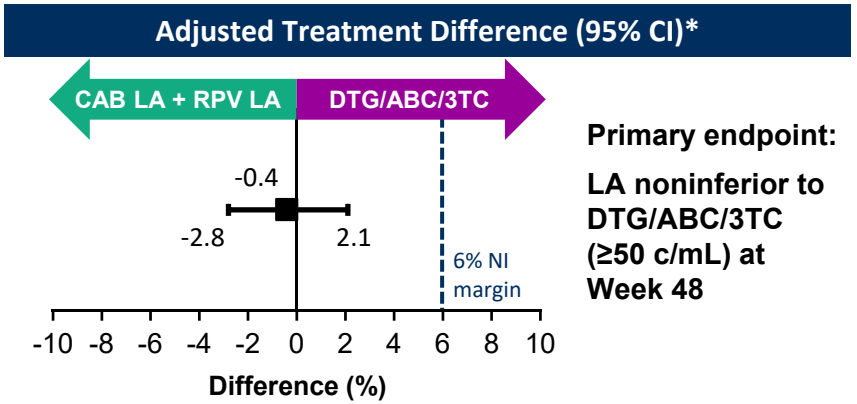
FLAIR Baseline* Characteristics: ITT-E Population

Parameter	CAB LA + RPV LA N=283	DTG/ABC/3TC N=283	Total N=566
Median age (range) – year	34 (19–68)	34 (18–68)	34 (18–68)
Age ≥50 years – n (%)	33 (12)	29 (10)	62 (11)
Female – n (%)	63 (22)	64 (23)	127 (22)
Race – n (%)			
White	216 (76)	201 (71)	417 (74)
Black or African American	47 (17)	56 (20)	103 (18)
Other or missing	20 (7)	26 (9)	46 (8)
Median body mass index (range) – kg/m^2	24 (17–45)	24 (13–47)	24 (13–47)
HIV-1 RNA, copies/mL – n (%)			
<100,000	227 (80)	227 (80)	454 (80)
≥100,000	56 (20)	56 (20)	112 (20)
Median baseline CD4+ cell count (IQR) – cells/mm^3	437 (314, 609)	452 (321, 604)	444 (320, 604)
<200 cells/mm^3 – n (%)	16 (6)	23 (8)	39 (7)
Median Day 1 CD4+ cell count (IQR) – cells/mm^3	624 (473, 839)	625 (472, 799)	625 (473, 818)
HIV-1–HCV co-infection – n (%)	19 (7)	9 (3)	28 (5)

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; DTG, dolutegravir; HCV, hepatitis C virus; IQR, interquartile range; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.
*Baseline was Week −20 .

FLAIR Virologic Snapshot Outcomes at Week 48





Primary endpoint:

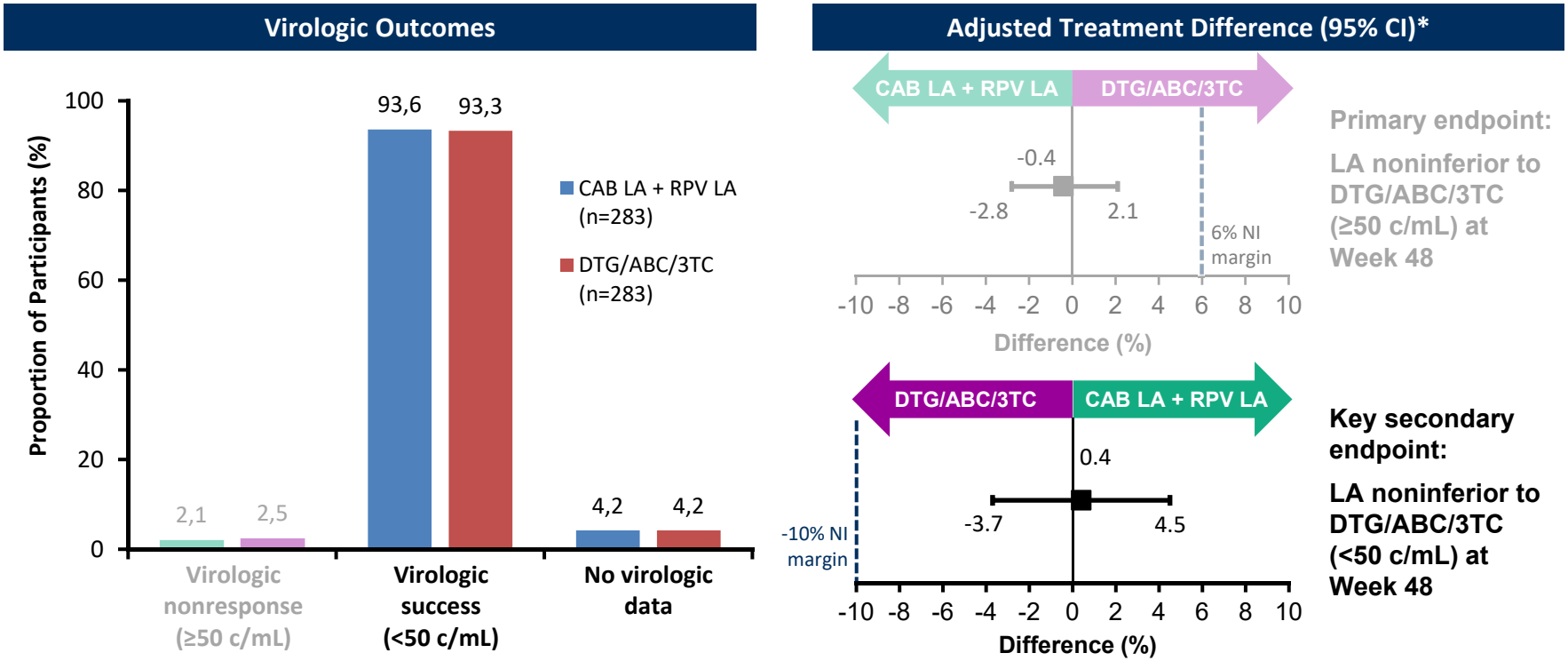
LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

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

FLAIR Virologic Snapshot Outcomes at Week 48:

Noninferiority Achieved for Primary and Secondary Endpoints



3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

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

FLAIR Snapshot Outcomes at Week 48

n (%)	CAB LA + RPV LA N=283	DTG/ABC/3TC N=283
HIV-1 RNA <50 copies/mL	**265 (93.6)**	**264 (93.3)**
HIV-1 RNA ≥50 copies/mL	**6 (2.1)**	**7 (2.5)**
Data in window not below threshold	2 (0.7)	2 (0.7)
Discontinued for lack of efficacy	4 (1.4)	3 (1.1)
Discontinued for other reason while not below threshold	0	2 (0.7)*
No virologic data	**12 (4.2)**	**12 (4.2)**
Discontinued due to AE†	8 (2.8)	2 (0.7)
Discontinued for other reasons‡	4 (1.4)	10 (3.5)

3TC, lamivudine; ABC, abacavir; AE, adverse event; CAB, cabotegravir; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

*Relocation (1), lost to follow-up (1); †LA arm: hepatitis A (1), acute hepatitis B (1), acute hepatitis C (1), transaminases increase (1), hepatitis A/secondary syphilis (1), injection site pain (1), injection site pain/discomfort/diarrhea/vomiting (1), adenocarcinoma of colon (1). DTG/ABC/3TC arm: renal failure (1), suicide attempt (1); ‡ LA arm: Tolerability of injections (1), incarceration (1), lost to follow up (2). DTG/ABC/3TC arm: frequency of visits (participant decision [4]), noncompliance with study treatment and protocol procedures (2), relocation (1), participant decision to stop treatment (1), late to attend visits (1), lost to follow up (1).

FLAIR Confirmed Virologic Failures: CAB LA + RPV LA Arm

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

- Plasma CAB and RPV concentrations at the time of failure were below the population means but within the range for the large majority of individuals who maintained virologic suppression
- One additional participant had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy had suspected VF that was confirmed
- Three participants in the DTG/ABC/3TC arm had CVF at Weeks 8, 12, and 16, respectively; no drug resistance mutations were selected

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure; VF, virologic failure.
*L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity; †Monogram biological /clinical cutoffs are: RPV=2.0, CAB=2.5, and DTG=4.0.

FLAIR Adverse Events (Excluding ISRs)

	CAB LA + RPV LA N=283	DTG/ABC/3TC N=283
Any AE (≥10%), n (%)		
Any event (per participant)	246 (87)	225 (80)
Nasopharyngitis	56 (20)	48 (17)
Headache	39 (14)	21 (7)
Upper respiratory tract infection	38 (13)	28 (10)
Diarrhea	32 (11)	25 (9)
Drug-related AEs (≥3%), n (%)		
Any event (per participant)	79 (28)	28 (10)
Headache	14 (5)	4 (1)
Pyrexia	13 (5)	0
All AEs leading to withdrawal*	9 (3)	4 (1)

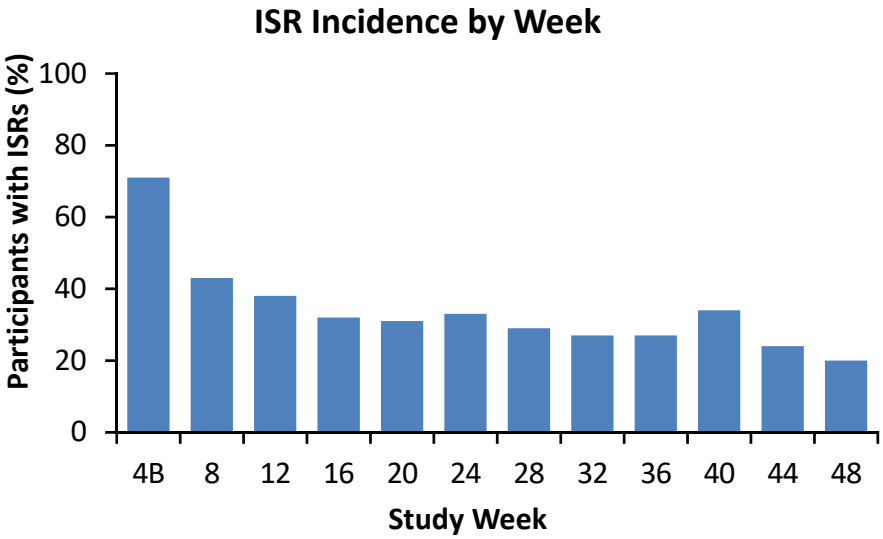
74/79 (94%) CAB LA + RPV LA participants had drug-related AEs at maximum grade 1 or 2

- **One drug-related SAE on CAB LA + RPV LA (right knee monoarthritis). None in DTG/ABC/3TC arm**
- **No cases of drug hypersensitivity or drug-induced liver injury observed**

3TC, lamivudine; ABC, abacavir; AE, adverse event; CAB, cabotegravir; DTG, dolutegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SAE, serious AE.

*Events leading to withdrawal included: CAB LA + RPV LA arm: acute hepatitis A (1), hepatitis B (2), hepatitis C (1), acute hepatitis A/secondary syphilis (1), injection site pain (1), injection site pain/general discomfort/diarrhea/vomiting (1), increased transaminases (1), and adenocarcinoma of colon (1); DTG/ABC/3TC arm: fatigue/nausea/dizziness (1), amnesia/disturbance in attention/dysarthria (1), suicide attempt (1), and renal failure (1).

FLAIR Injection Site Reactions



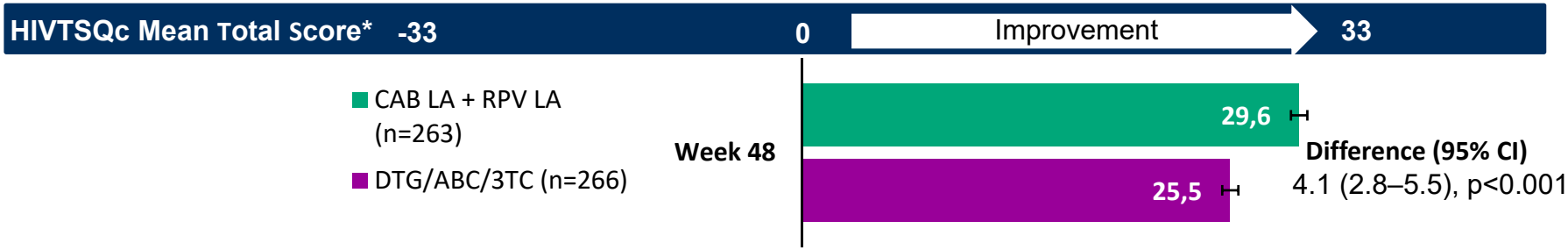
The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

Event	CAB LA + RPV LA N=283*
Participants receiving injections, n	278
Injections given, n	7704
ISR events, n (%)	2203 (28.6)
Pain	1879 (85.3)
Nodule	86 (3.9)
Induration	82 (3.7)
Swelling	38 (1.7)
Warmth	38 (1.7)
Grade 3 ISR pain	12 (<1)[†]
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	2 (<1)[‡]

CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.
*Table shows data up to Week 72; [†]No events worse than grade 3 were reported; [‡]ISR leading to withdrawal: 2 due to ISR pain. Two additional participants withdrew due to injection intolerability.

FLAIR: High Participant Satisfaction (HIVTSQc) and Preference for Injectable Therapy



Change in satisfaction with current treatment vs induction phase treatment was significantly higher for LA vs DTG/ABC/3TC

- HIVTSQs exhibited a ceiling effect, with very high baseline satisfaction scores in both groups (data not shown)[†]

Patient Preference Survey

Single-item question on participants' preference at Week 48:

- ITT-E population: 91% (257/283) preferred LA; 1% (2/283) preferred daily oral therapy
  - **Responding participants: 99% (257/259) preferred the LA regimen over previous oral therapy**

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; HIVTSQc, HIV Treatment Satisfaction Questionnaire (change version); HIVTSQs, HIV Treatment Satisfaction Questionnaire (status version); ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine; SE, standard error.

*Adjusted for baseline HIV-1 RNA (< vs ≥100,000 c/mL), sex, age, and race, ± SE. Based on observed dataset of participants who completed the questionnaire at Week 48 or early withdrawal;
[†]Maintenance (Day 1) HIVTSQs baseline mean score comparable between both arms with the same mean value of 59 out of 66 points.

FLAIR Conclusions

- Monthly CAB LA + RPV LA was noninferior to continued oral DTG/ABC/3TC at Week 48 for maintaining suppression of HIV-1
- Low confirmed virologic failure rate across both treatment arms: 1.4% vs 1.1%
  - Three participants on CAB LA + RPV LA had treatment-emergent resistance for NNRTI and INSTI at CVF. All harbored HIV-1 subtype A1, warranting further investigation
- Injection site reactions in the LA arm were common but mainly grade 1 or 2, with few associated discontinuations
- Highly positive treatment satisfaction and preference outcomes with LA regimen
- Overall, these results support the therapeutic potential of monthly CAB LA + RPV LA for maintenance after oral induction in previously ART-naïve individuals

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine.

Long-acting injectables: the future

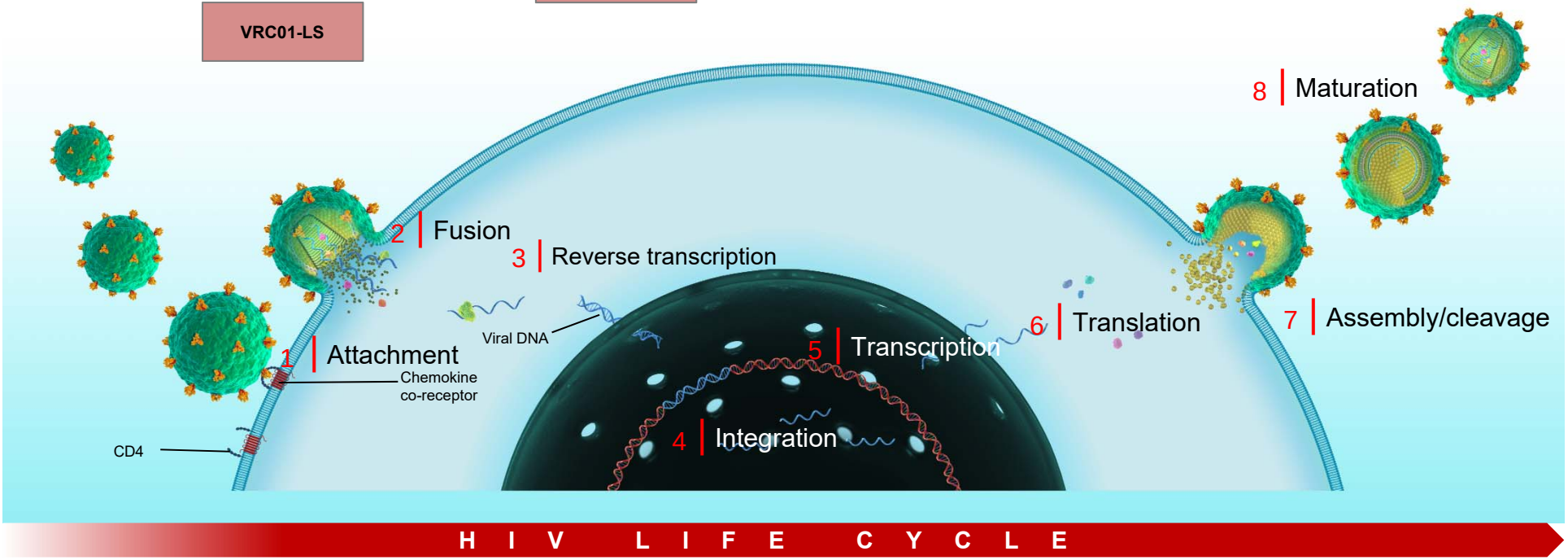
- Bi-monthly injections…
- Who will be the ideal candidates?
- Implementation: feasibility?
  - Where will people receive injections?
  - How to track injection schedules?

The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline***

HIV drug pipeline under clinical evaluation (Phase I–III)

Entry inhibitors	Monoclonal antibodies (mAb)	NRTIs/NtRTIs ('nukes')	NNRTIs ('non-nukes')	Integrase inhibitors	Protease inhibitors	Capsid inhibitors	Maturation inhibitors	Unique/ unknown MoA
Fostemsavir (GSK-934; FTR)	UB-421 (CD4 receptor)	Islatravir (MK-8591)	Elsulfavirine (VM1500)	Cabotegravir-LAI (GSK-744; CAB)	GS-PI1	GS-CA1	GSK2838232	MK-8507
Cenicriviroc (TBR-652; CVC)	PRO-140 (CCR5 receptor)	GS-9131	Rilpivirine-LAI (TMC278; RPV)	MK-2048				ABX464
Sifuvirtide (FS-0101)	Ibalizumab (TMB-355)		Dapivirine (TMC120; DPV)					LEDGINs
Albuvirtide (FB006M; ABT)	VRC01		PC-1005 (MIV-150/zinc acetate)					
	VRC01-LS							



H I V L I F E C Y C L E

Thank you

- Chloe Orkin
- Laura Waters
- ViiV