Second 95-95-95: What to Start?

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Chonburi, Rayong,

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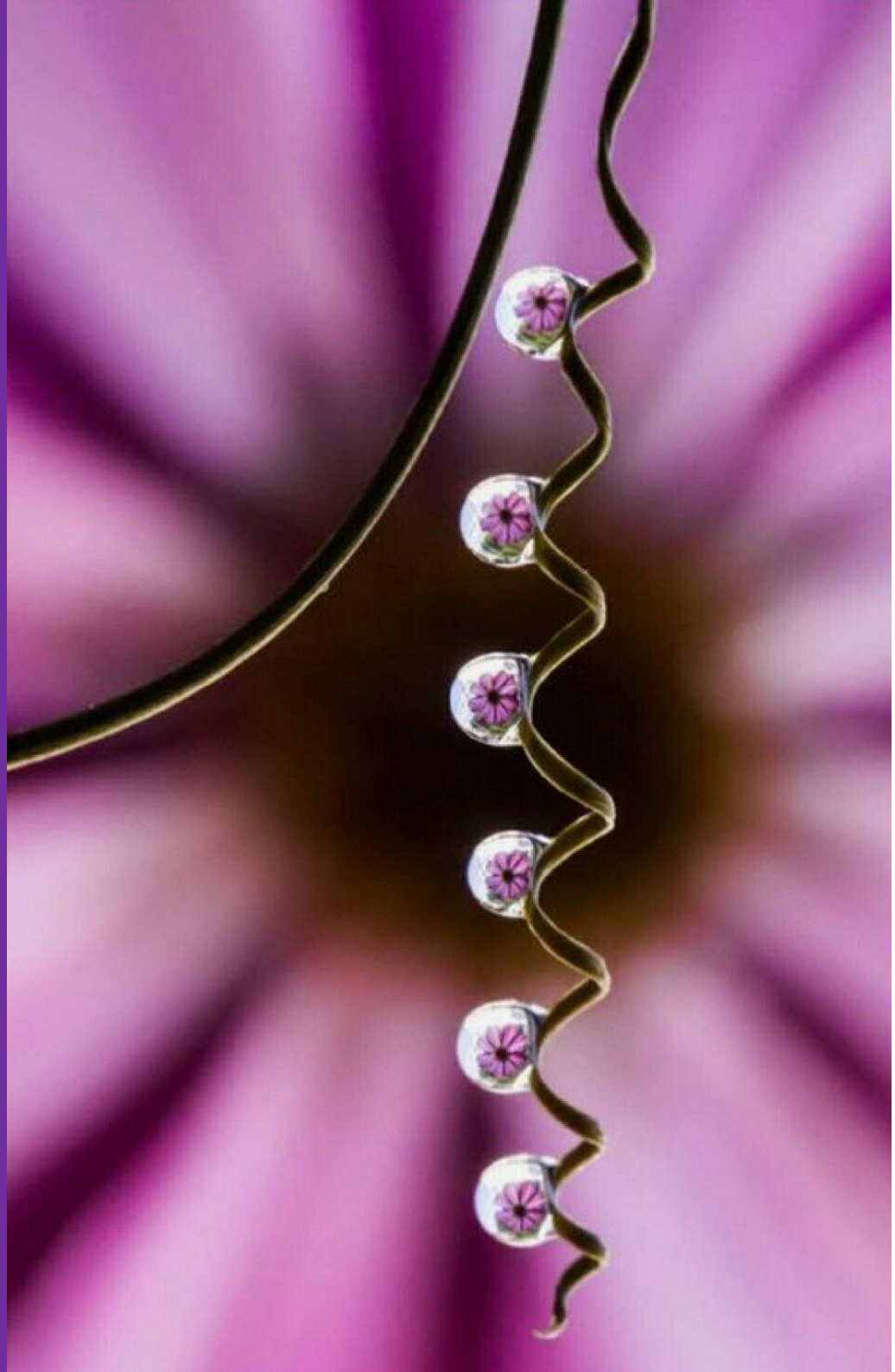
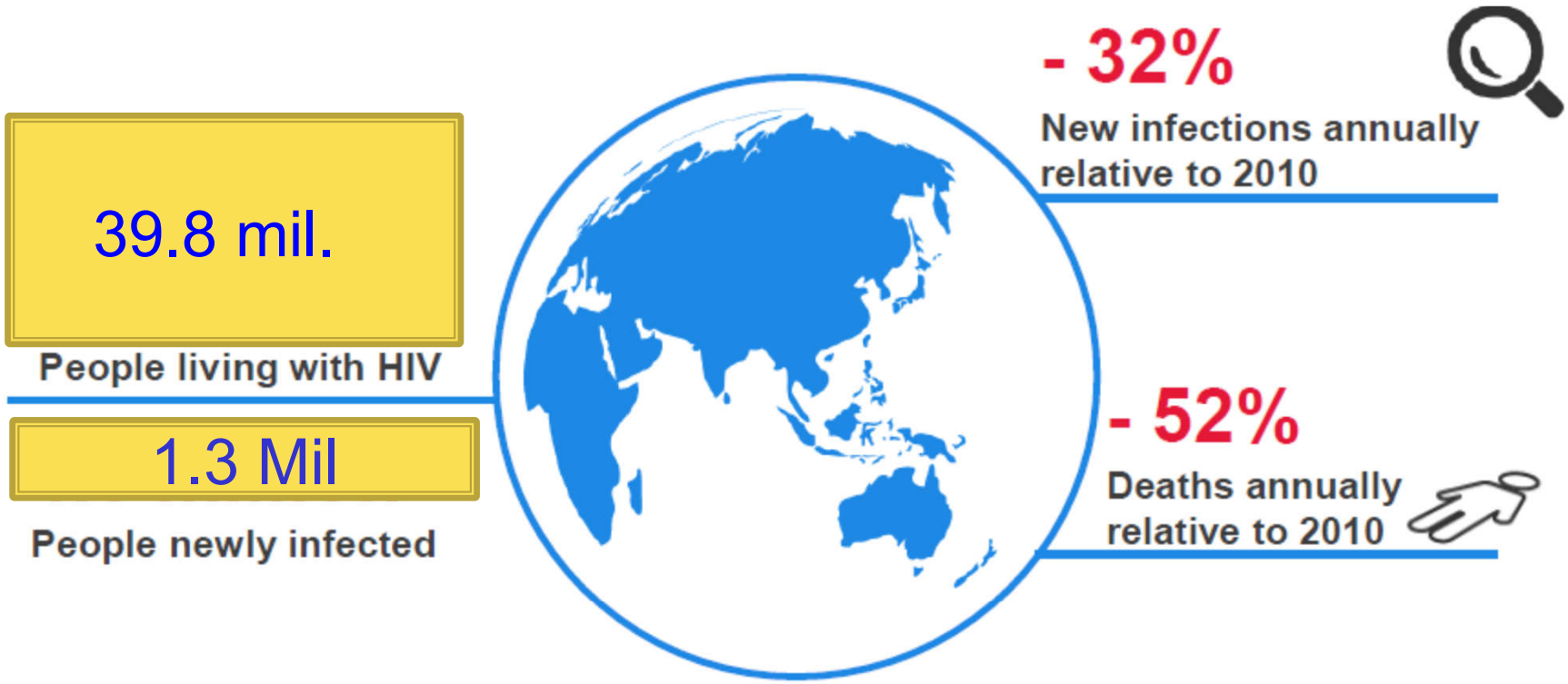
All patients who permitted

their clinical for presentations



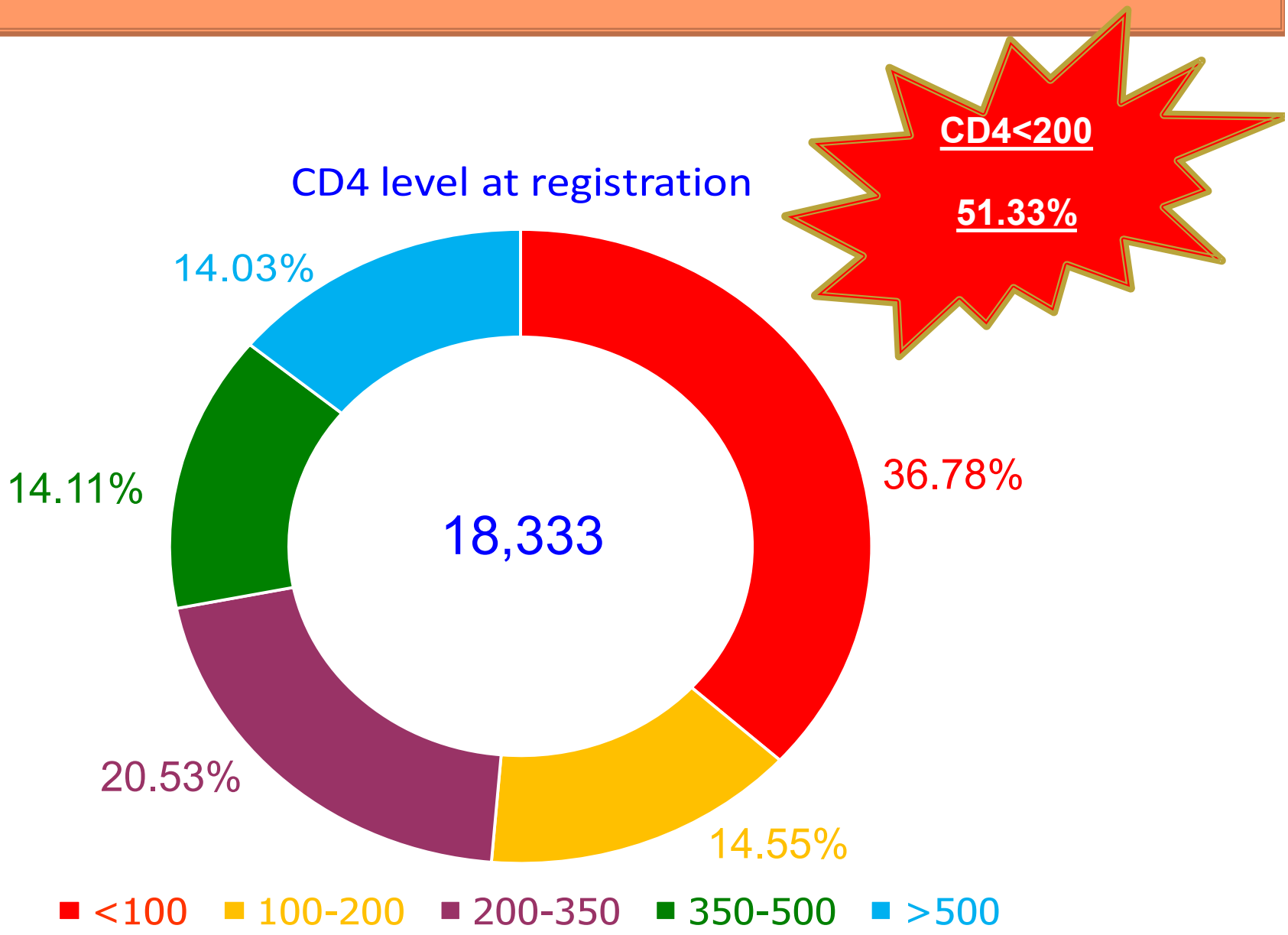
Global HIV Epidemic: 2022



630,000 People died from AIDS-related illnesses

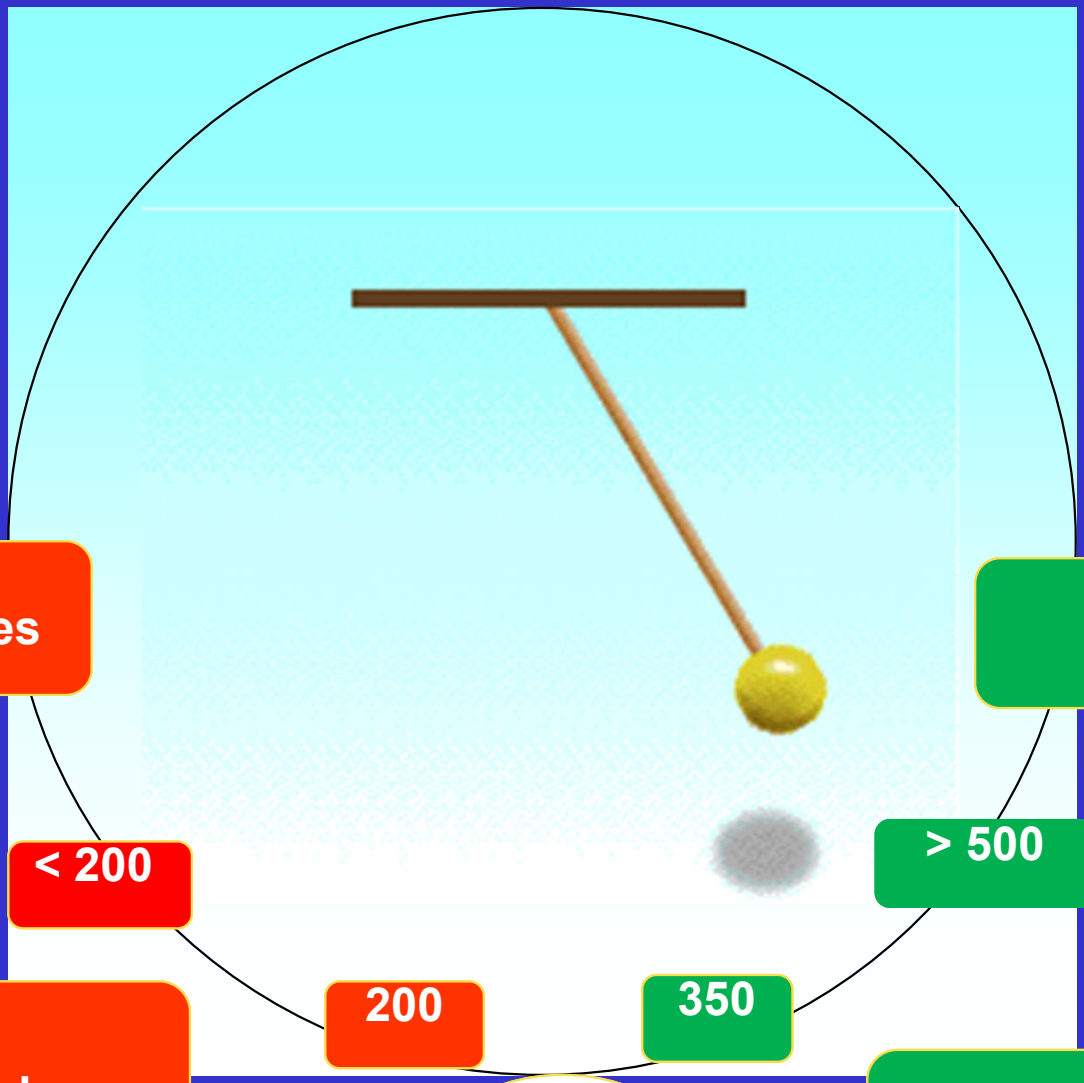
UNAIDS/WHO 2023

New HIV Patients Registered in National AIDS Program (NAP) 2022



When to Start?

When to Start?



Late clinical stages

Early clinical stages

< 200

> 500

200

350

Any viral load

High viral load

CD4

Adapted from Schechter M, *JID* 2004;**190**:1043-1045

START Study
(Strategic Timing of Antiretroviral Treatment

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

CONCLUSIONS

The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter. (Funded by the National Institute of Allergy and Infectious Diseases and others; START ClinicalTrials.gov number, NCT00867048.)

Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asyr mmunodeficiency virus (HIV) infection who have a CD4+ co) cells per cubic millimeter.

The members of the writing group (Jens D. Lundgren, M.D. [cochair], Abdel G. Babiker, Ph.D. [cochair], Fred Gordin, M.D. [cochair], Sean Emery, Ph.D., Birgit Grund, Ph.D., Shweta Sharma, M.S., Anchalee Avihingsanon, M.D., David A.

When to Start?

As soon as possible, same day ART

ART is recommended for all pts to reduce disease progression

CD4 > 500 cell/mm3 (AI) START Study

ART is also recommended to prevent HIV transmission

Perinatal transmission (AI)

Heterosexual transmission (AI) (HPTN 052 Study)

What to Start?

What to Start?

Old

1.NRTI (1987)

2.PI (1995)

3.NNRTI (1996)

4.Fusion inhibitors (2003)

5.CCR5 inhibitors (2007)

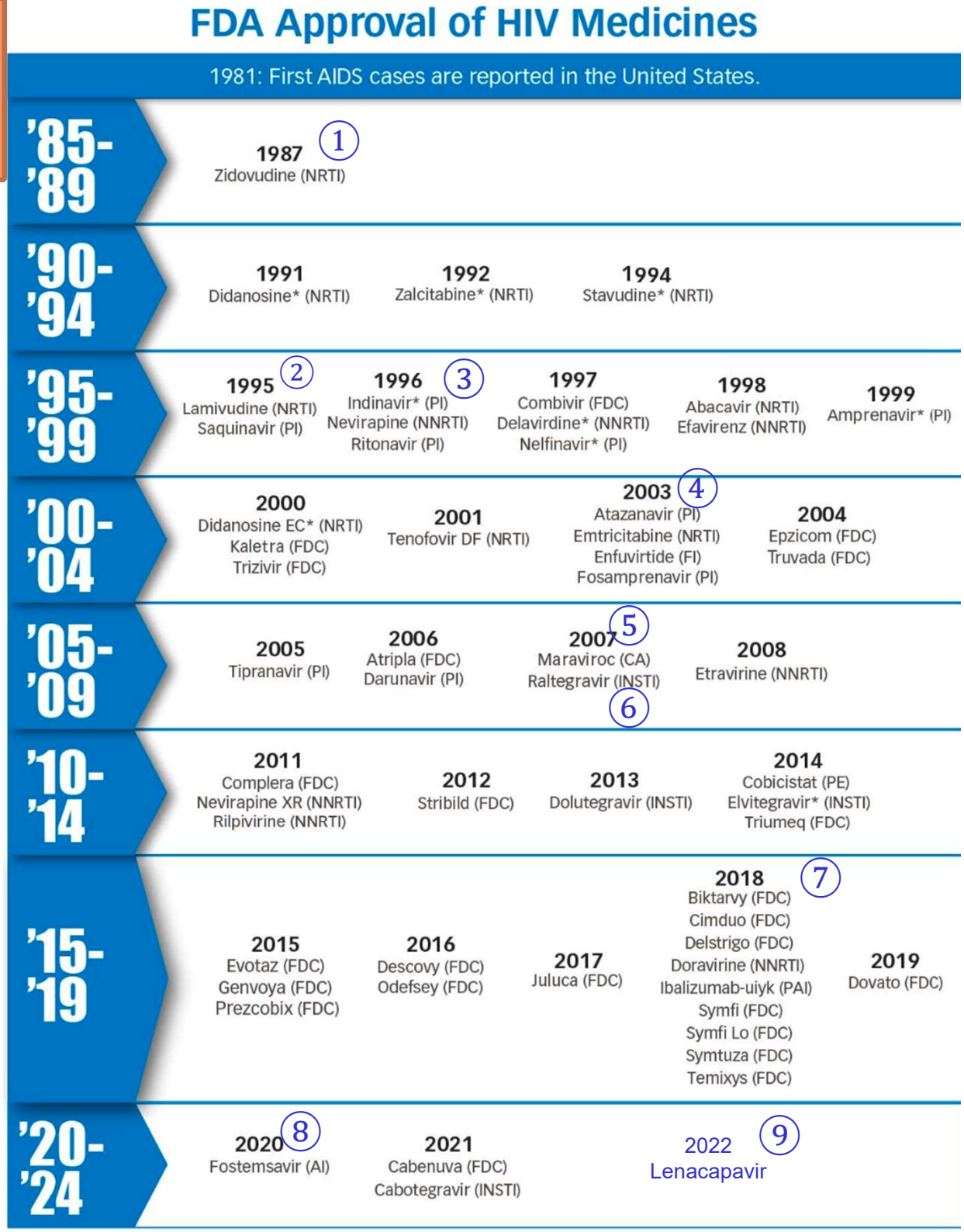
6.INSTI (2007).

New

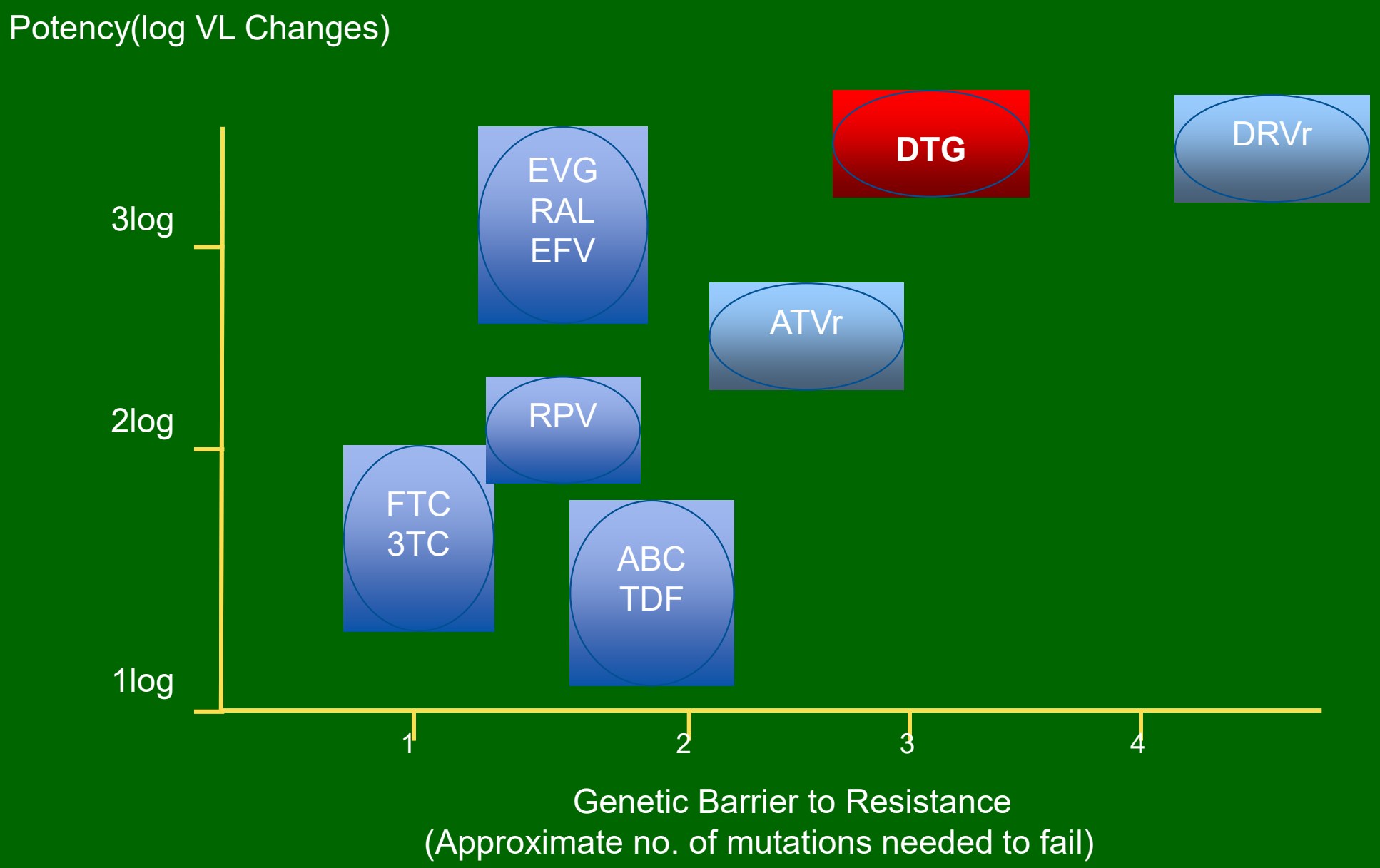
7. Post-attachment inhibitors (2018)
8. Attachment inhibitors (2020)
9. Capsid inhibitors (2022)

In development

10. NRTTI (Nucleoside revervse transcriptase translocation inhibitors) – long-acting



ARV Potency and Generic Barrier to Resistance



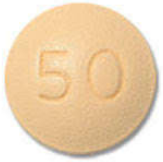
DTG Based (3DRs) as First line Regimens vs other ART

Clinical Controlled Study

	Comparable drug	Study Duration	Result
SINGLE	EFV	144 wk	Non inferior
SPRING 2	RAL	96 wk	Superior
FLAMINGO	DRVr	96 wk	Superior
ARIA	ATVr	48 wk	Superior
GS-US-380 1490&1498	BIC	48 wk	Noninferior

Second Generation INSTI: Dolutegravir

- Superior or non inferior to EFV-, DRVr-, RAL based
- High barrier resistance, active against R' strain to RAL, EVG
- OD administration without the need for boosting, STR
- Well tolerated with few serious adverse events



DTG 50 mg.

TLD
TDF 300 mg.
3Tc 300 mg.
DTG 50 mg,

TAF 25.
FTc 200 mg.
DTG 50 mg,

Current Adult HIV Treatment Guidelines

DHHS (Mar 2023)	IAS-USA (2022)	EACS (Oct. 2022)	WHO (Jul. 2021)
BIC/FTC/TAF	BIC/FTC/TAF	BIC/FTC/TAF	DTG+(3TC or FTC) /TDF
DTG/3Tc/ABC	DTG/3Tc/ABC	DTG/3Tc/ABC	
DTG+FTC/TAF or TDF	DTG+FTC/TAF or TDF	DTG+FTC/(TAF or TDF)	
DTG/3TC	DTG/3TC	DTG/3Tc	
		RAL+FTC/(TAForTDF)	
		DOR+XTC/(TAF or TAF	

DTG:Dolutegravir, RAL: Raltegravir, 3TC: Lamivudine, ABC: Abacavir
TDF: Tenofovir disoproxil fumarate TAF: Tenofovir alafenamide, DOR: Doravirine

Thai Guideline 2020: First line Regimen

NRTI backbone		Third drug
(TDF or TAF) + (3TC or FTC)	+	DTG
Alternative		Alternative
ABC + 3TC AZT + 3TC		EFV or RPV

Fixed Dose Combination (FDC)

Note: 2 drugs regimen: 3TC/DTG

2021-2024 Teevir/TLD/TAF based Transition

TDF 300 mg.
FTc 200 mg.
EFV 600 mg,

TDF 300 mg.
3Tc 300 mg.
DTG 50 mg,

TAF 25.
FTc 200 mg.
DTG 50 mg,

What to Start?

1. TDF vs TAF
2. DTG
3. 2 Drug regimen DTG/3Tc

TDF

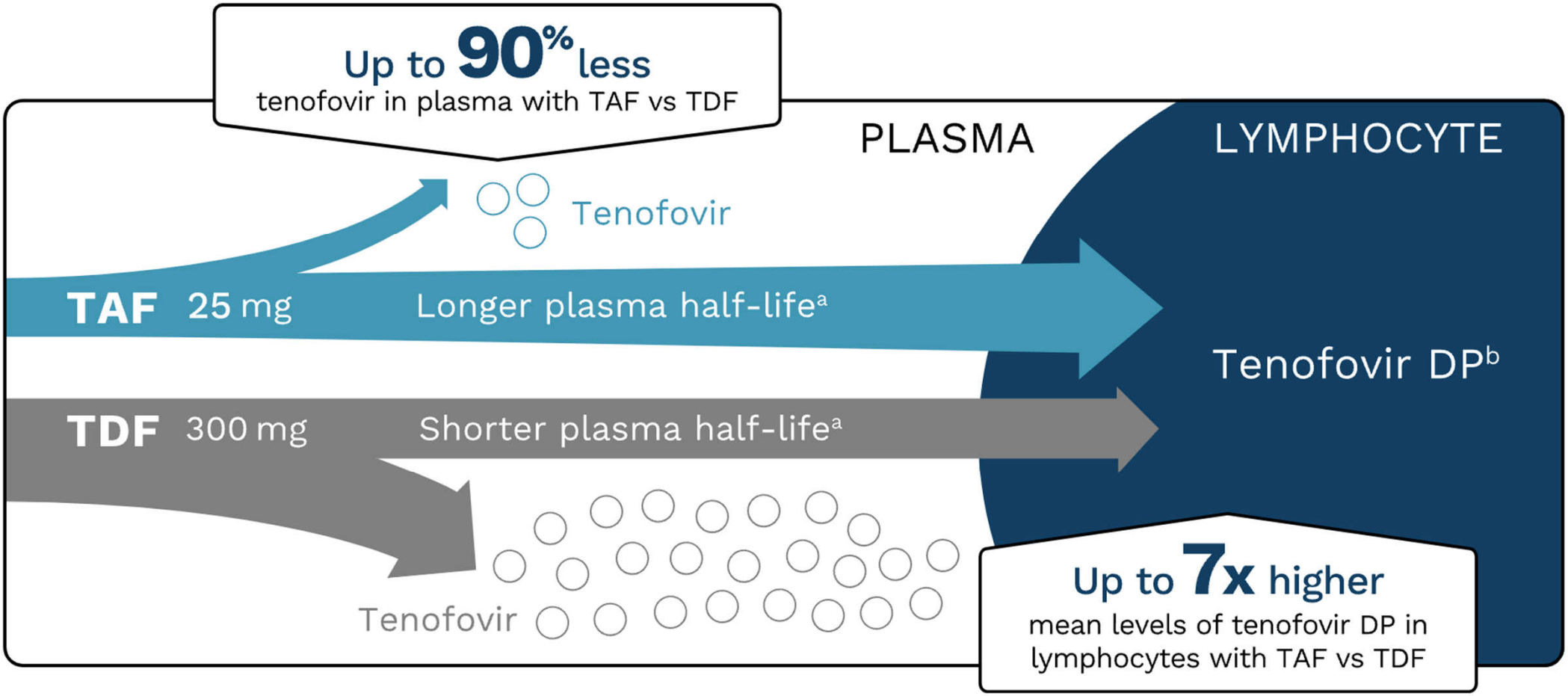
tenofovir disoproxil fumarate

TAF

tenofovir alafenamide

TDF 300 mg vs TAF 25 mg.,

Tenofovir alafenamide (TAF) vs Tenofovir disoproxil fumarate (TDF)



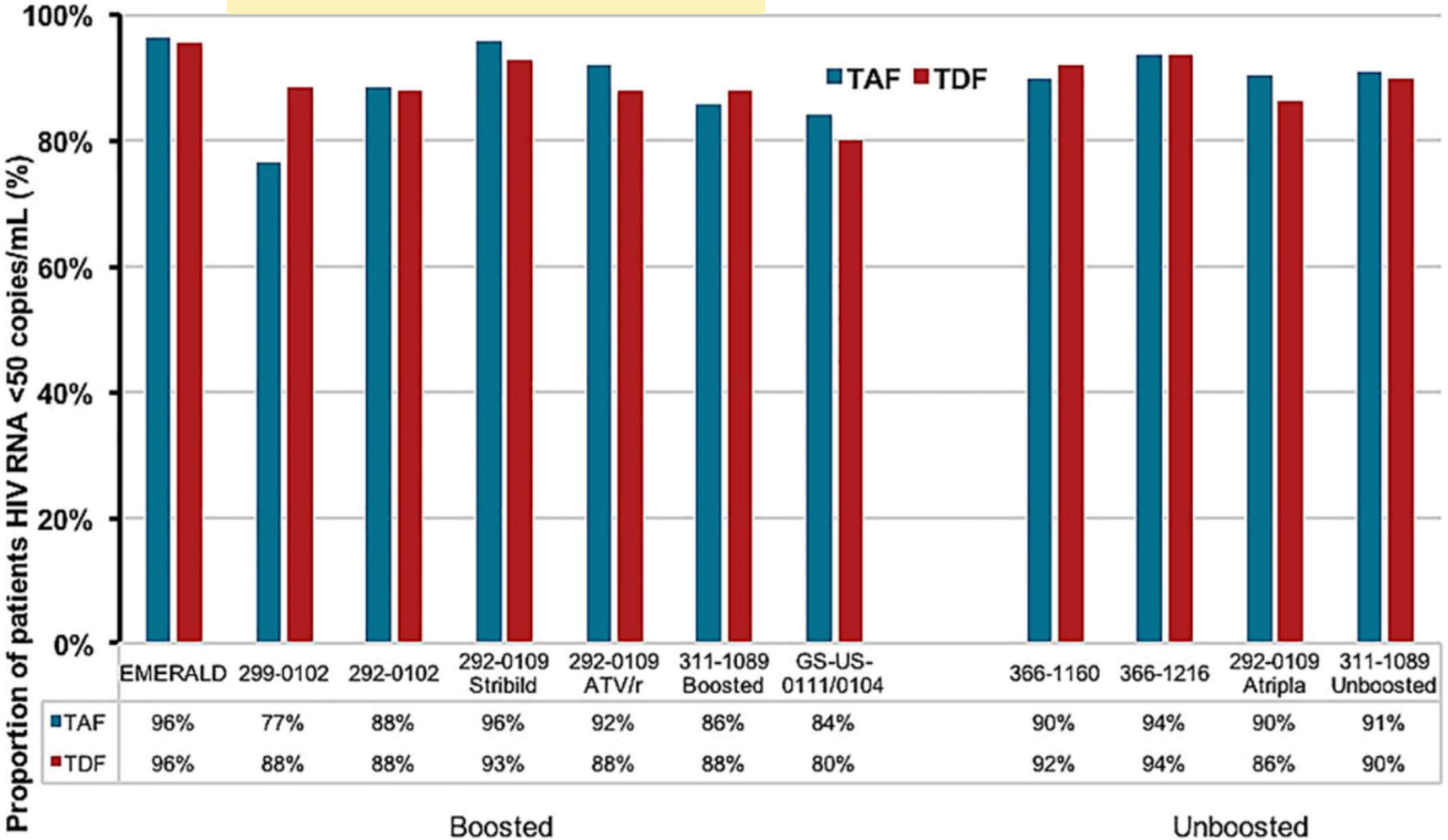
Higher intracellular levels of the active metabolite TFV-DP

and lower plasma levels of TFV

Similar Efficiency Data for HIV RNA <50 cpmil

TAF had 2% higher rates (p=.05)

No difference



	EMERALD	299-0102	292-0102	292-0109 Stribild	292-0109 ATV/r	311-1089 Boosted	GS-US-0111/0104	366-1160	366-1216	292-0109 Atripla	311-1089 Unboosted
TAF	96%	77%	88%	96%	92%	86%	84%	90%	94%	90%	91%
TDF	96%	88%	88%	93%	88%	88%	80%	92%	94%	86%	90%

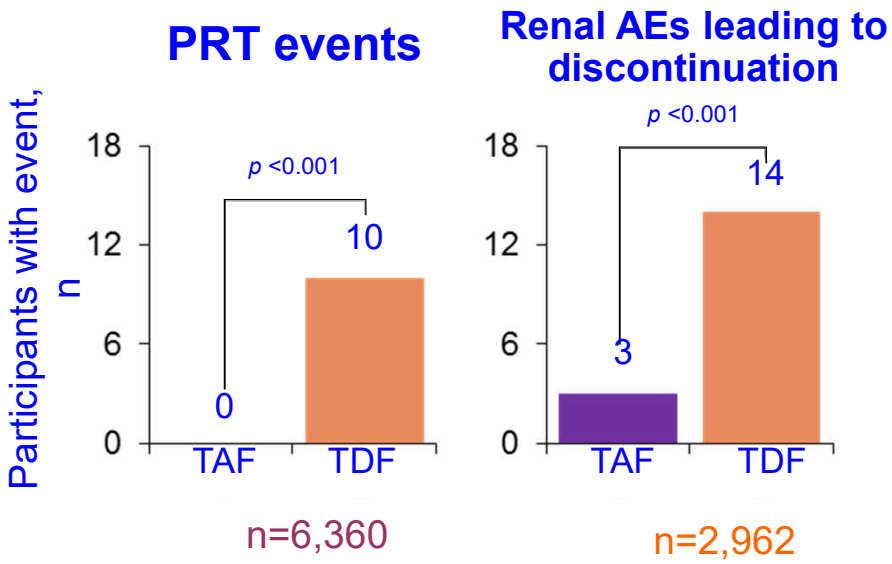
8,111 pts

Hill A. J Virus Erad. 2018.

Renal Safety of TAF over TDF

- 26 clinical trials (N=9,322 TAF 6,360, TDF 2,962)
  TAF 12,519 person-years (PY) vs TDF 5,947 PY on TDF

Primary outcomes: clinical events1



Secondary outcomes: renal biomarkers2

[N=7 trials; n=2 naïve (1733 PLWH), n=5 suppressed (4092 PLWH)]

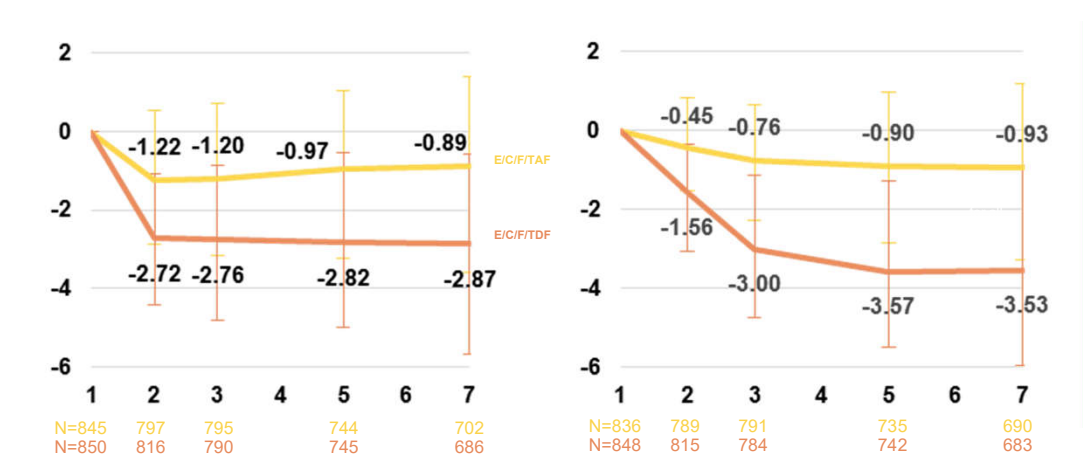
Renal biomarker, W 96	Naïve	Suppressed
eGFR	Favored TAF*	Favored TAF*
Proteinuria by dipstick	Favored TAF	Favored TAF
UACR	Favored TAF*	Favored TAF*
Urine RBP:Cr ratio	Favored TAF*	Favored TAF*
Urine β2M:Cr ratio	Favored TAF*	Favored TAF*

1. Gupta S, et al. AIDS 2019;3:1455-65. 2. Gilead Sciences. Data on File

Bone Safety of TAF over TDF

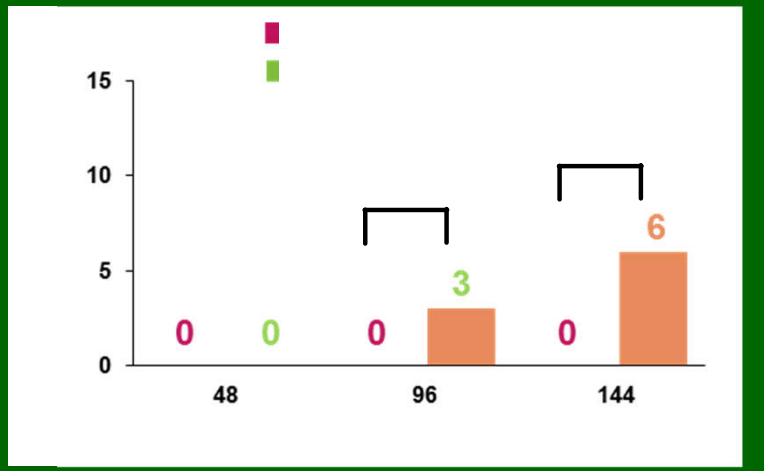
Two randomized, double-blind studies in treatment-naïve PLWH (N=1,733)

Median Change in Spine and Hip BMD through Week 144 1



Significantly greater losses in spine and hip BMD in TDF group through 144 weeks

Bone AEs* Leading to Discontinuation through W144 1,2

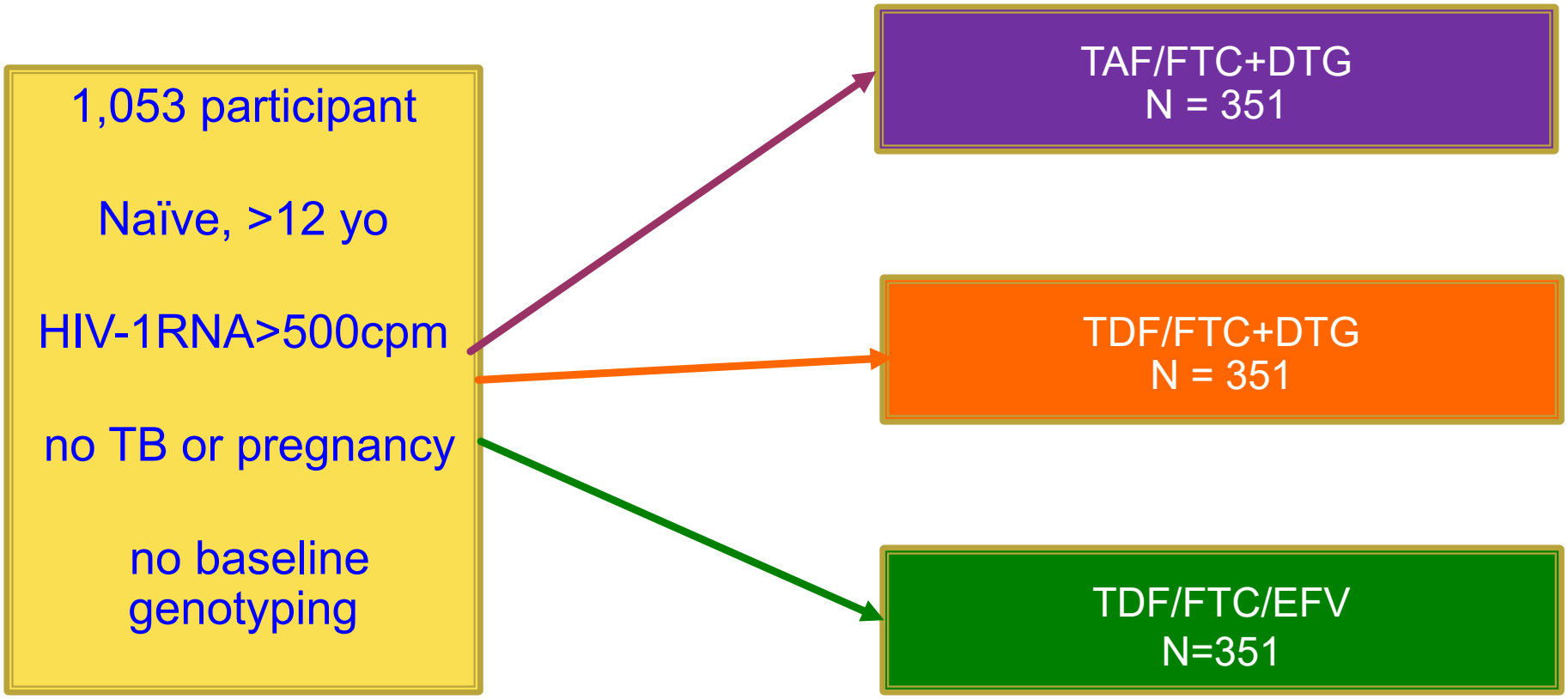


Zero discontinuations due to bone AEs with E/C/F/TAF through 144 weeks

*AEs include bone density decrease, bone loss, osteopenia and osteoporosis

1. Arribas J, et al. J Acquir Immune Defic Syndr 2017;75:211-8. 2. Wohl D, et al. J Acquir Immune Defic Syndr 2016;72:58-64, supplemental materials. 3. Data on File, Gilead Sciences Inc.

ADVANCE STUDY



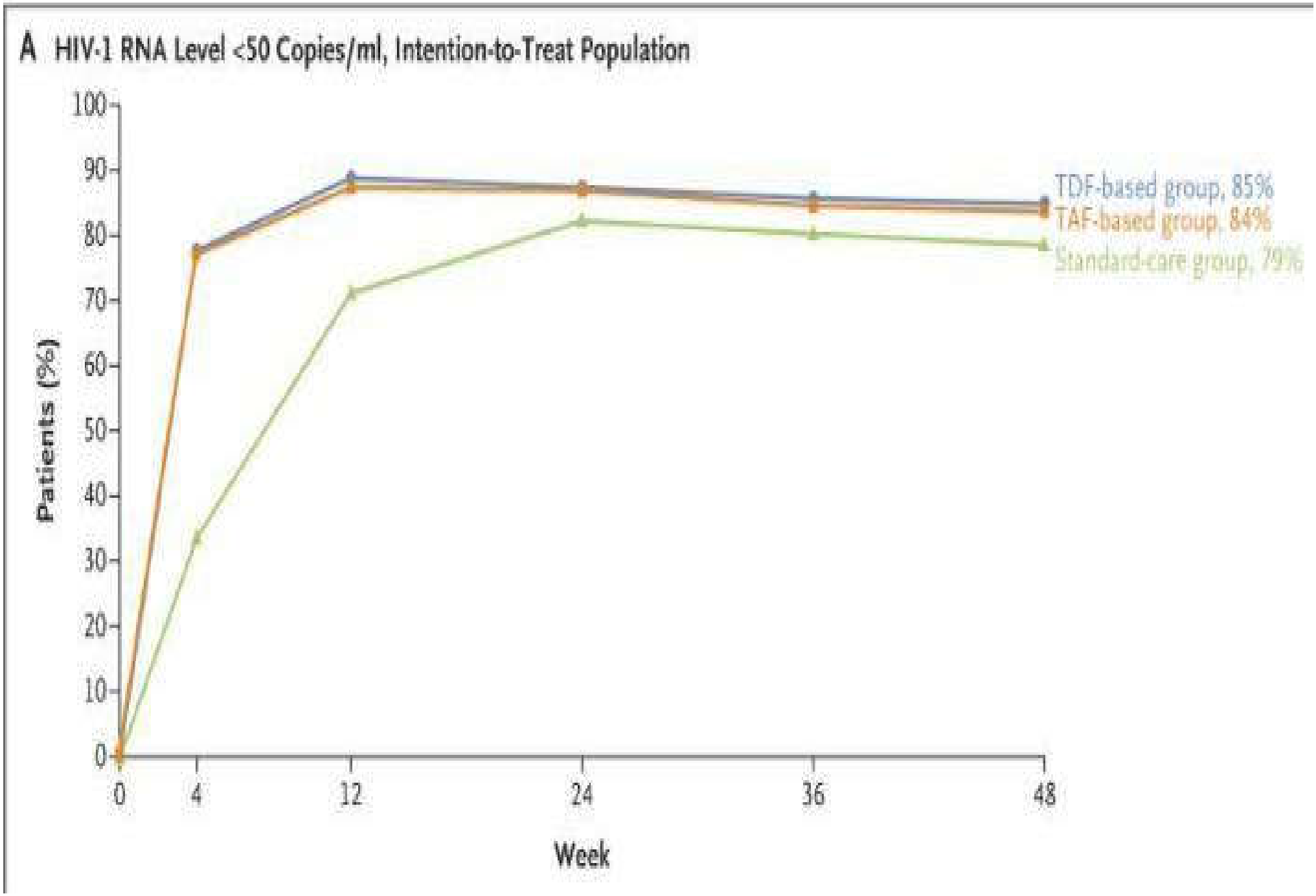
96 wk Analysis

192 wk study

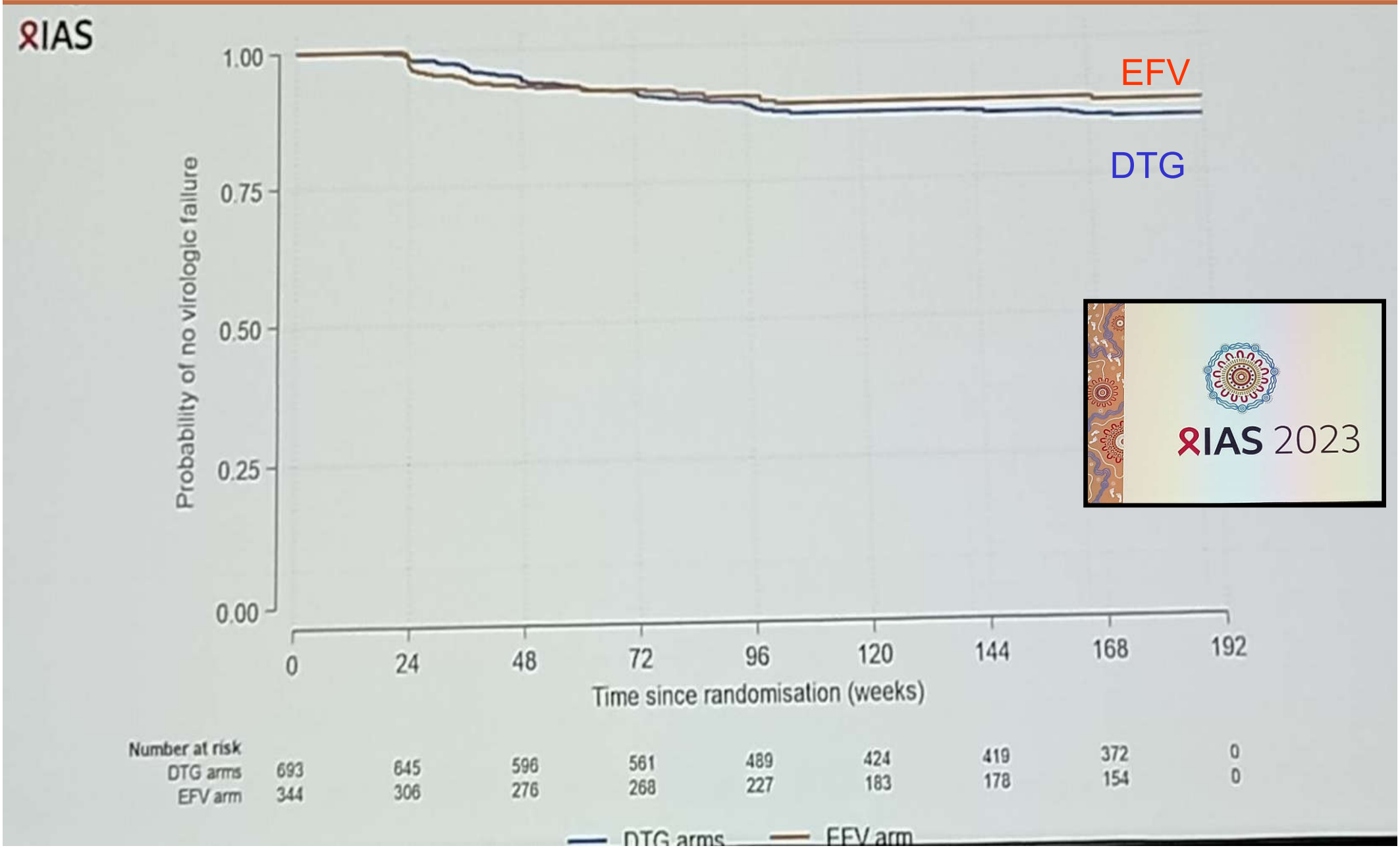
N Engl J Med 2019: 381:8033

ADVANCE STUDY: Baseline Characteristics

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Median age (yrs)	32	32	32
Female	61%	59%	57%
Weight (median, kg)	66.1	66.4	66
BMI (kg/m2)	24.1	24.1	24.1
Median CD4	349	322	337
Baseline HIV RNA			
< 100,000	272(77%)	279 (79%)	270 (77%)
100,000-500,000	66 (19%)	62 (18%)	72 (21%)
>500,000	13 (4%	10 (3%)	9 (3%)


A HIV-1 RNA Level <50 Copies/ml, Intention-to-Treat Population
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0
4
12
24
36
48
Week
TDF-based group, 85%
TAF-based group, 84%
Standard-care group, 79%

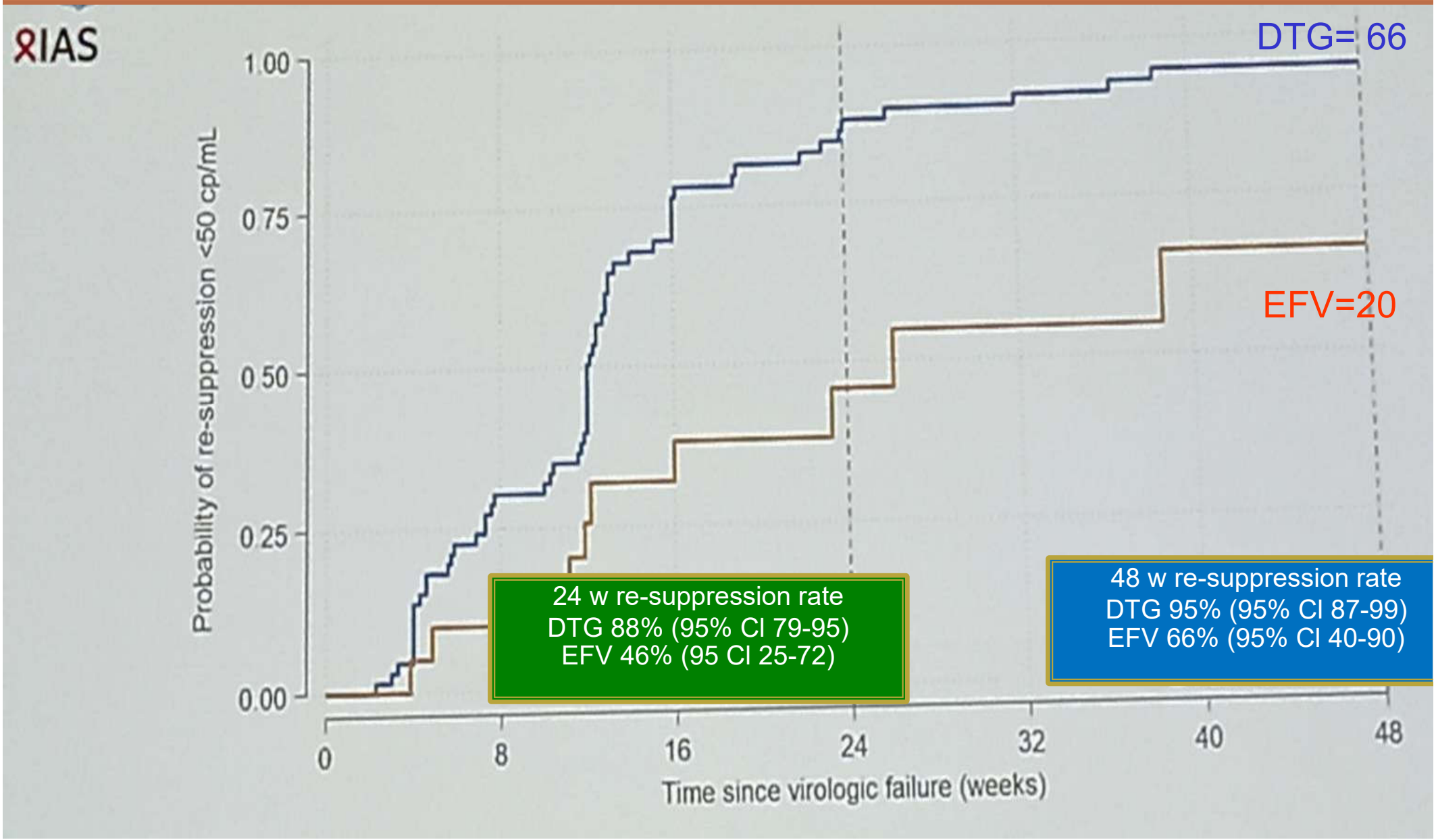
ADVANCE STUDY: Proportion Virological Success



ADVANCE STUDY: Re-suppression Study

Q) Should people with HIV RNA elevations on DTG-based treatment be switched to other ARVs?

ADVANCE STUDY: Re-suppression



ADVANCE STUDY: Re-suppression Study

Q) Should people with HIV RNA elevations on DTG-based treatment be switched to other ARVs?

1. 95% of people with HIV RNA elevations>1,000 cpmL showed re-suppression < 50 cpml after 48 weeks, with adherence counselling : keeping people on DTG-based

2. No INSTI resistance in ADVANCE, or in meta analysis of First-line Studies.

Disadvantages TAF/FTc Backbone

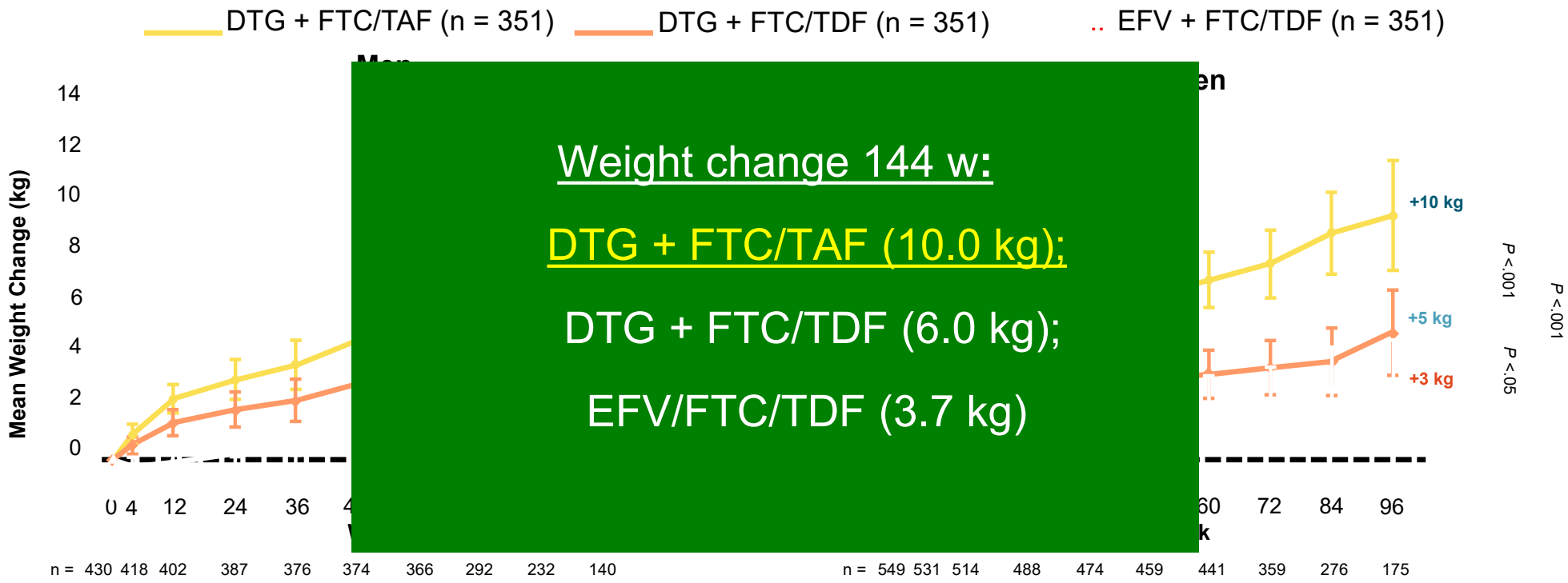
- Weight gain
- TAF is associated with higher lipid levels than TDF
- Drug Interaction with Rifampicin

Weight gain and ART

INSTIs regimen induce greater weight gain than comparator regimens

ADVANCE: Mean Weight Change at wk 96

N=1,053, F 56%, Black 99%, South African 62%



Weight change 144 w:

DTG + FTC/TAF (10.0 kg);

DTG + FTC/TDF (6.0 kg);

EFV/FTC/TDF (3.7 kg)

- **DTG** > **EFV**, **TAF** > **TDF** at Wk 96;
- plateauing in weight gain after Wk 48 observed in men but not in women

Lancet HIV. 2020;7:e666.

Weight Gain in DHHS Guidelines

- Significant weight gain appears to be more pronounced with DTG, BIC, TAF

- The mechanism is unclear and under investigation

- Risk Factors for Weight Gain in PLHIV

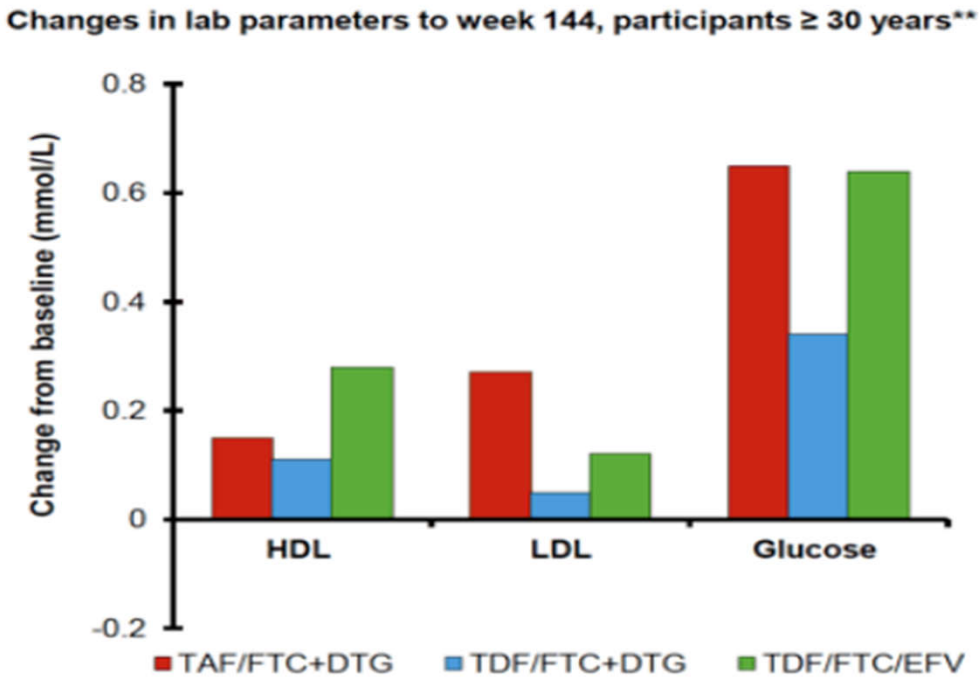
  Female sex, non white, older age, CYP2B6 genotype

  Base line HIV RNA>100,000, CD4 < 200 cell/ml

  baseline BMI, ARTs

ADVANCE 144 wk: Dyslipidemia and Risk of CVD

- Weight change 144 wk after ART initiation:
  - DTG + FTC/TAF (10.0 kg); DTG + FTC/TDF (6.0 kg); EFV/FTC/TDF (3.7 kg)



Estimated 10-Yr Risk of CVD, % (QRISK)	DTG + FTC/TAF	DTG + FTC/TDF	EFV/FTC/ TDF
BL	0.60	0.50	0.50
Median Δ from BL to Wk 144	+0.36*	+0.25	+0.20

*Sig. higher vs EFV/FTC/TDF (*P* = .016).

Slide credit: CCO

Hindley. CROI 2021. Abstr 117.

Lipid Changes after Switch from TDF to TAF in OPERA Cohort

OPERA Cohort: Observational Phamaco-Epidemiology Research and Analysis

84 clinics 93,170 PLWHIV HER (Electronic health record), TDF to TAF

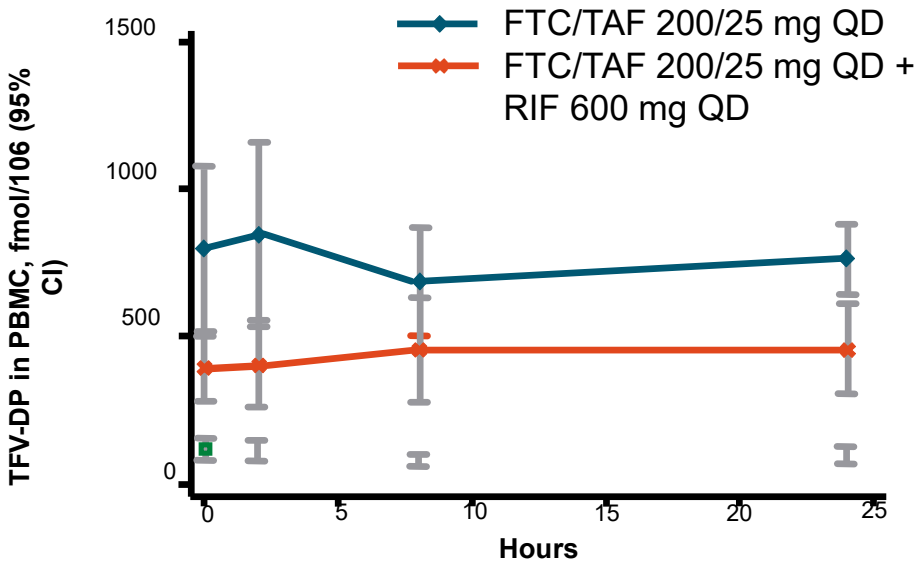
6,451 (All Switches), 4,328 (maintained all other agents)

	LDL-C mg/dL/mo (95% CI)	TG mg/dL/mo (95% CI)
0-3 m	+ 1.72 (1.47 to 1.96)	4.58 (3.25 to 5.92)
3-9 m.	0.27 (0.11 to 0.42)	1.18 (0.32 to 2.04)
9-16 m	0.10 (-0.03 to 0.23)	0.79 (0.11 to 1.47)
16 m	-0.00 (-0.11-0.11)	-0.61 (-1.18 to -0.03)

Mallon. AIDS 2020. Abstr OAB0604.

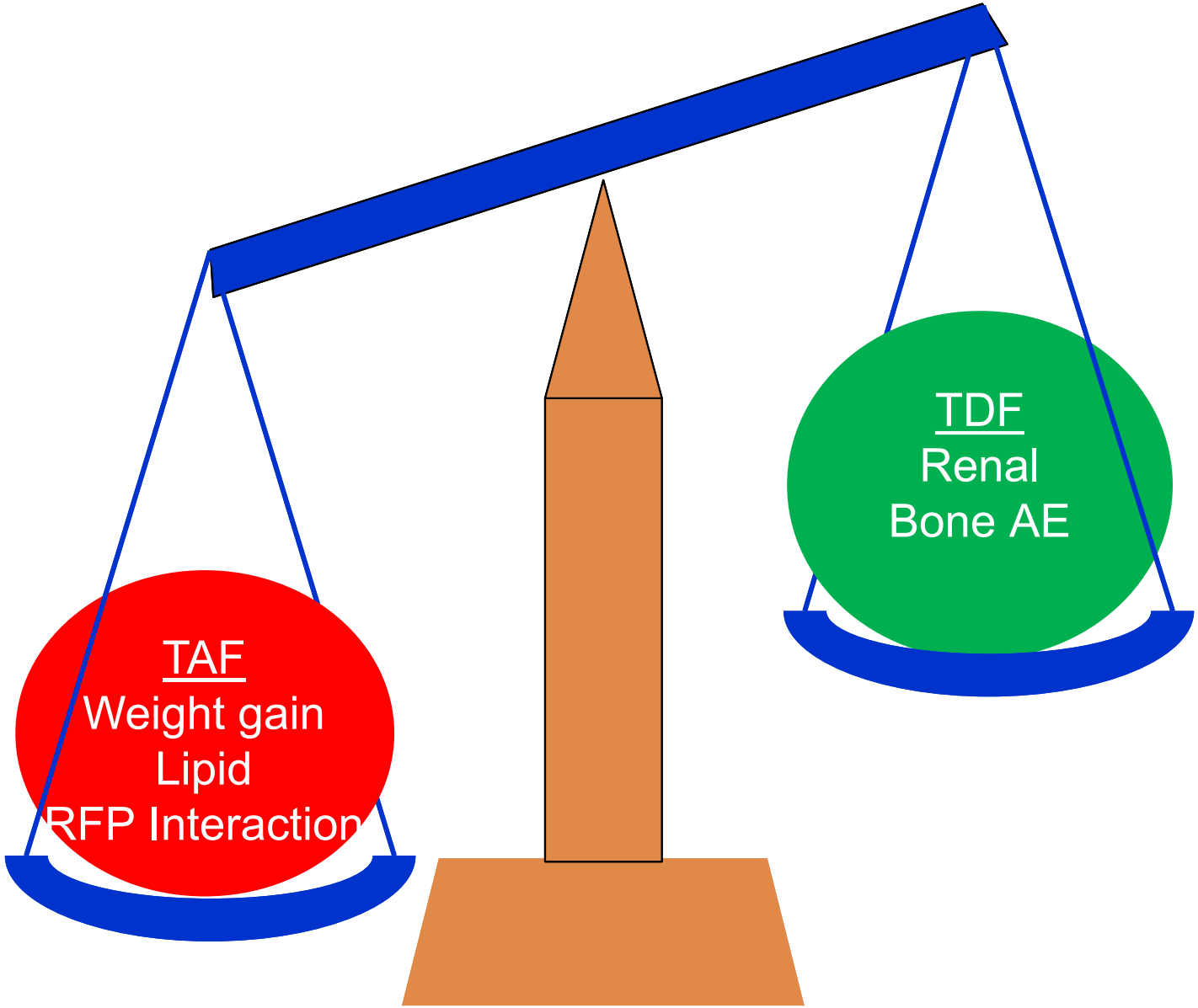
TAF and Rifampin

- TAF is a P-gp substrate, its plasma concentrations may be reduced by rifamycin antibiotics
- Not recommend concomitant administration of TAF and any rifamycin antibiotic[1]



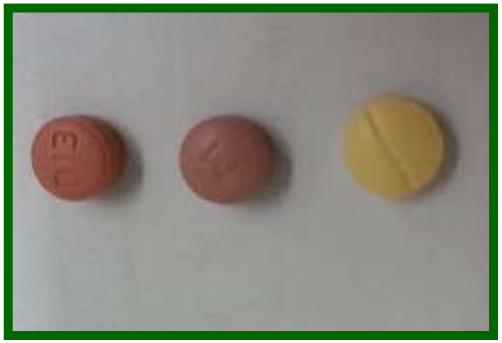
1. Descovy package insert [package insert]. Gilead. 2016.

A Role for TDF or TAF in First-line Regimens



1. NAMSAL ANRS 12313 Study Group. N Engl J Med 2019;381:816-26.
2. McCann K, et al. EACS 2019. Abstract PS3/3.
3. Sax PE, et al. Lancet 2015;385:2606-15.

DTG 50 mg.

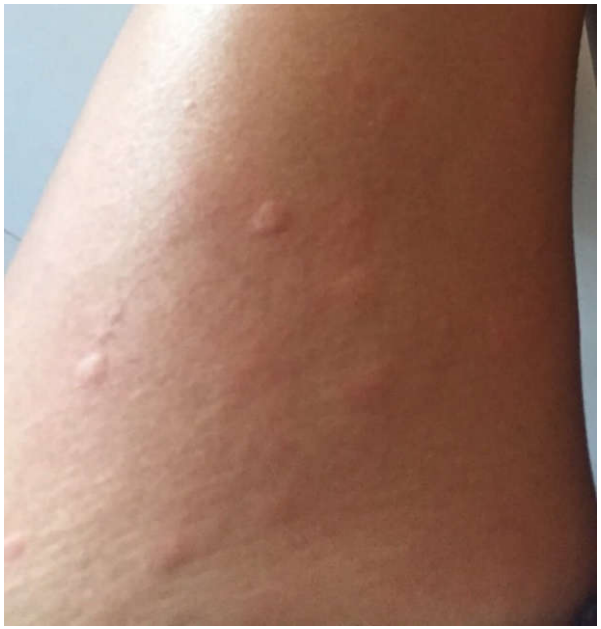


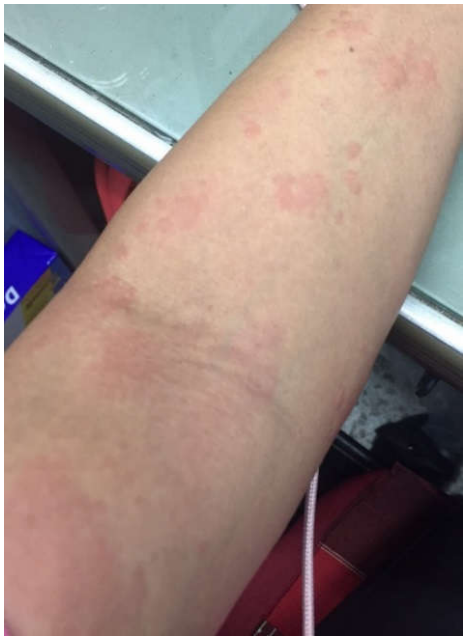
DTG: Undesirable Effects

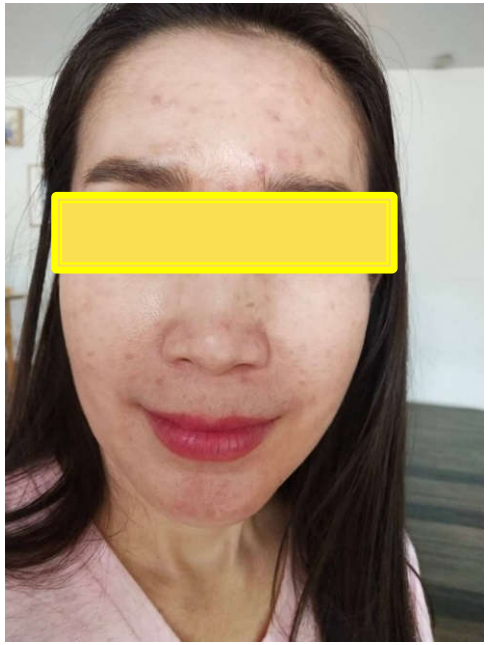
- Neuropsychiatric disorders: Insomnia, headache, dizziness, depression
- Skin reactions rash, acne like
- Renal AE: Pseudo decrease Creatinine Clearance
- Liver enzyme elevations
- Weight gain
- GI disorder: Nausea, abdominal pain, vomiting, flatulence
- DTG Drug-drug interactions

DTG Neuro Psychiateric Undesirable Effects

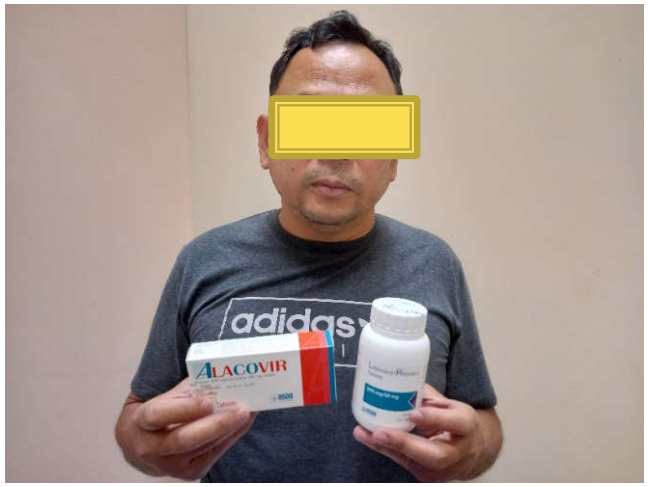
	(%)
Insomnia	4-19
Abnormal dreams	9.5
Anxiety	2-33.3
Headache	3-33.3
Depression	2-10.1
Suicidal	0.1-2







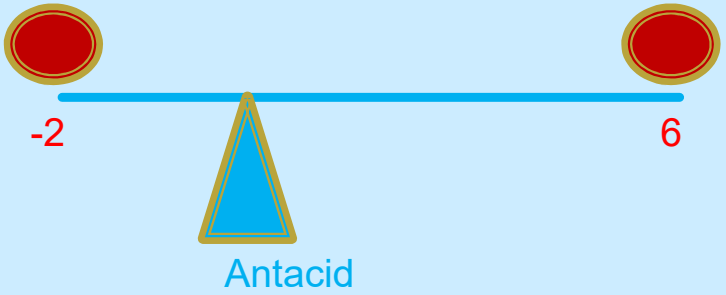
DTG Rash
Acne like



SGOT/SGPT 93/125

With permission

Dolutegravir: Important drug-drug interactions

1. Antacid: Major Cation containing Al, Mg	a reduction in the exposure to DTG 
2. Vitamin, minor cation Fe, Ca	With food
3. Metformin	Plasma metformin increased with DTG

Dolutegravir: Important drug-drug interactions

4. Anticonvulsant: Phenyltoin, phenobarbial	DTG bid, adjustment maintain 2 wk after stopping phenyltoin
5. Rifampicin	Contraindication

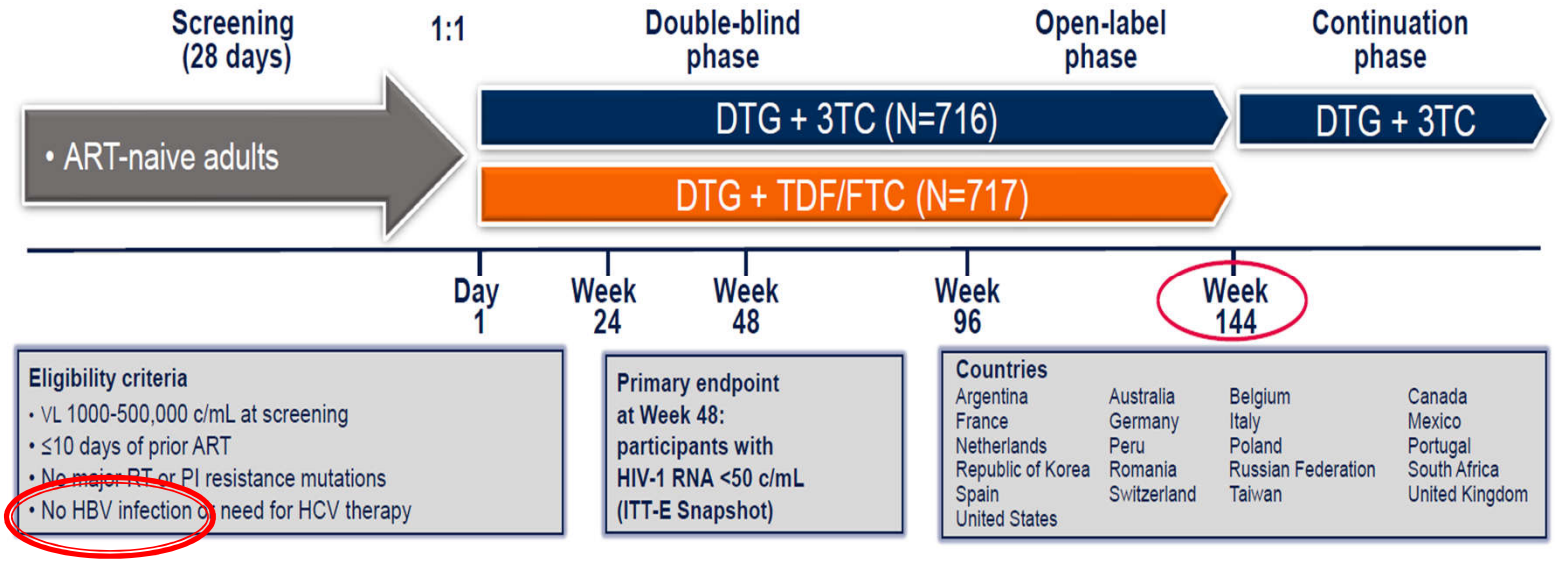
DTG, 3Tc (2DRs) as First line Regimens

: GEMINI-1&2

: D2ARLING Study

DTG, 3Tc (2DRs) as First line Regimens: GEMINI-1&2

DTG + 3TC in GEMINI-1 & -2: HIV-1 Replication at <50 C/ML AND VL 'BLIPS' THROUGH 144 WEEKS

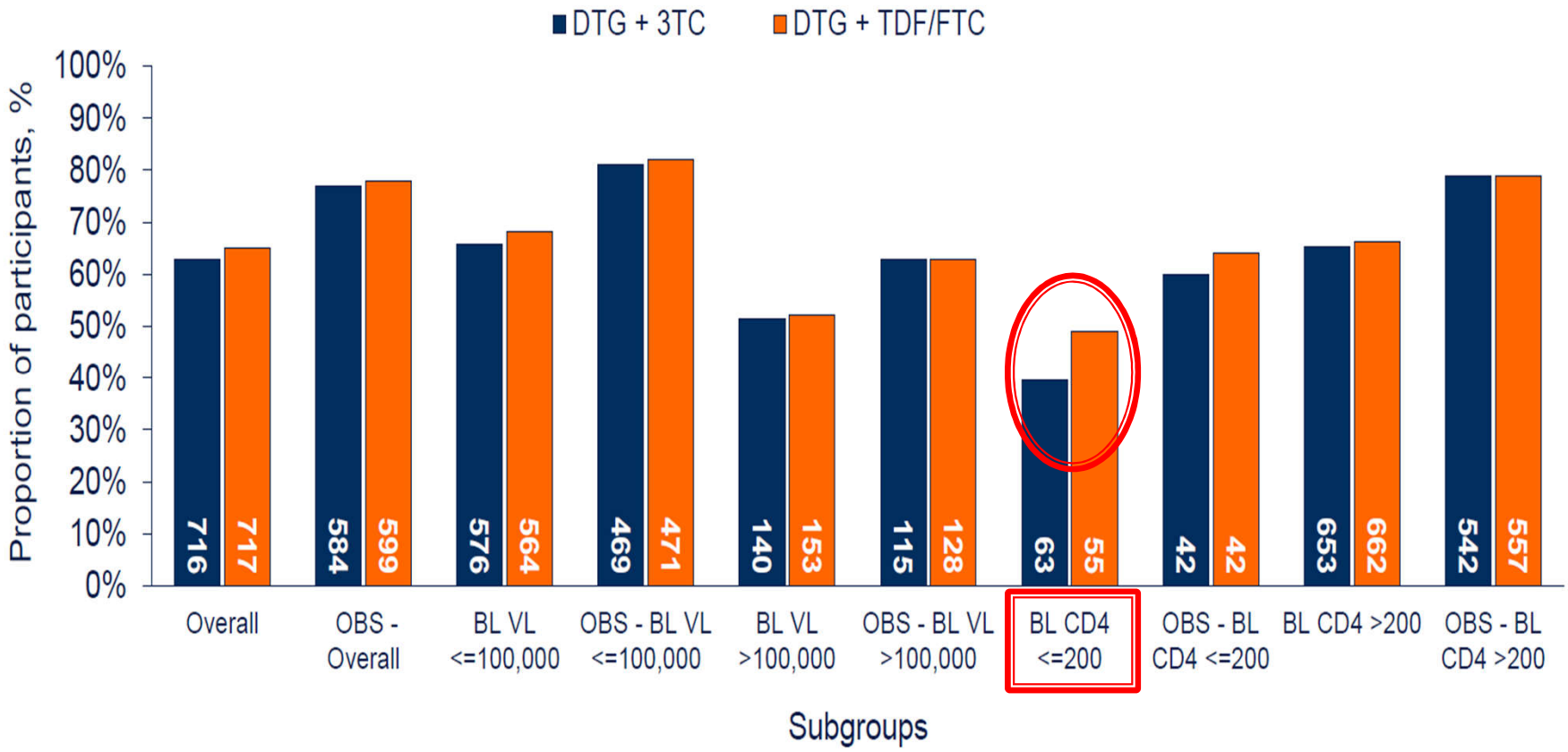


Mark Underwood,1 Rimgaile Urbaityte,2 Ruolan Wang,1 Joe Horton,3 Linshan Yuan,4 Brian Wynne,1 Justin Koteff,1 Jean van Wyk,5 Choy Man,1 Jörg Sievers5

11th IAS conference on HIV Science, Jul 18-21, 2021

DTG, 3Tc (2DRs) as First line Regimens: GEMINI-1&2

Proportions of Participants With TND by BL Subgroups Were Similar Across Arms at Week 144



Mark Underwood,1 Rimgaile Urbaityte,2 Ruolan Wang,1 Joe Horton,3 Linshan Yuan,4 Brian Wynne,1 Justin Koteff,1 Jean van Wyk,5 Choy Man,1 Jörg Sievers5

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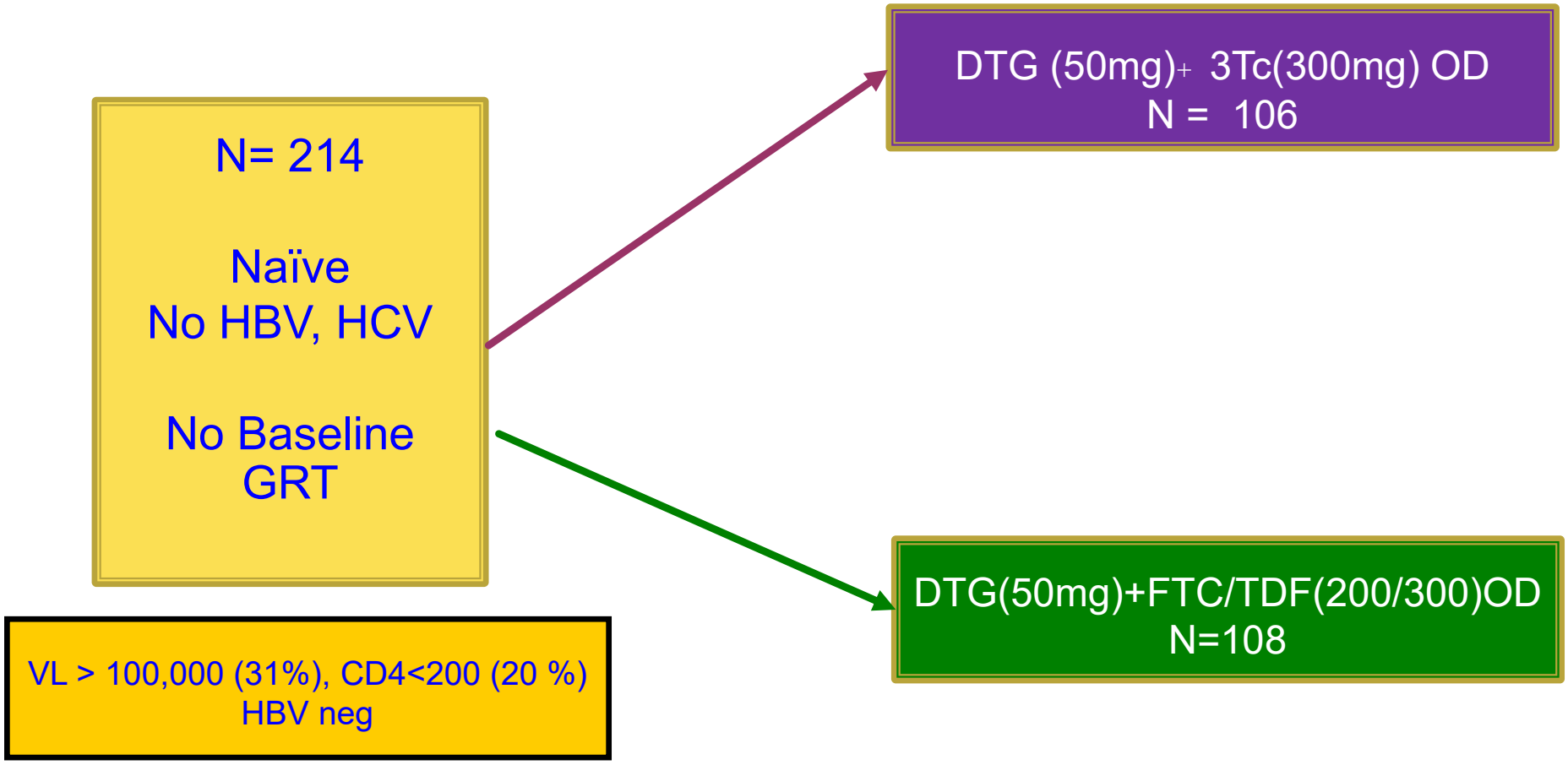
D2ARLING Study

IAS 2023

Efficacy of Dolutegravir Plus Lamivudine inHIV-1infected Treatment naïve Adults Without a Baseline Genotyping test (D2ARLING)



Primary endpoint proportion of PLWHIV with VL<50 copies/ml at w 48

Cordova E et al, Poster TUPEB02

D2ARLING Study: 24 wk Result

	DTG/3TC arm	DTG+FTC/TDF
Proportion VL < 50 cpml	94.34%	95.37%
Proportion with VL>50 cpml	0.94% (n=1)	1.85(n=2)

	DTG/3TC arm	DTG+FTC/TDF
Withdrawal due to AE	1%	0%
Weight gain (kg)	2	0

Conclusion: At wk 24, DTG+3Tc was non inferion to DTG+FTC/TDF

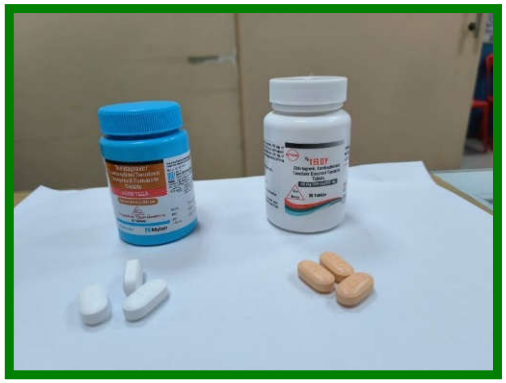
in ARV naïve without baseline resistance testing

Second 95-95-95: What to Start?

DHHS (Mar 2023)	IAS-USA (2022)	EACS (Oct. 2022)	WHO (Jul. 2021)
BIC/FTC/TAF	BIC/FTC/TAF	BIC/FTC/TAF	DTG+(3TC or FTC) /TDF
DTG/3Tc/ABC	DTG/3Tc/ABC	DTG/3Tc/ABC	
DTG+FTC/TAF or TDF	DTG+FTC/TAF or TDF	DTG+FTC/(TAF or TDF)	
DTG/3TC	DTG/3TC	DTG/3Tc	
		RAL+FTC/(TAForTDF)	
		DOR+XTC/(TAF or TAF	

DTG:Dolutegravir, RAL: Raltegravir, 3TC: Lamivudine, ABC: Abacavir
TDF: Tenofovir disoproxil fumarate TAF: Tenofovir alafenamide, DOR: Doravirine

Second 95-95-95: What to Start?



TDF 300 mg.
3Tc 300 mg.
DTG 50 mg,

TAF 25.
FTc 200 mg.
DTG 50 mg,

TDF (Bone, Renal)
vs TAF
(Weight gain, lipid elevation)

DTG

2DR

DTG/3Tc

Gemini 1,2

D2ARING

Single tablet regimens (STR)

Fixed Dose Combination (FDC)

=

Tenofovir 300 mg.

Dose adjustment :

CCr < 50

3c 300 mg.

Dose adjustment :

CCr 30-49 300 q 48 hr

10-29 300 biw

< 10 not recommended

Thank you for your attention