The Future of Antiretroviral Therapy

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The Future of ART

- Where we are now – why current treatment is so great
- Current knowledge gaps and problems (yes there are still problems), illustrated by cases
- Possible changes coming in the future
- Several interactive questions to generate discussion

Question

- If you had a time machine and were transported back to the early 1990s – *before* effective combination ART – which fact about HIV treatment today would you find *most* exciting and/or surprising?

A. That most treatments are 1-2 pills a day.

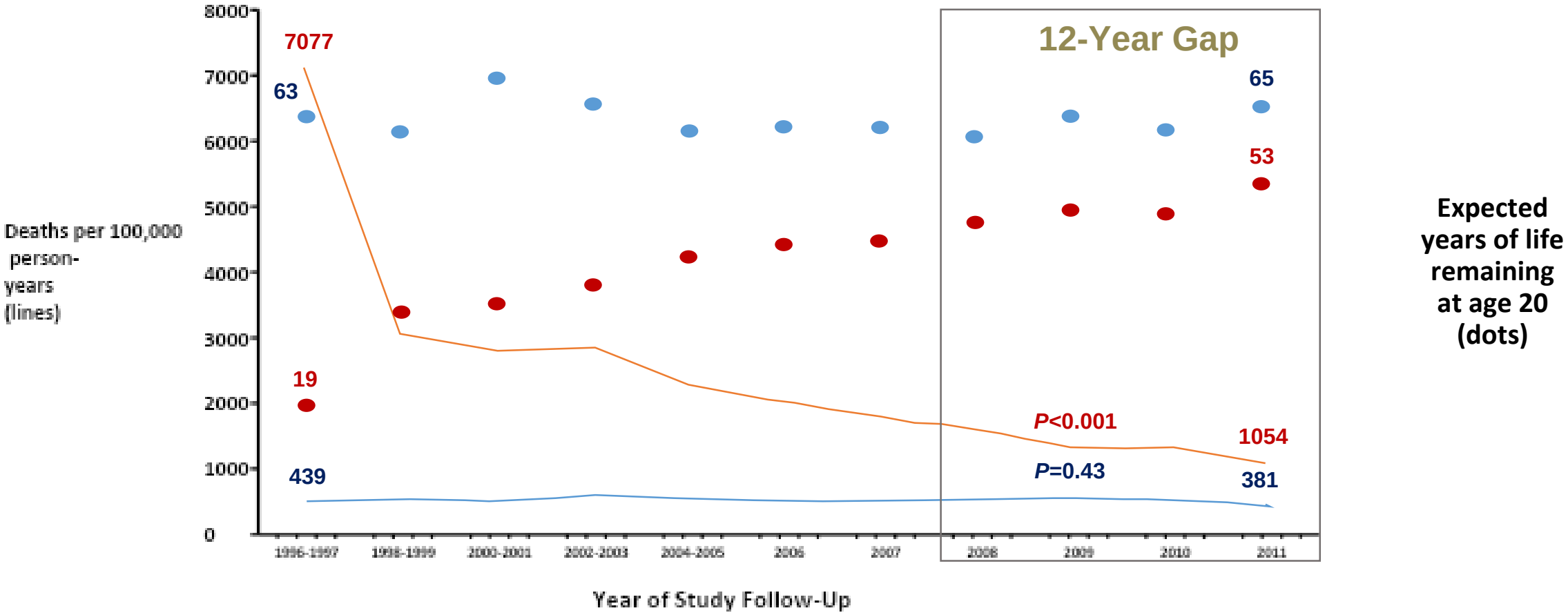
B. That almost everyone who takes HIV therapy is virally suppressed, and these treatments will never fail if patients remain adherent.

C. That opportunistic infections are vanishingly rare among people on ART.

D. That survival for some people with HIV is projected to be comparable to people without HIV.

E. That suppressive HIV therapy eliminates the risk of sexual transmission.

Kaiser: The "Survival Gap" Continues to Shrink



8 year gap with ART initiation at CD4 ≥ 500. Life expectancy Blacks & IDU.
Gap narrowed further if no hepatitis, drugs/alcohol, or smoking.

Marcus J, et al. J Acquir Immune Defic Syndr. 2016

HIV Treatment Options Are Getting Simpler

DHHS (7/2019) Recommended for Most People With HIV
Bictegravir/FTC/TAF
Dolutegravir/ABC/3TC Dolutegravir + FTC/TDF or FTC/TAF
Raltegravir + FTC/TAF or FTC/TDF

IAS-USA (7/2018) Recommended Initial Regimens
Bictegravir/FTC/TAF
Dolutegravir/ABC/3TC*† Dolutegravir + FTC/TAF*‡

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision Oct, 2018; Saag MS, et al. *JAMA.* 2018;320:379-396.

… And The Boosters Are Gone!

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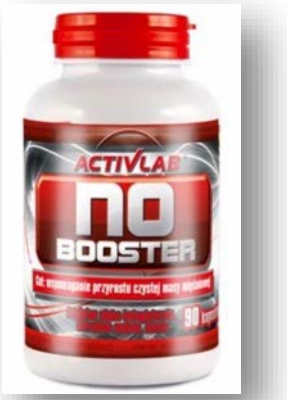
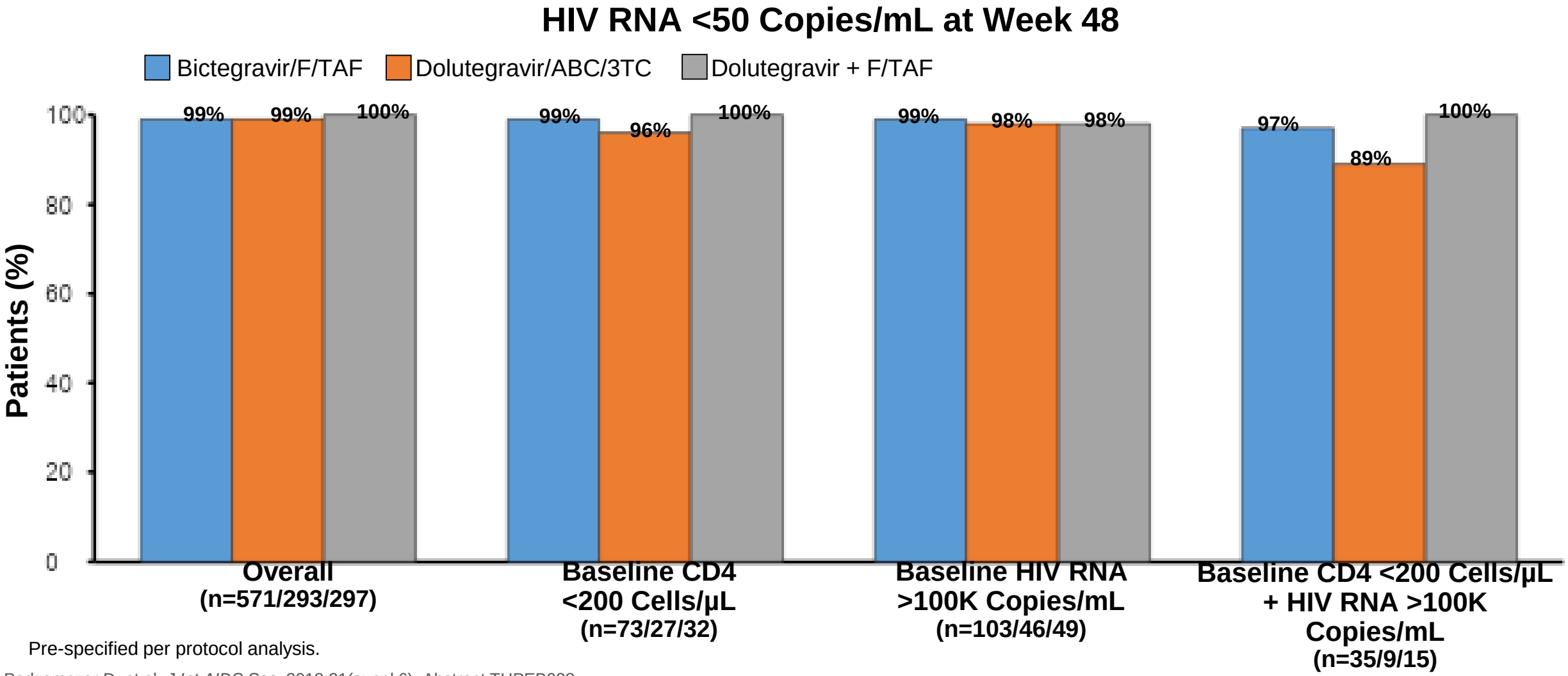


DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision Oct, 2018; Saag MS, et al. *JAMA.* 2018;320:379-396.

BIC and DTG-based Regimens Are Extraordinarily Effective



Pre-specified per protocol analysis.

Podzamczer D, et al. *J Int AIDS Soc*. 2018;21(suppl 6). Abstract THPEB038.

NEJM Journal Watch

April 8th, 2018

Latest DHHS Guidelines for Initial HIV Therapy Now Include 5 Choices — But Really 2 Are Best

As of April 8, 2018 (the day I'm writing this post), the choice between the two remaining options reflects how we and our patients feel about two issues.

If giving one pill rather than two is most important, then go with bictegravir/TAF/FTC.

If accumulated safety and "real world" experience is most important, then go with dolutegravir plus TAF/FTC.

Hey, isn't HIV treatment simple these days?

https://blogs.jwatch.org/hiv-id-observations/index.php/latest-dhhs-guidelines-initial-hiv-therapy-now-include-5-choices-really-2-best/2018/04/08/

Best Regimens for Starting Therapy in 2019: One Opinion

tenofovir AF/emtricitabine

\+

dolutegravir

OR

bictegravir/tenofovir AF/emtricitabine

- Reasons
  - Once daily
  - Clinically significant transmitted drug resistance extremely rare
  - Well-tolerated
  - No treatment-emergent resistance in clinical trials
  - Reduced renal and bone toxicity c/w TDF
  - No known excess cardiovascular risk c/w ABC
  - Small tablet sizes
  - Taken with or without food
  - Active vs hepatitis B
  - Ideal for same-day ART

Summary: HIV Today Treatment is Awesome

- Effective
- Well-tolerated
- Safe
- Simple
- Prevents HIV transmission
- *So are we done here?*

- Not yet!
- These cases will illustrate ongoing challenges and areas of uncertainty

Case #1

- A 31 year old woman with stable HIV infection returns for routine follow-up.
- She was diagnosed at age 28 during pregnancy; started TDF/FTC, RAL, which was changed to ABC/3TC/DTG after delivery.
- Reports no side effects, excellent adherence.
- Says she and her boyfriend are considering having another baby – irregular use of birth control.
- Lab tests fine. Pregnancy test negative.

Question

- What should we do with the HIV treatment?

A. No change in ART.
B. Switch back to TDF/FTC, RAL.
C. Switch to TDF/FTC, ATV/r
D. Switch to TDF/FTC, DRV/r
E. Something else

What to Start in Pregnancy: DHHS Guidelines Dec 7, 2018

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection *and* Interventions to Reduce Perinatal HIV Transmission in the United States

Developed by the HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Two NRTIs

Abacavir/3TC

or

TDF/FTC or TDF/3TC

Plus

Integrase inhibitor:

Raltegravir (twice daily) or

Dolutegravir (only after 1st trimester; not in someone trying to conceive)

or

Protease inhibitor:

Darunavir/ritonavir (twice daily) or

Atazanavir/ritonavir

DO NOT USE:

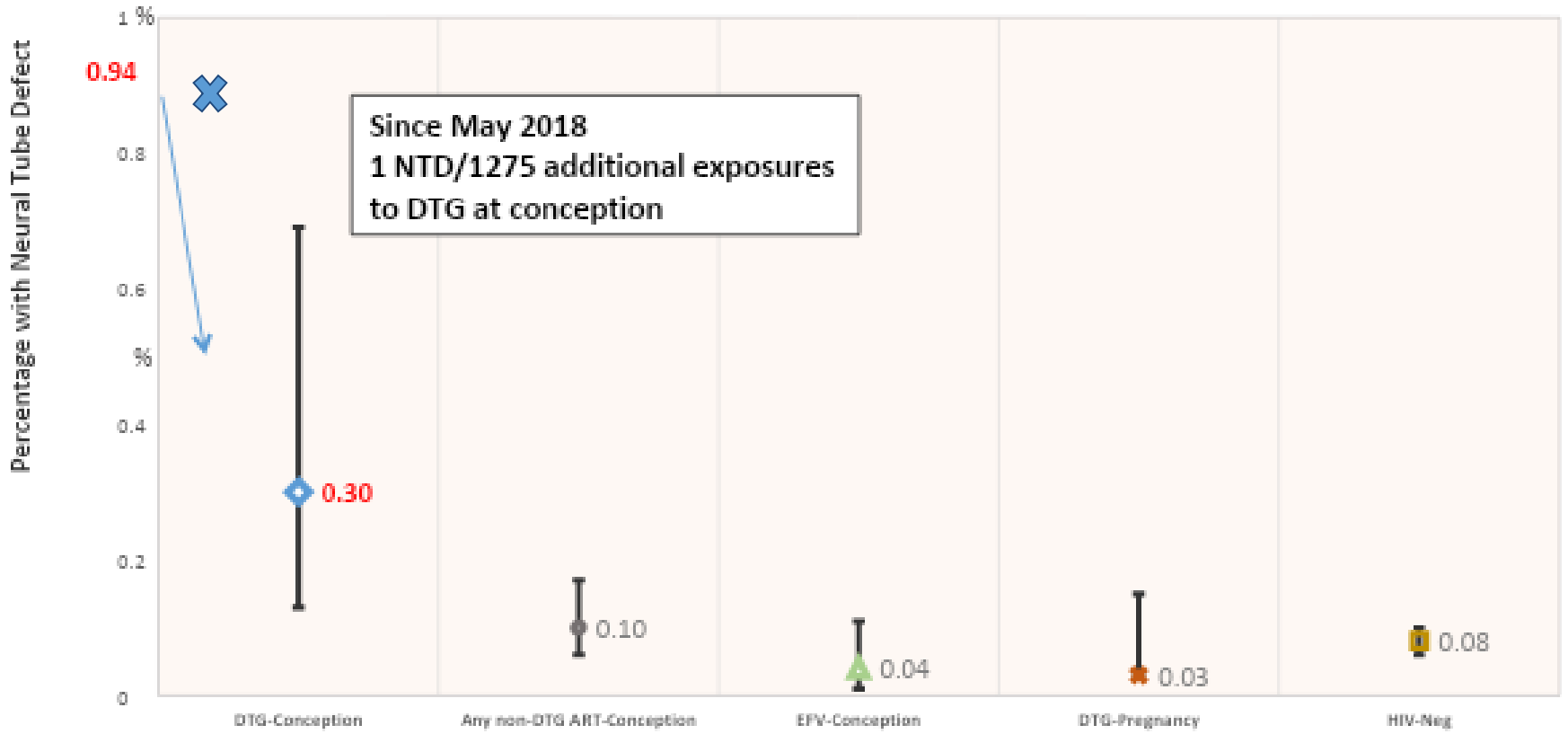
TAF (insufficient data)
Bictegravir (insufficient data)
Elvitegravir/cobi (PK concerns)
DRV/cobi (PK concerns)
ATV/cobi (PK concerns)
DOR (insufficient data)

Tsepamo:
Birth Outcomes Surveillance Study in Botswana

- May 2018: unplanned analysis found higher incidence of neural tube defects among infants born to women who conceived while on DTG
  - 4/426 (0.94%) on DTG- vs. 0.12% on non-DTG ART
- WHO, US DHHS, others recommended against use of DTG in women who want to become pregnant or are sexually active and not using contraception
- Current analysis: updated as of March 2019
  - From July to September 2018, surveillance area expanded to capture 72% of all births in Botswana
  - Study population: 1,683 DTG from conception; 14,792 non-DTG from conception

Zash R NEJM. 2018; 379:979. Zash R IAS 2019. Abstr MOAX0105LB; Zash R NEJM, July 22, 2019.

Neural Tube Defects by Exposure Category



NTDs/Exposures	5/1683	15/14792	3/7959	1/3840	70/89372
% with NTD (95% CI)	0.30% (0.13, 0.69)	0.10% (0.06, 0.17)	0.04% (0.01, 0.11)	0.03% (0.0, 0.15)	0.08% (0.06, 0.10)
Prevalence Difference (95% CI)	**ref**	**0.20% (0.01, 0.59)**	**0.26% (0.07, 0.66)**	**0.27% (0.06, 0.67)**	**0.22% (0.05, 0.62)**

Zash R IAS 2019. MOAX0105LB;
Zash R NEJM, July 22, 2019.

POLICY BRIEF

UPDATE OF RECOMMENDATIONS ON FIRST- AND SECOND-LINE ANTIRETROVIRAL REGIMENS

JULY 2019

Box 1. Recommendations: first- and second-line ART regimens

First-line ART regimens[a]
1. Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART (NEW) • Adults and adolescents[b] *(strong recommendation, moderate-certainty evidence)* • Infants and children with approved DTG dosing *(conditional recommendation, low-certainty evidence)*
2. Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART[c] *(strong recommendation, moderate-certainty evidence)* (NEW)
3. A raltegravir (RAL)-based regimen may be recommended as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available *(conditional recommendation, low-certainty evidence)*
4. A RAL-based regimen may be recommended as the preferred first-line regimen for neonates *(conditional recommendation, very-low-certainty evidence)*

[a] See Table 1 for ARV drug selection.
[b] See Box 2 on women and adolescent girls of childbearing potential using DTG.
[c] Except in settings with pretreatment HIV drug resistance to EFV/nevirapine (NVP) exceeding 10%.

"A woman-centered and rights-based approach should be applied to antiretroviral delivery. Women should be provided with information about benefits and risks to make an informed choice regarding the use of DTG or other ART"

World Health Organization, July 2019

ART and Pregnancy – So Many Questions

- A small relative risk (and even smaller absolute risk) for DTG at conception and NTD remains – is it real?
- Does it apply to all settings?
- If so, is this a class effect of all INSTIs?
- Right now – *today* – what what is the optimal regimen for women who desire pregnancy?
- What is the best regimen for women of childbearing potential independent of whether they say they want to become pregnant?
- What is the right way to counsel about this information?
- What is the safest treatment *during* pregnancy?

Case #2

- A 38-year-old man is admitted to the hospital with fever, weight loss, and cough.
- *Pneumocystis* pneumonia is suspected; started on TMP/SMX and prednisone.
- PMHx: Outside records – known HIV+ for 10 years, no sustained HIV treatment or regular follow-up.
- Also – substance use disorder (multiple); bipolar disease. Inconsistent housing.
- Labs: WBC 2.1; **CD4 10; HIV RNA 740,000 copies/mL**; genotype sent.

Question

- What regimen should we start?

A. TAF/FTC, DTG
B. TAF/FTC/BIC
C. TAF/FTC/DRV/c
D. ABC/3TC/DTG
E. Something else

Recent Clinical Trials in USA/Europe Do Not Include Many Patients with Advanced HIV Disease

Study (year)	Regimens	CD4 < 200 (%)	HIV RNA >100K (%)
GS-102 (2012)	ECF-TDF vs TDF/FTC/EFV	13	34
GS-103 (2012)	ECF-TDF vs ATV/r, TDF/FTC	13	40
SINGLE (2013)	ABC/3TC, DTG vs TDF/FTC/EFV	14	30
SPRING-2 (2013)	DTG vs RAL	12	28
ACTG 5257 (2014)	RAL vs ATV/r vs DRV/r	29	30
GARDEL (2014)	LPV/r + NRTIs vs 3TC	20	44
GS-104/111 (2015)	ECF-TDF vs ECF-TAF	13	23
DRIVE AHEAD (2017)	TDF/3TC/DOR vs TDF/FTC/EFV	12	21
GS-1489 (2017)	TAF/FTC/BIC vs ABC/3TC/DTG	11	16
GS-1490 (2017)	TAF/FTC/BIC vs DTG, TAF/FTC	12	19

… And They Don’t Include Many Women, Either!

Study (year)	Regimens	Women (%)
GS-102 (2012)	ECF-TDF vs TDF/FTC/EFV	11
GS-103 (2012)	ECF-TDF vs ATV/r, TDF/FTC	9
SINGLE (2013)	ABC/3TC, DTG vs TDF/FTC/EFV	15
SPRING-2 (2013)	DTG vs RAL	15
ACTG 5257 (2014)	RAL vs ATV/r vs DRV/r	24
GARDEL (2014)	LPV/r + NRTIs vs 3TC	16
GS-104/111 (2015)	ECF-TDF vs ECF-TAF	15
DRIVE AHEAD (2017)	TDF/3TC/DOR vs TDF/FTC/EFV	15
GS-1489 (2017)	TAF/FTC/BIC vs ABC/3TC/DTG	9
GS-1490 (2017)	TAF/FTC/BIC vs DTG, TAF/FTC	11

NAMSAL: DTG vs EFV, Baseline Characteristics

Characteristic	TDF/3TC + DTG (N=310)	TDF/3TC + EFV400 (N=303)	TOTAL (N=616)	p-value
Age, median (IQR), y	38 (31-46)	36 (29-43)	36 (29-43)	0.02
Female, n (%)	197 (64%)	207 (68%)	207 (68%)	0.21
Hepatitis B virus surface antigen positive	25 (8%)	34 (11%)	34 (11%)	0.19
HIV RNA, median (IQR), log_{10} c/mL	5.3 (4.8-5.8)	5.3(4.7-5.8)	5.3(4.8-5.8)	0.99
≥100,000	207(67%)	200 (66%)	407(66%)	0.84
≥500,000	93 (30%)	95 (31.3%)	188 (30.5%)	
CD4+ cell count, median (IQR), cells/mm^3	289(157-452)	271(147-427)	281(154-44)	0.30
<200	97(31%)	107(35%)	204(33%)	0.67
200-350	89(29%)	88(29%)	117(29%)	
350-500	63(20%)	56(18%)	119(19%)	
>500	31(20%)	52(17%)	113(18%)	

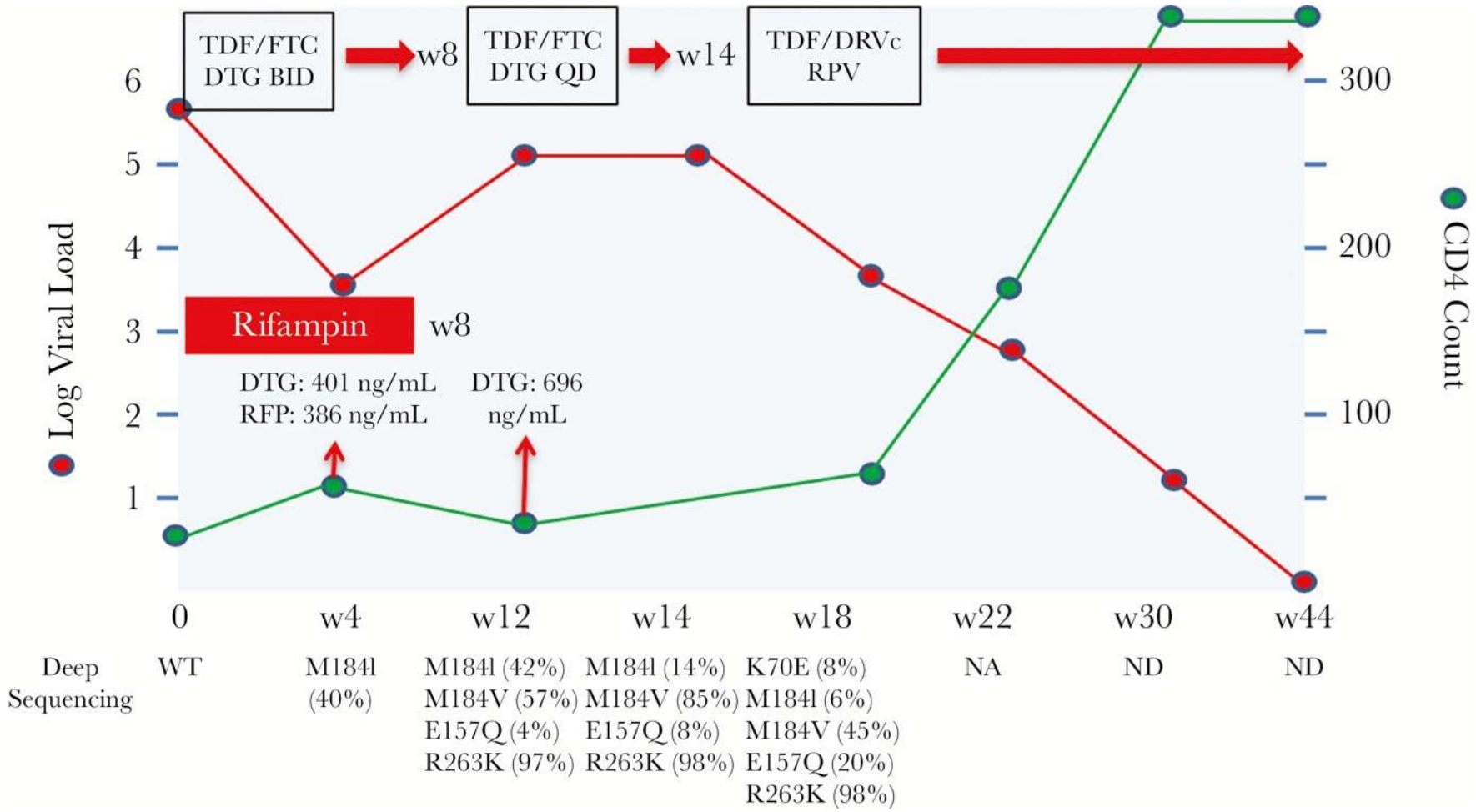
Delaporte E, et al. NEJM 2019

NAMSAL: Results in Advanced Disease Suboptimal

	DTG N=310	EFV 400 N=303	Difference A-B IC 95%	Superiority Test p-value
HIV RNA< 50 copies/ml	**231 74.5%**	**209 69%**	**5.5% (-1.6;+12.7)**	**0.13**
HIV RNA> 50 Stop for death Stop for other reasons (LTF, withdrawn)	62 6 9	70 7 15		
HIV RNA< 100 000	94/103 91.3%	86/103 83.5%	7.8% (-1.2;+16.8)	
HIV RNA> 100 000	137/207 (66.2%)	123/200 (61.5%)	4.7% (-4.6;+14.0)	
HIV RNA> 500 000	51/93 (54.8%)	55/95 (57.9%)		

Delaporte E, et al. NEJM 2019

Virologic Failure and DTG Resistance in a Treatment-naïve Patient with Advanced HIV Disease



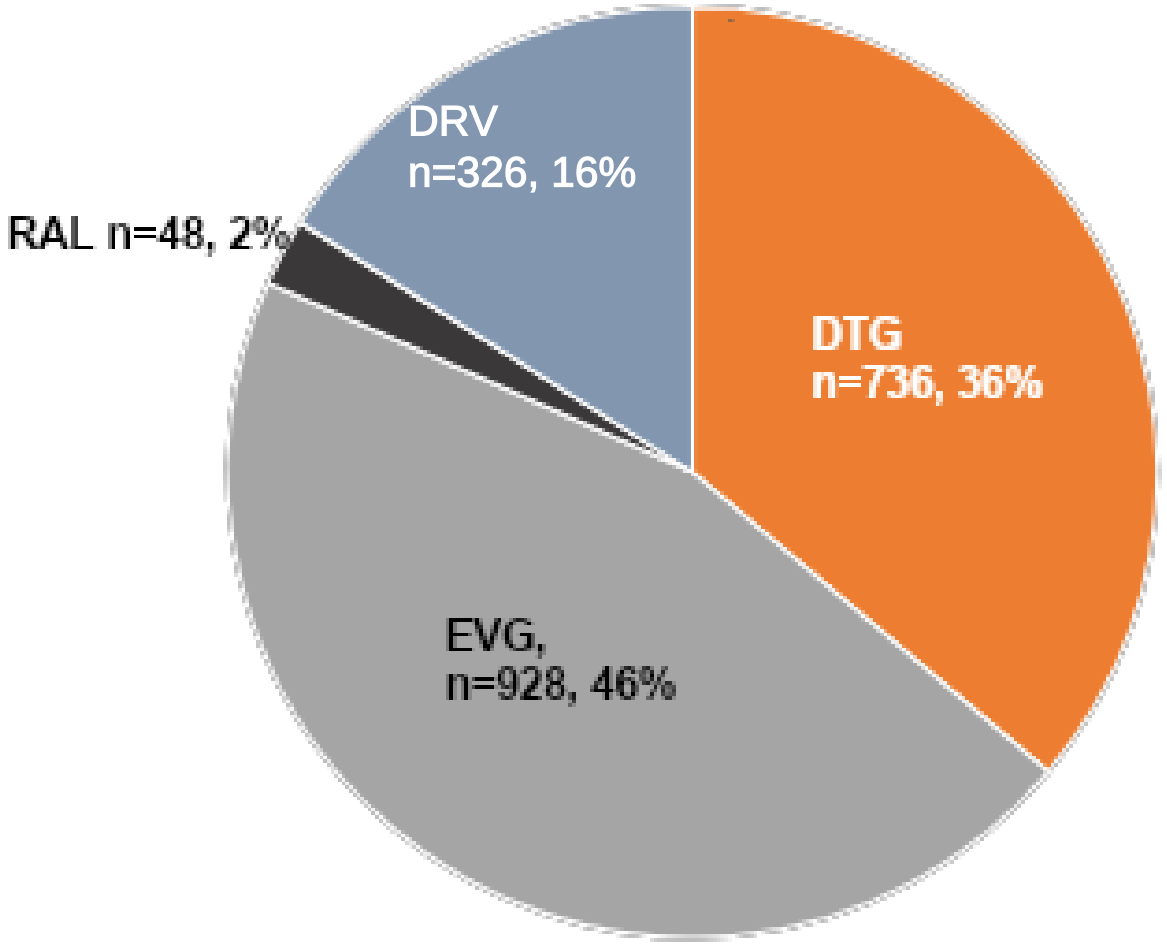
Pena MJ, et al. Open Forum Infect Dis 2019.

DHHS: A Remaining Role for PI-based Therapy?

“For those individuals in whom ART needs to begin urgently before resistance test results are available, boosted DRV may be an appropriate choice, as there is a low rate of transmitted PI resistance, it has a high barrier to resistance, and there is a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is now available as an STR.”

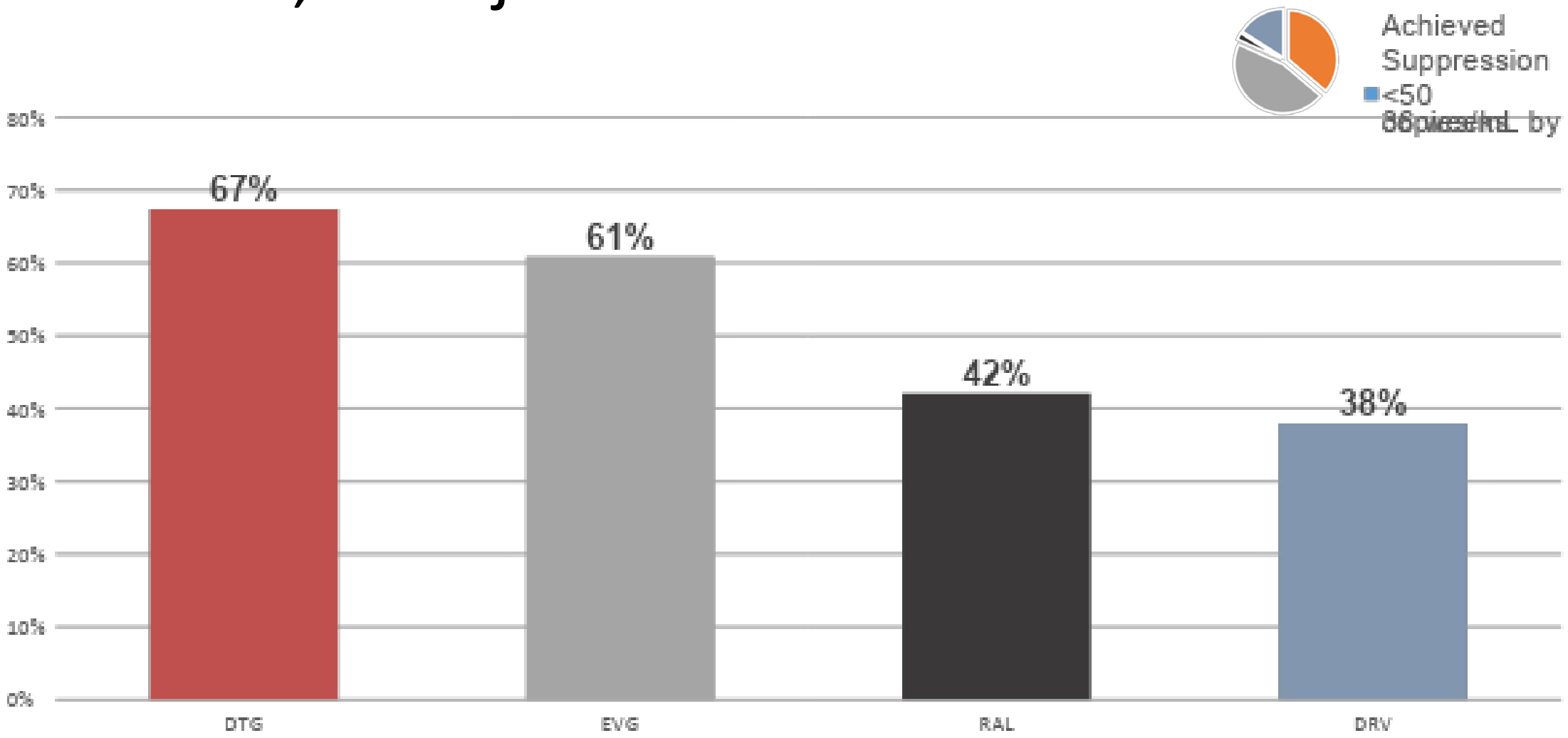
DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision Jul 2019.

CHORUS cohort: Evaluation of ART efficacy with baseline high HIV RNA

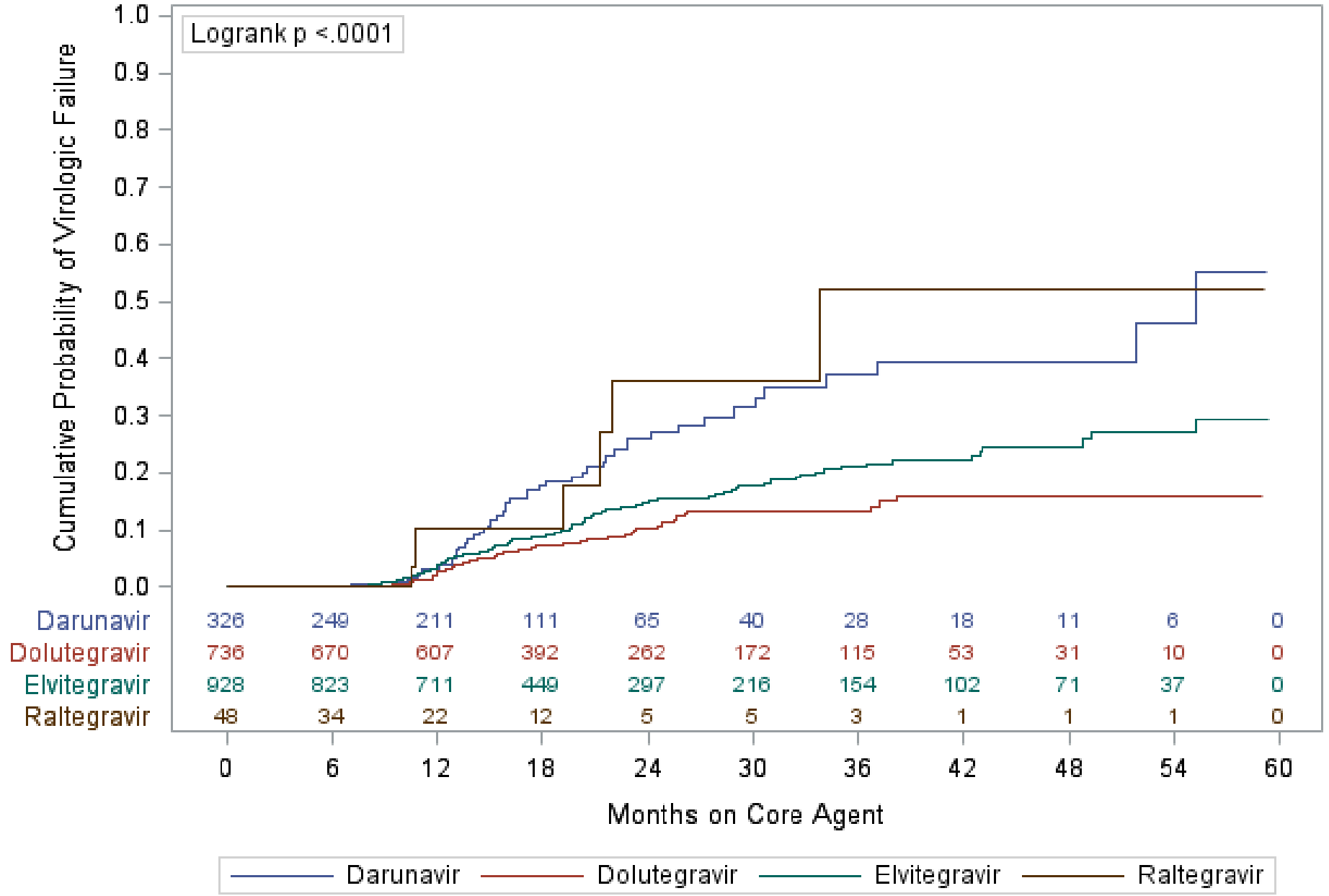


Mills A. IAS 2019. Abstr WEAB0404LB.

≥ 100,000 copies/mL With Virologic Suppression by 36 Weeks, Unadjusted



Mills A. IAS 2019. Abstr WEAB0404LB.



Mills A. IAS 2019. Abstr WEAB0404LB.

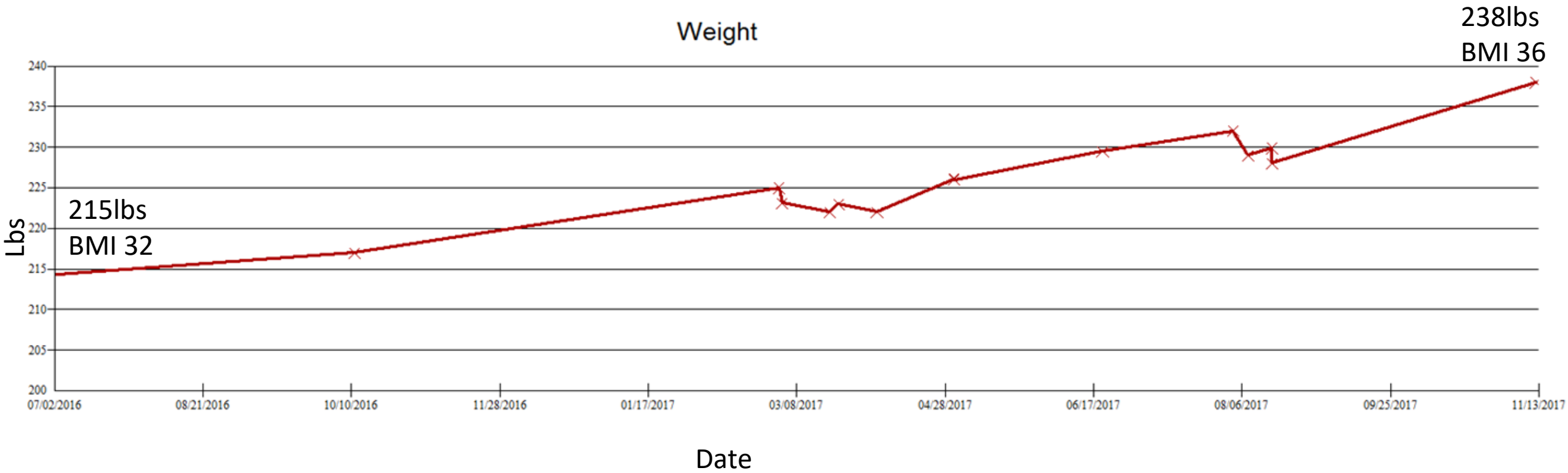
Will “LAPTOP” tell us something different?

- Eligible: Active OI or other serious infection, or asymptomatic with CD4 < 100 (n=440)
- BIC/FTC/TAF vs DRV/c/FTC/TAF

https://clinicaltrials.gov/ct2/show/NCT03696160

Case #3

- 55 year old woman, diagnosed 2008
- Initial CD4 350, HIV RNA 33,000, weight 210 pounds, BMI 31
- Began TDF/FTC/EFV – no side effects, no treatment failure
- Gained 5 pounds between 2008 and 2016
- Diagnosed with osteopenia by DEXA scan – switched to TAF/FTC, DTG in July 2016
- One year later – now very upset about rapid weight gain – denies change in diet or activity level
- He's *sure* it's the new meds, asks to go back on TDF/FTC/EFV



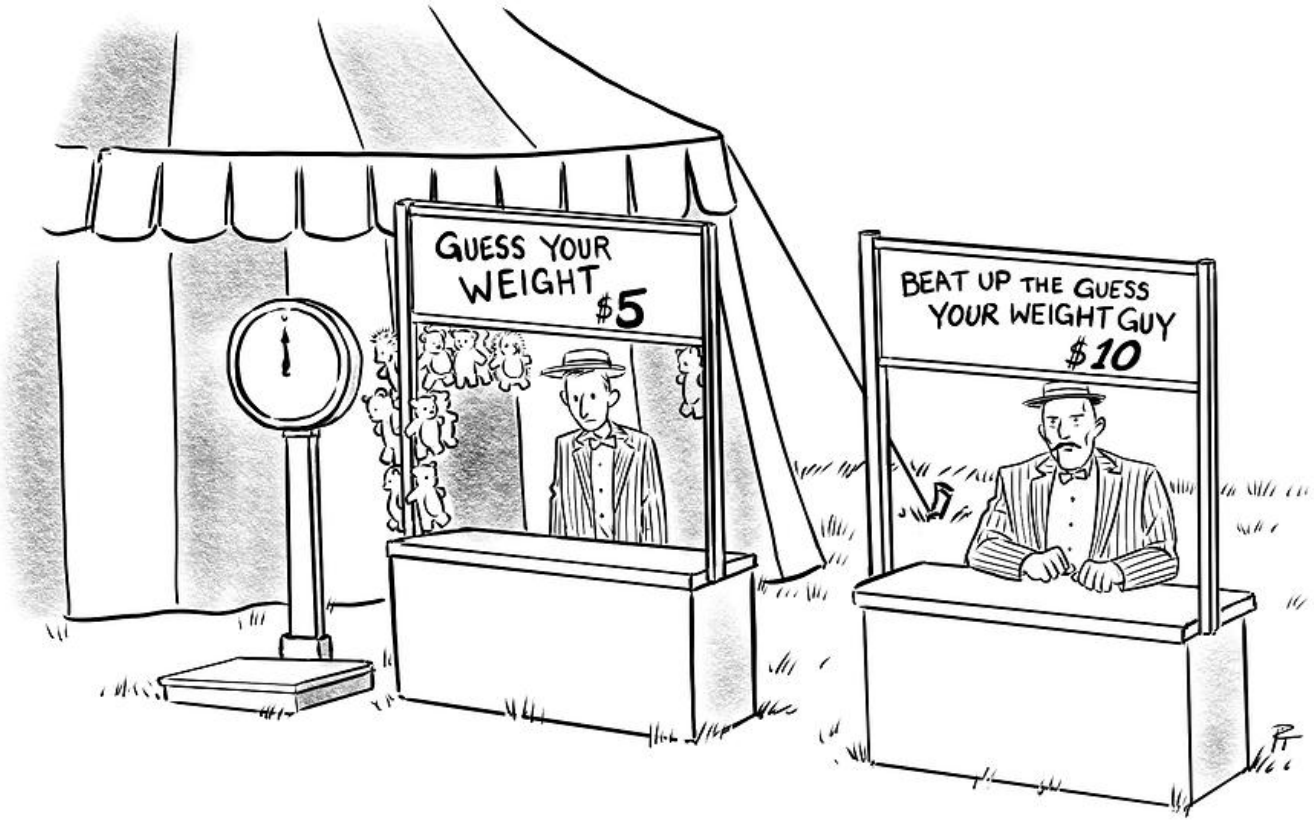
Slide courtesy Mary Montgomery, MD

Question

- Work-up for medical causes of weight gain are negative. What would you do now?

A. Continue current therapy (TAF/FTC, DTG)
B. Switch back to TDF/FTC/EFV
C. Switch to TDF/FTC/DOR
D. Something else

HIV Therapy and Abnormal Weight Gain – Emerging Clinical Evidence Implicating ART



Obesity among patients with HIV: the latest epidemic

Crum-Cianflone N, et al. AIDS Patient Care STDs 2008;22:925-30.

HIV infection and obesity: where did all the wasting go?

Tate T, et al. Antivir Ther 2012;17:1281-9.

Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons

Lakey W, et al. AIDS Res Hum Retroviruses 2013;29:435-40.

The Fat of the Matter: Obesity and Visceral Adiposity in Treated HIV Infection

Lake JE, et al. Curr HIV/AIDS Rep 2017;14:211-9.

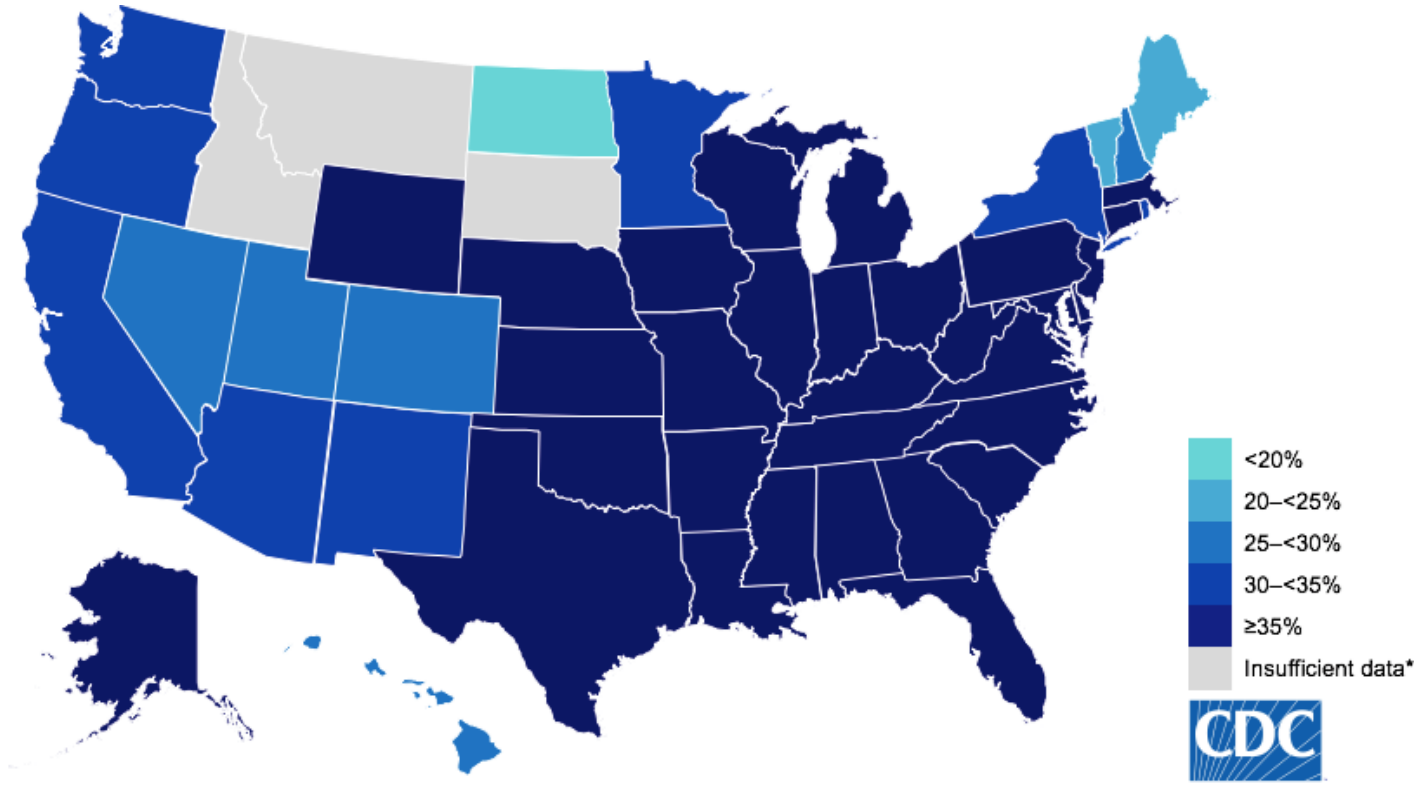
Practical Review of Recognition and Management of Obesity and Lipohypertrophy in Human Immunodeficiency Virus Infection

Lake JE, et al. Clin Infect Dis 2017;64:1422-9.

Factors Driving Increased Obesity Among People with HIV

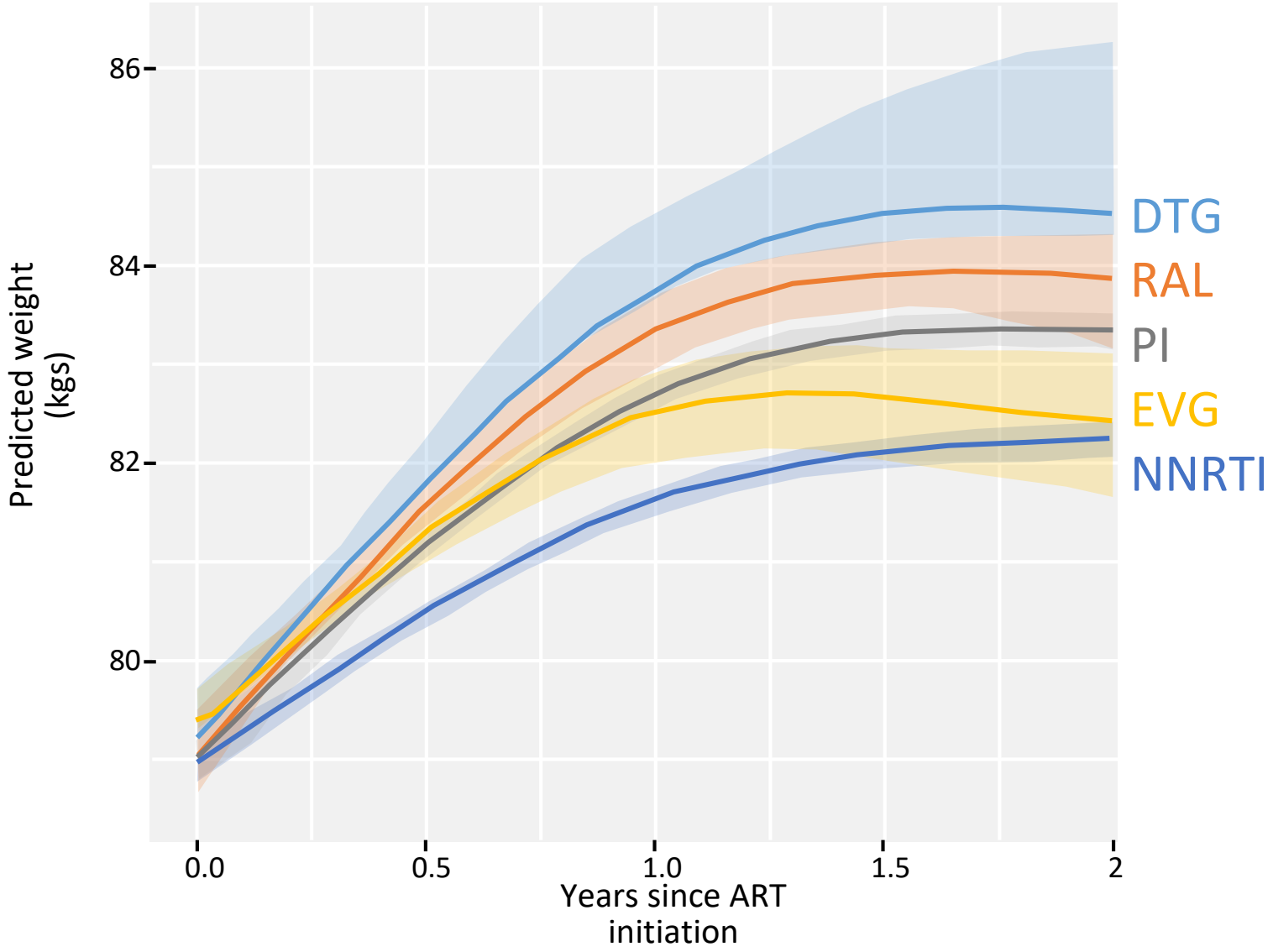
- Geographic region
- Race
- Poverty
- Food insecurity

- But what about the HIV meds?



Self-Reported Obesity Among Blacks, 2015-2017

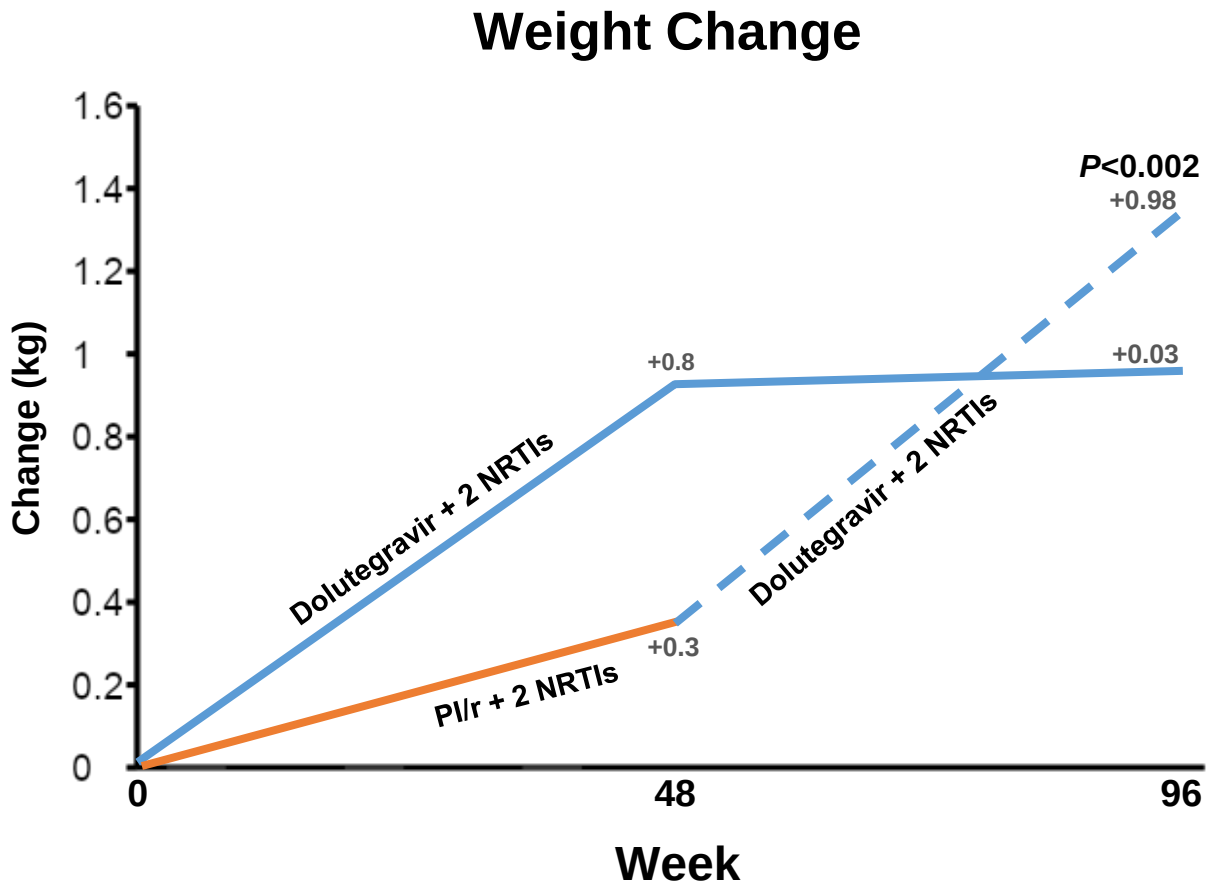
NA-ACCORD: Weight Gain After ART Initiation (n=21,867)



Bourgi K, et al. CROI 2019.

NEAT 022: Change in Weight After Switching PI to DTG in Patients at High CV Risk

- Factors associated with BMI gain on DTG in multivariable analysis:
  - Framingham >15% (P=0.042)
  - Hypertension (P=0.035).
- Protective factors:
  - Switching from PIs other than DRV or ATV (P=0.032)
  - Current smoking (P=0.006)
  - Daily exercise (P=0.036)
  - HDL-chol (P<0.001)



Gatell JM, et al. *Clin Infect Dis.* 2018;Jun 14. [Epub ahead of print].
Waters L, et al. *J Int AIDS Soc*. 2018;21(suppl 8):77. Abstract P102.

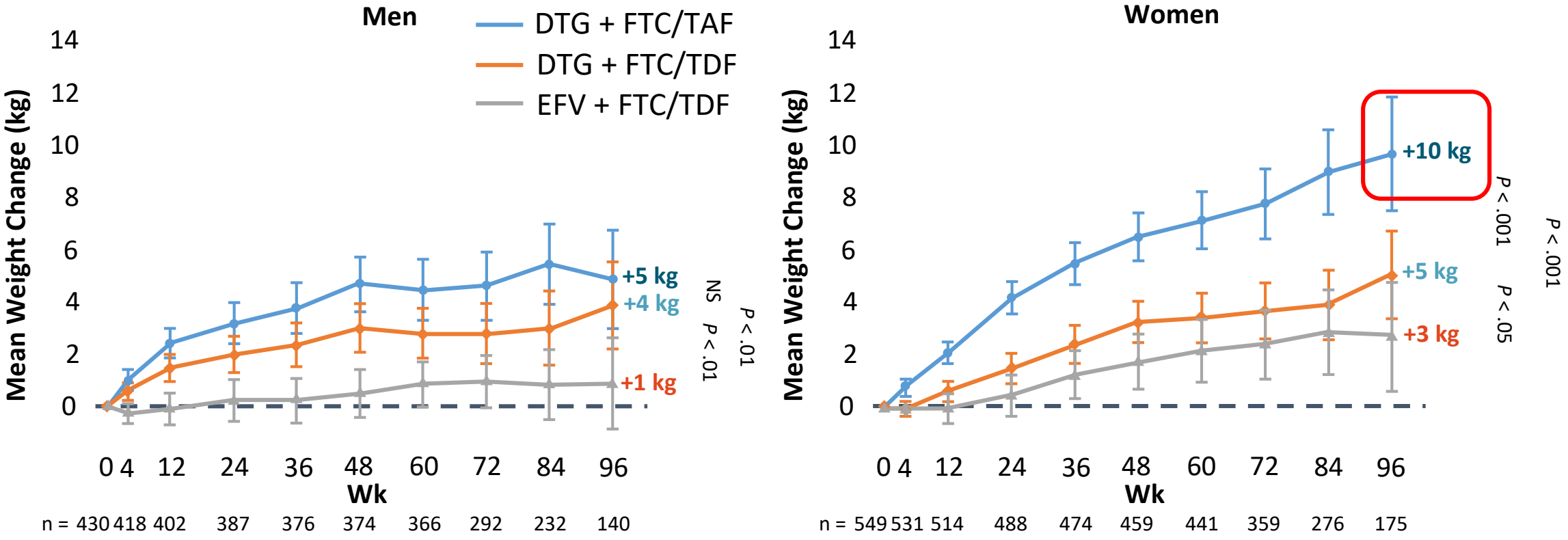
NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

Outcome	NAMSAL			ADVANCE			
	DTG + 3TC/TDF (n = 293)	EFV + 3TC/TDF (n = 278)	P Value	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF	P Value
Mean Δ in weight, kg ▪ Wk 48 ▪ Wk 96	 +5 NA	 +3 NA	< .001	 +6 +8	 +3 +5	 +1 +2	< .001
Mean Δ in BMI at Wk 48	+1.7	+1.2	< .001	NR	NR	NR	
Treatment-emergent overweight (BMI 25-29.9), % ▪ Wk 48 ▪ Wk 96	 16 NA	 17 NA	NS	 23 25	 14 13	 9 11	NS
Treatment-emergent obesity (BMI ≥ 30), % ▪ Wk 48 ▪ Wk 96	 12 NA	 5 NA	< .01	 14 19	 7 8	 6 4	< .01

Hill. IAS 2019. Abstr MOAX0102LB.

ADVANCE: Mean Change in Weight to Wk 96

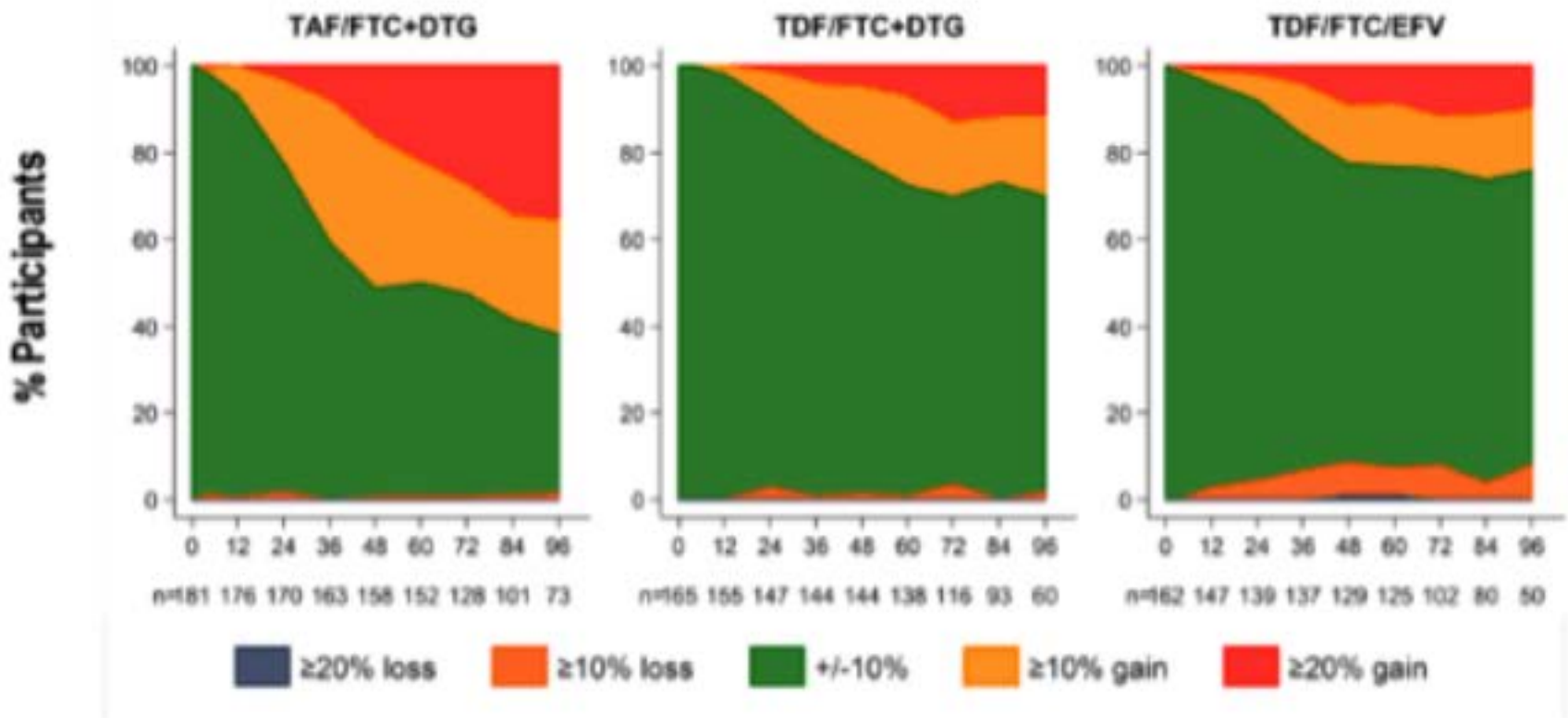
- Significantly greater weight increase* with DTG vs EFV, with TAF vs TDF; plateauing in weight gain after Wk 48 observed in men but not in women



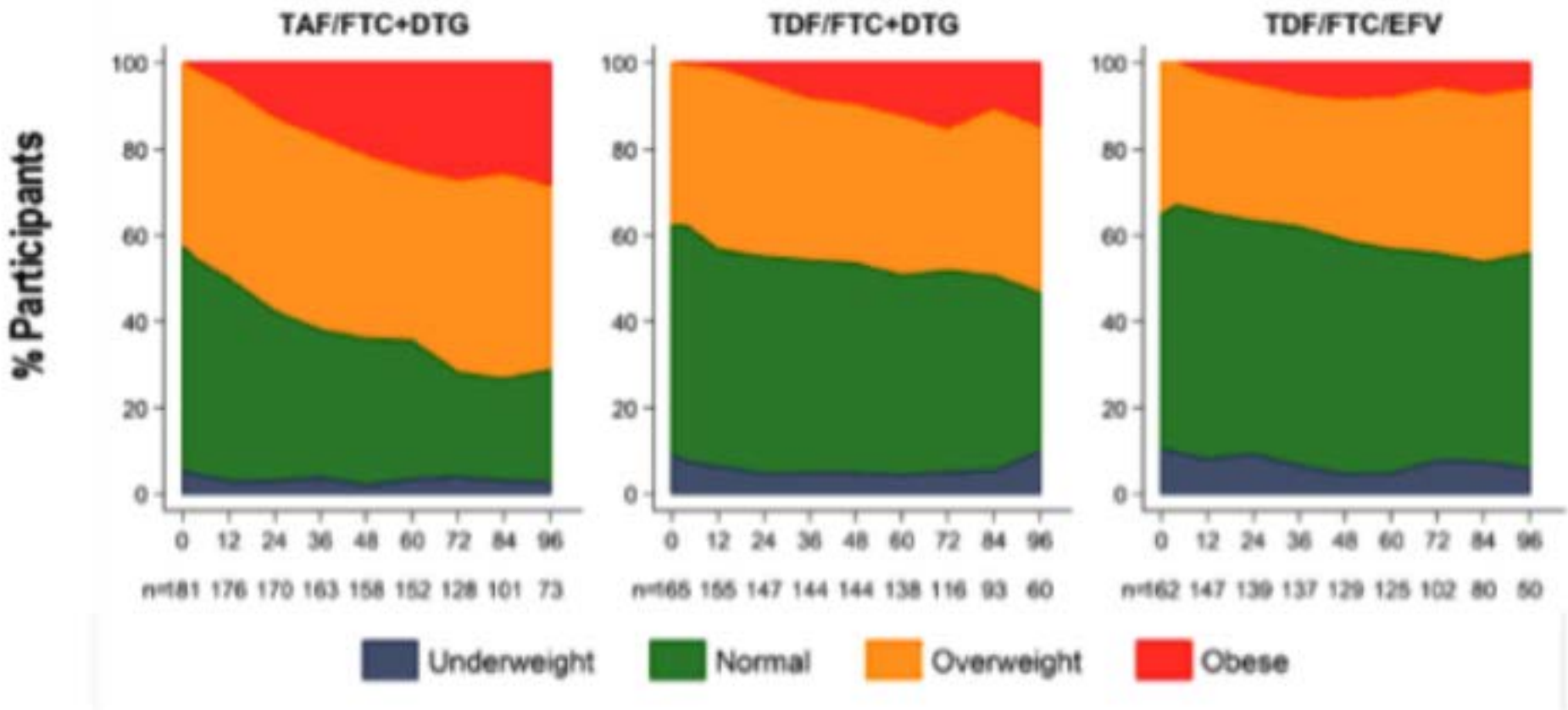
Hill. IAS 2019. Abstr MOAX0102LB.

*Wilcoxon rank-sum comparison at Wk 96.

ADVANCE: Percentage change in weight over time: women



ADVANCE: BMI category over time: women (obese at baseline excluded)



ART and Weight Gain: Questions

- Patients have been *convinced* the HIV medications are to blame – it appears they are correct!
- INSTI-based treatment lead to more weight gain than other strategies. Is there a difference between INSTIs?
- What is going on with TAF vs TDF?
- Is excess weight gain reversible by stopping the offending drug(s)?
- How does ART, or a specific drug class, cause weight gain? Is it just better tolerated ART? Or an off-target effect altering appetite or metabolism?
- Are there adverse metabolic or other consequences of ART-induced weight gain?
- Should these emerging data change clinical practice?

Question

- Should the data on weight gain from INSTIs and TAF change clinical practice?

A. Yes.
B. No.
C. Depends.

Case #4

- 36 year old man, diagnosed with HIV earlier this year
- Started on TAF/FTC/BIC – rapid virologic suppression
- No side effects, 100% reported adherence
- Says he's terrified of diagnosis being discovered by his family
- Wants the "new injectable" treatment he's read about so he doesn't need to keep pills at home

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Scarlet Virus

Ila Mulasi, M.D.

N Engl J Med 2018; 378:2157-2159

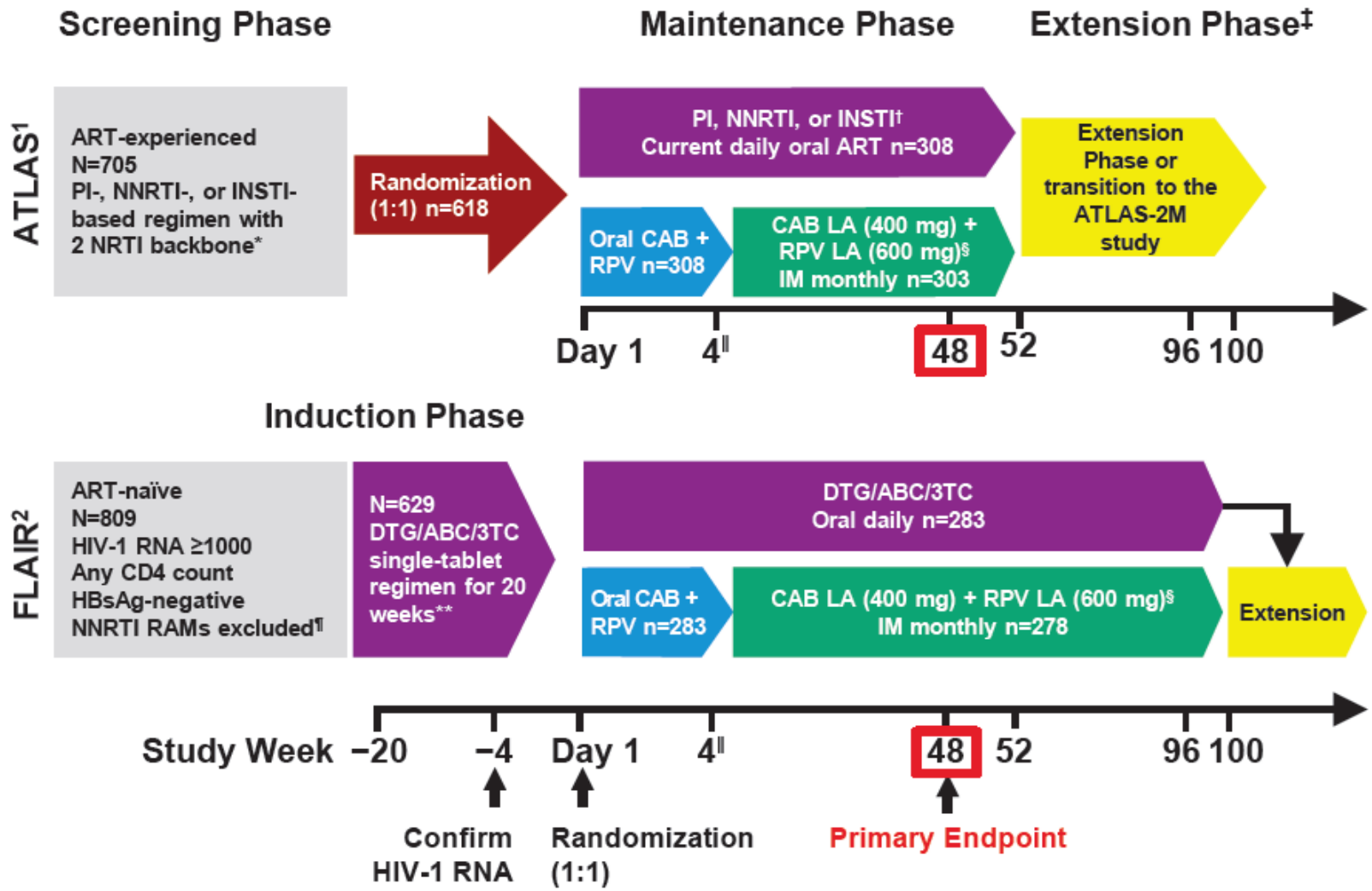
Question

- Injectable cabotegravir and rilpivirine will likely be FDA- approved in 2020. It will be two 3 ml injections given every 4 weeks, not self-administered. What percentage of patients will want this treatment?

A. <5%
B. 5-10%
C. 11-25%
D. >25%

Phase 3 Clinical Trials: ATLAS/FLAIR Week 48

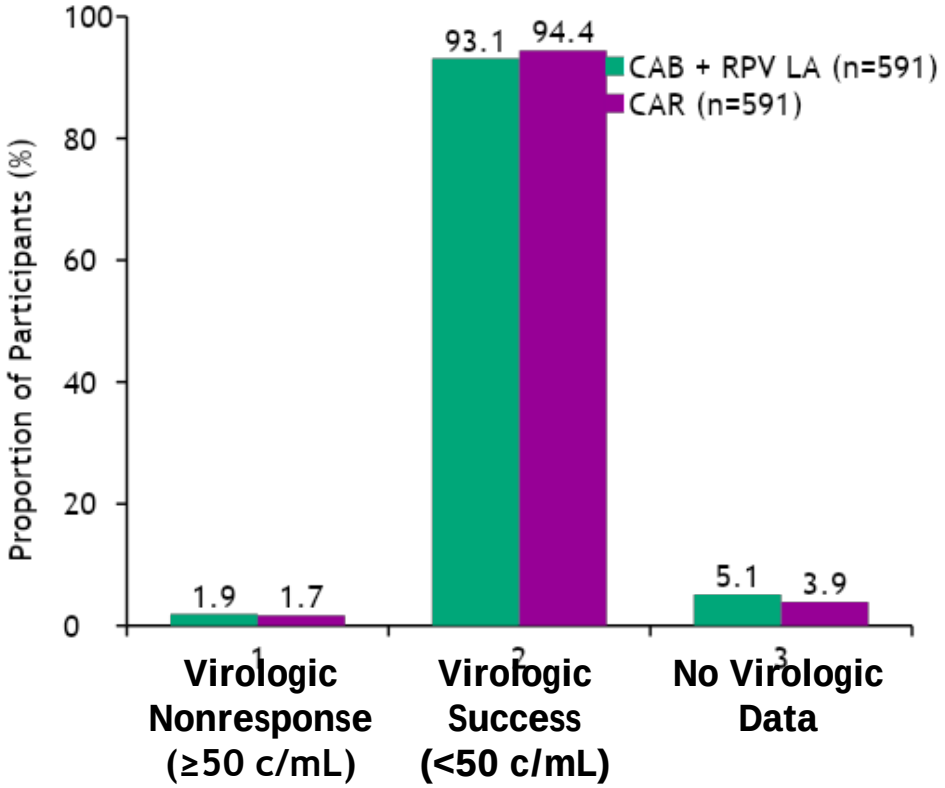
- ATLAS: virologically suppressed; switch to monthly IM LA CAB/RPV vs. continue oral ART
- FLAIR: Treatment naïve; suppress with oral ART; switch to monthly IM LA CAB/RPV vs. continue oral ART



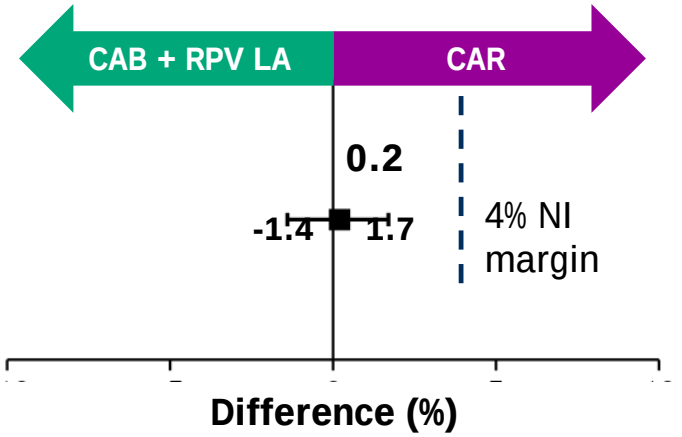
Overton E IAS 2019 MOPEB257

ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes

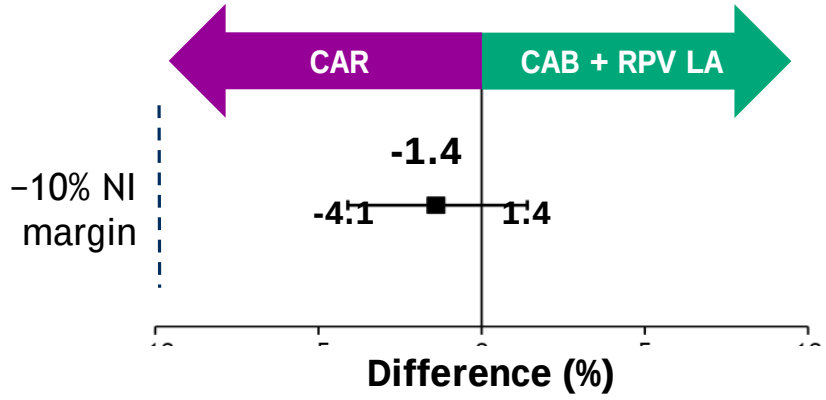


Adjusted treatment difference (95% CI)*



Primary Endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48



Key Secondary Endpoint:

LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

Overton E IAS 2019 MOPEB257

ATLAS: Patient Views on Long-Acting CAB + RPV

- 86% to 90% of LA CAB + RPV recipients scored **ISRs and pain** at Wk 48 as **totally or very acceptable** in PIN questionnaire

Acceptability, %		LA CAB + RPV	
		Wk 5 (n = 296)	Wk 48 (n = 303)
ISRs	▪Totally	48	67
	▪Very	26	23
	▪Moderately	18	7
	▪A little	5	3
	▪Not at all	3	1
Pain	▪Totally	29	55
	▪Very	35	31
	▪Moderately	20	9
	▪A little	10	4
	▪Not at all	6	1

P < .001 for Δ over time in "acceptability of ISRs" domain of PIN.

- **Greater improvement** in **treatment satisfaction** by HIVTSQ at Wks 24, 44 with LA CAB + RPV vs daily oral ART

Adjusted Mean Δ From BL in Tx Satisfaction*	LA CAB + RPV	BL Oral ART	Difference (95% CI)†
Wk 24	6.43	1.05	5.39 (4.17-6.60)
Wk 44	6.12	0.44	5.68 (4.37-6.98)

*Adjusted for BL score, sex, age, race, and BL third agent class.
†*P* < .001 for all listed differences.

Patient Preference for ART Delivery Method by Population, % (n/N)	Long-acting IM	Daily PO
ITT-E	86 (266/308)	2 (7/308)
Responding patients	97 (266/273)	3 (7/273)

Murray. IAS 2019. Abstr MOAB0103.

Treatment Emergent Resistance (CAB/RPV Groups)

Site/HIV subtype	Baseline Resistance (HIV DNA)		Resistance at Virologic failure	
	RT	IN	RT	IN
ATLAS				
Russia/A1	E138E/A	L74I	E138A	L74I
France/AG	V108V/I, E138K	None	V108I, E138K	None
Russia/A1	None	I74I	E138E/K	N155H, L74I
FLAIR				
Russia/A1	None	L74I	E138E/A/K/T	L74I, Q148R
Russia/A1	None	L74I	K101E	L74I, G140R
Russia/A1	None	L74I	E138K	L74I, Q148R

CAB and RPV concentrations at time of failure below population means but within range for majority of individuals who maintained suppression

Swindells S, et al. CROI 2019; #139 Orkin C, et al. CROI 2019; #140.

Case #5

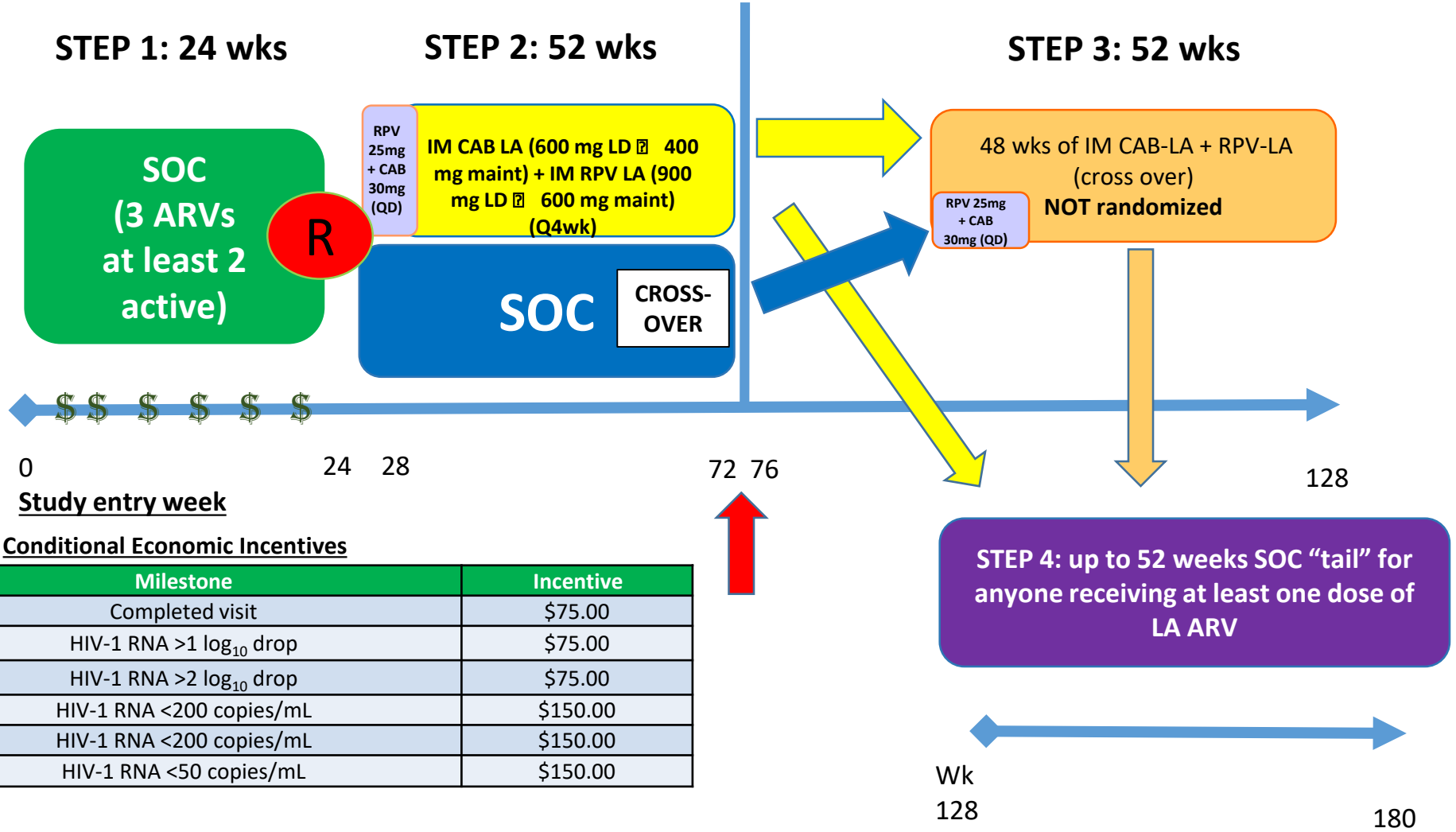
- A 48-year-old woman with a long history of HIV infection is referred for evaluation of novel ART strategies.
- History is notable for several complications of advanced HIV disease, including PCP, disseminated zoster, wasting syndrome – all occurring during poor (i.e., zero!) medication adherence.
- Current HIV RNA < 20 copies/mL, CD4 250 on TAF/FTC/RPV + DTG – administered via G-tube, which is to be removed shortly.
- Over a dozen HIV genotypes – either wild-type or M184V only.
- Requests an injectable ART option, as she cannot take pills.

Question

- The label for injectable CAB/RPV will likely be for people similar to ATLAS/FLAIR population – adherent with no history of treatment failure.
- Will you be using it in people who struggle with adherence, such as in this case?

A. Yes
B. No

ACTG 5359: Long-acting Cabotegravir + Rilpivirine in Non-adherent Persons with HIV



Conditional Economic Incentives

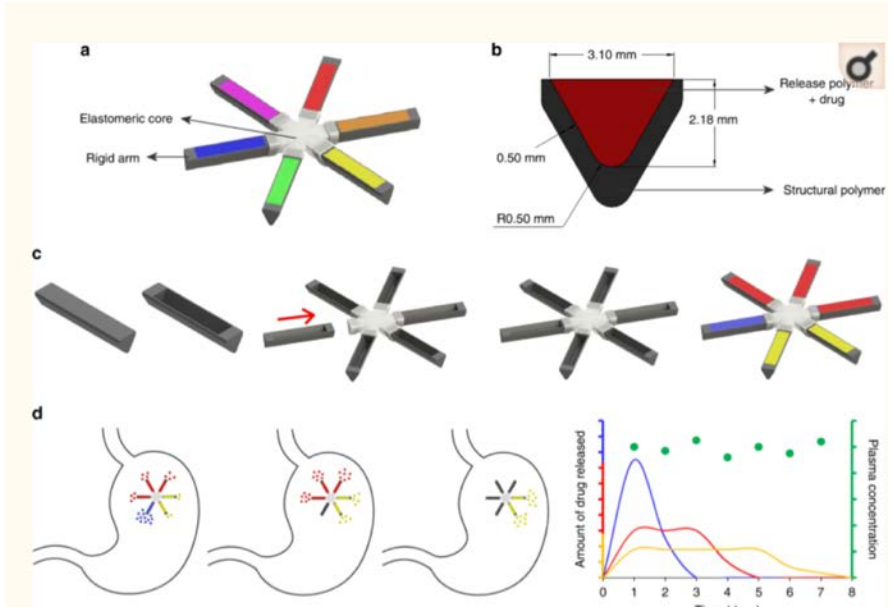
Step 1, Week	Milestone	Incentive
2	Completed visit	$75.00
4	HIV-1 RNA >1 $\log_{10}$ drop	$75.00
8	HIV-1 RNA >2 $\log_{10}$ drop	$75.00
12	HIV-1 RNA <200 copies/mL	$150.00
16	HIV-1 RNA <200 copies/mL	$150.00
20	HIV-1 RNA <50 copies/mL	$150.00

Questions Regarding LA-CAB+RPV

- How will the strategy work outside of a clinical trials population?
- Oral lead-in – is it required?
- How will drug toxicity be managed?
- Who will administer the injections, and where?
- The every 8 week regimen appears preferred – will it comparably effective, with an acceptable risk of resistance? (ATLAS-2M study)
- How does a patient stop this regimen?

Long-Acting ART Options in Development

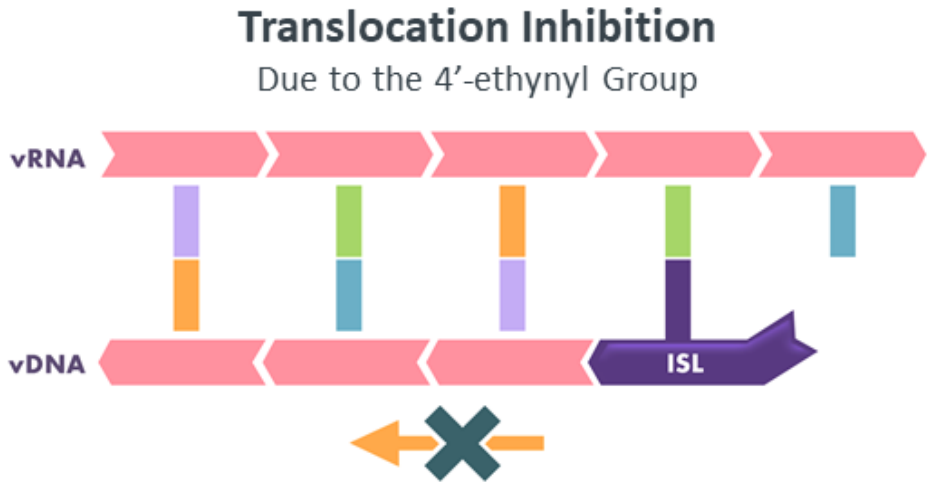
- Islatravir
- GS-6207
- Monoclonal antibodies
  - PRO140
  - UB-421
  - *Many* broadly neutralizing antibodies (bNAbs) with “extendification”
- Subcutaneous implants
- Gastric drug reservoir



Kirtane AR, et al. Nat Commun. 2018;9:2.

Islatravir (MK-8591)

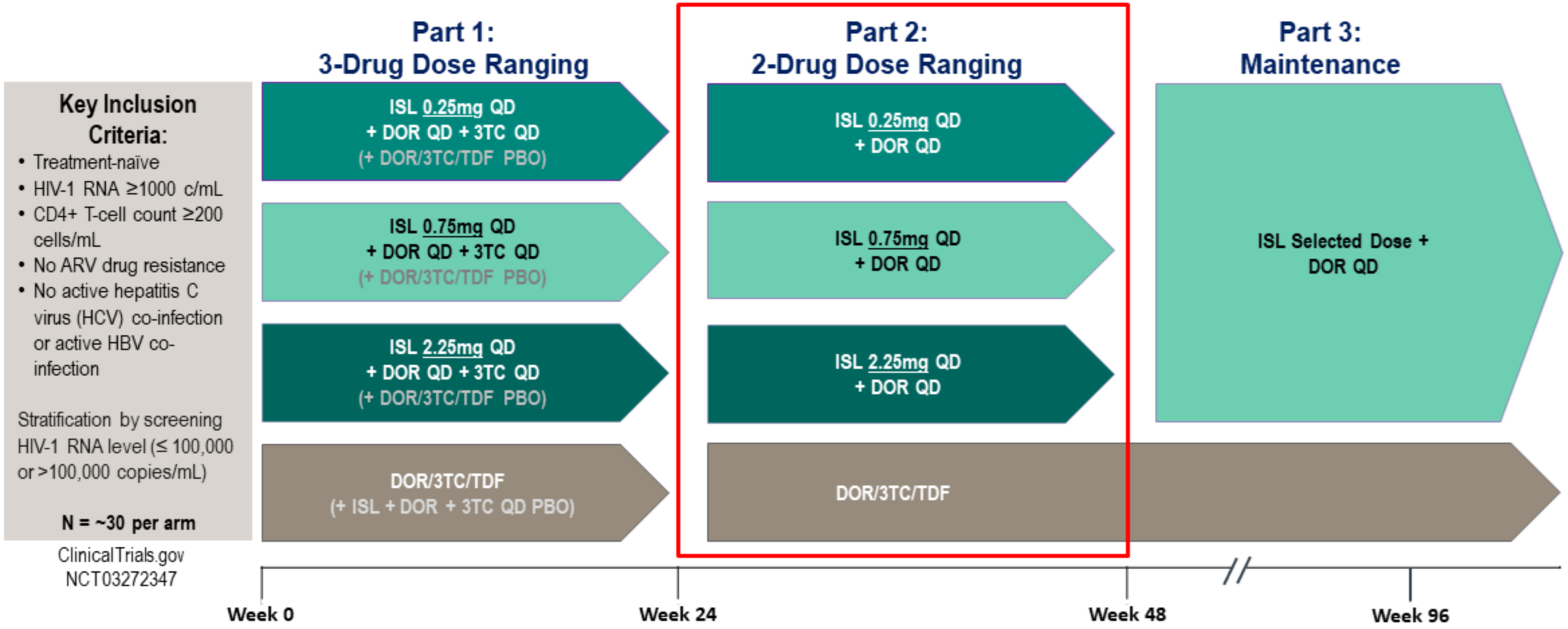
- ISL: nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Potent at low doses
- High barrier to resistance
- Long intracellular half life (about 120 h in healthy adults)
- Potential for once daily, once weekly or less frequent dosing



Molina J-M IAS 2019 WEAB0402LB

DRIVE2Simplify: Phase 2b Dose Ranging Trial of ISL + DOR vs. DOR/3TC/TDF

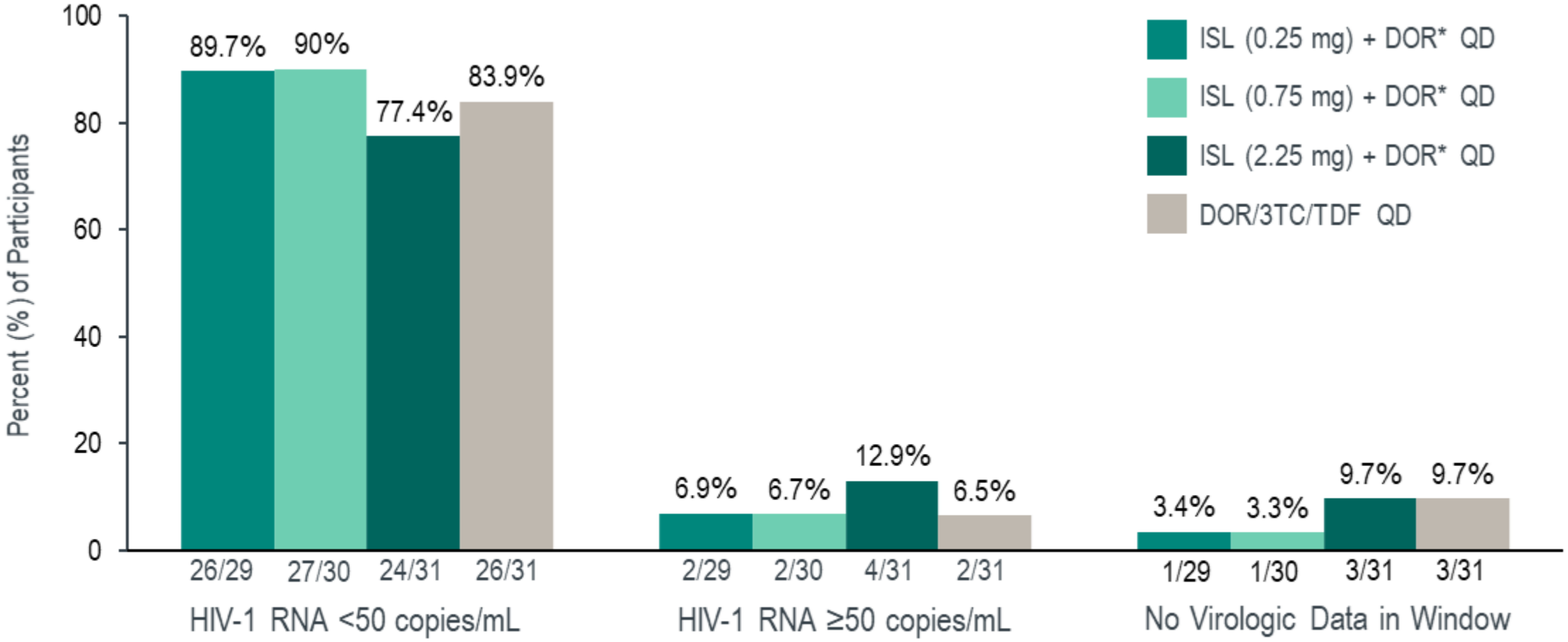
Efficacy and safety at Wk 48 of different doses of ISL + DOR following ISL + DOR + 3TC induction for 24 wks vs DOR/3TC/TDF (n=121)



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.

Molina J-M IAS 2019 WEAB0402LB

Virologic Outcomes Through Week 48 (FDA Snapshot)



*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

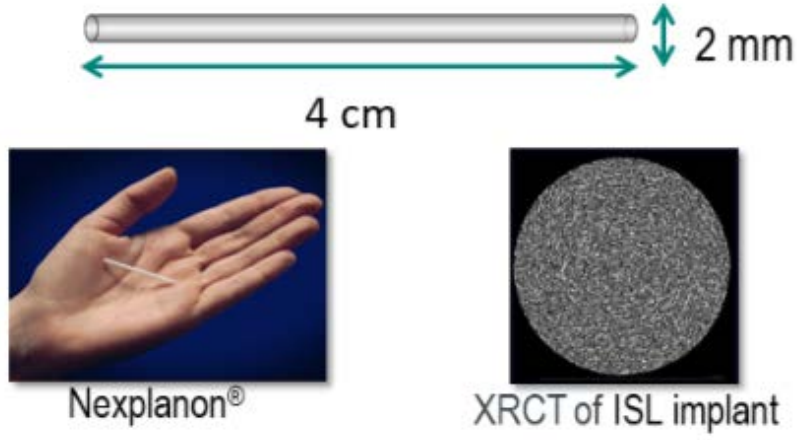
Molina J-M IAS 2019 WEAB0402LB

ISL + DOR: Other Results

- All participants with protocol defined virologic failure had confirmed VL <80
- No participants met criteria for resistance testing
- Plan: phase 3 trial of this two-drug regimen

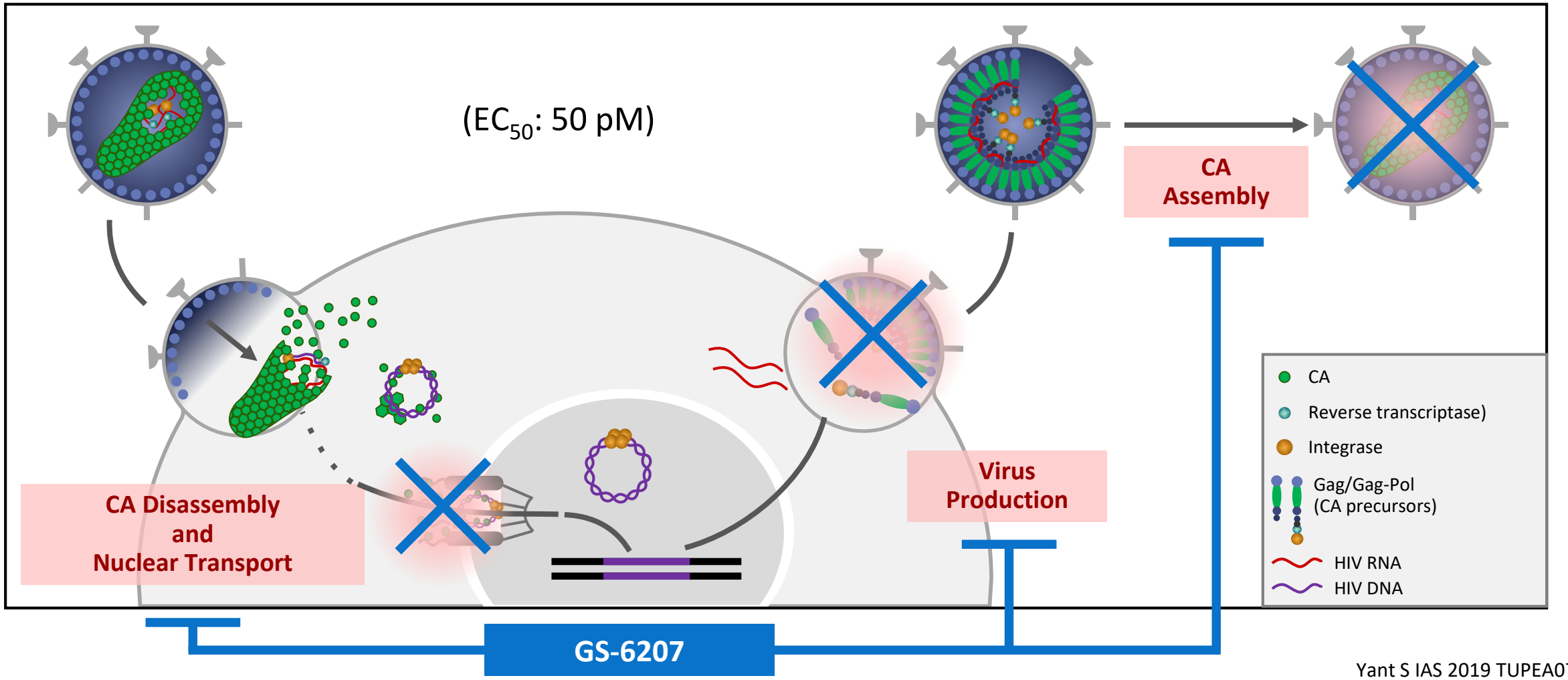
<u>Future possibilities:</u>

- Based on PK considerations, ISL has potential for once weekly dosing for treatment – partner TBD
- Also being considered for PrEP – ISL implant could potentially maintain protective concentrations for 12 months



Molina J-M IAS 2019 WEAB0402LB

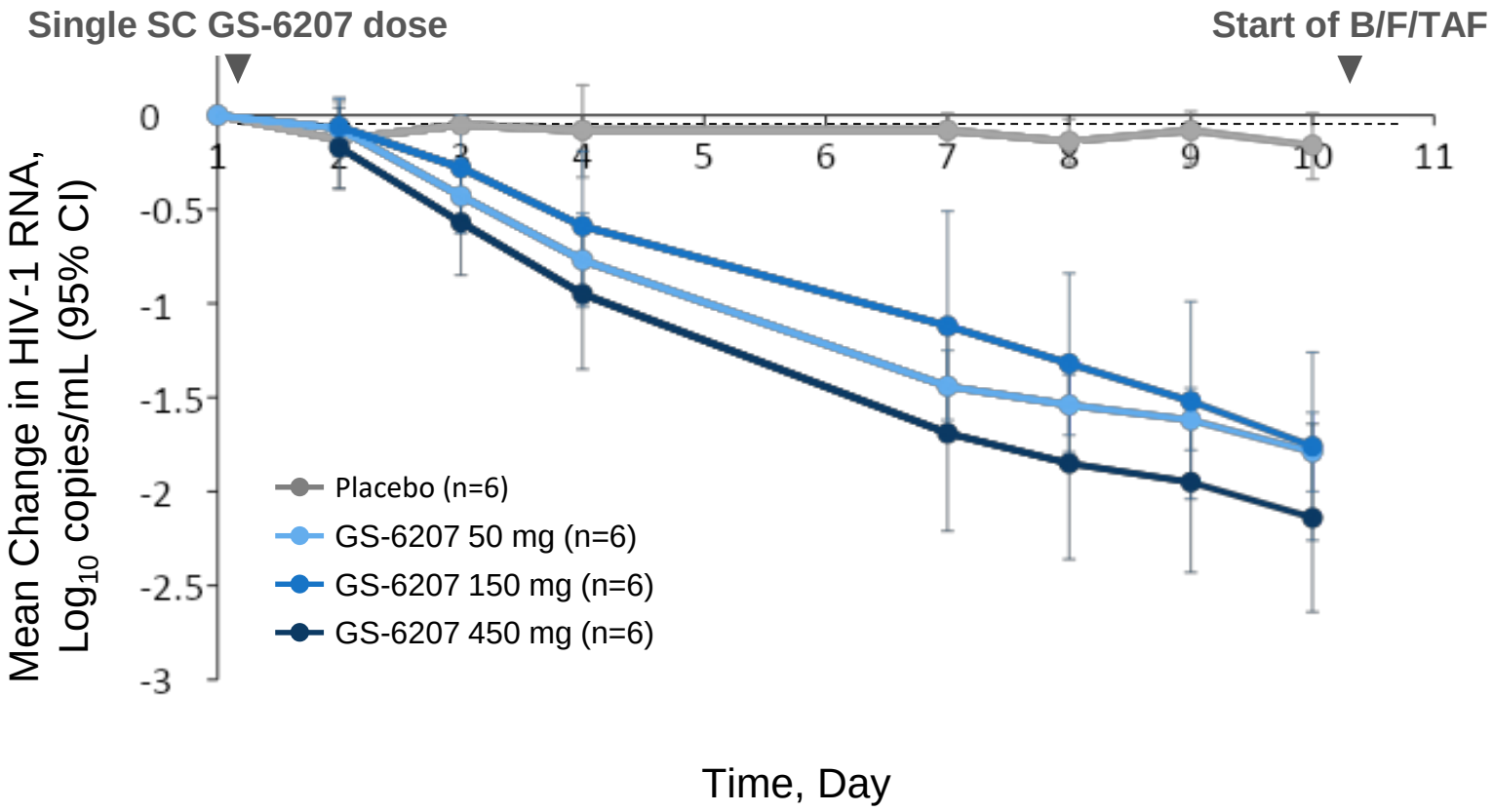
GS-6207: HIV Capsid Inhibitor



Yant S IAS 2019 TUPEA075

In people without HIV, single subcutaneous injection maintained exposures for >24 wks

GS-6207, HIV Capsid Inhibitor: HIV RNA Decline After a Single Subcutaneous Dose

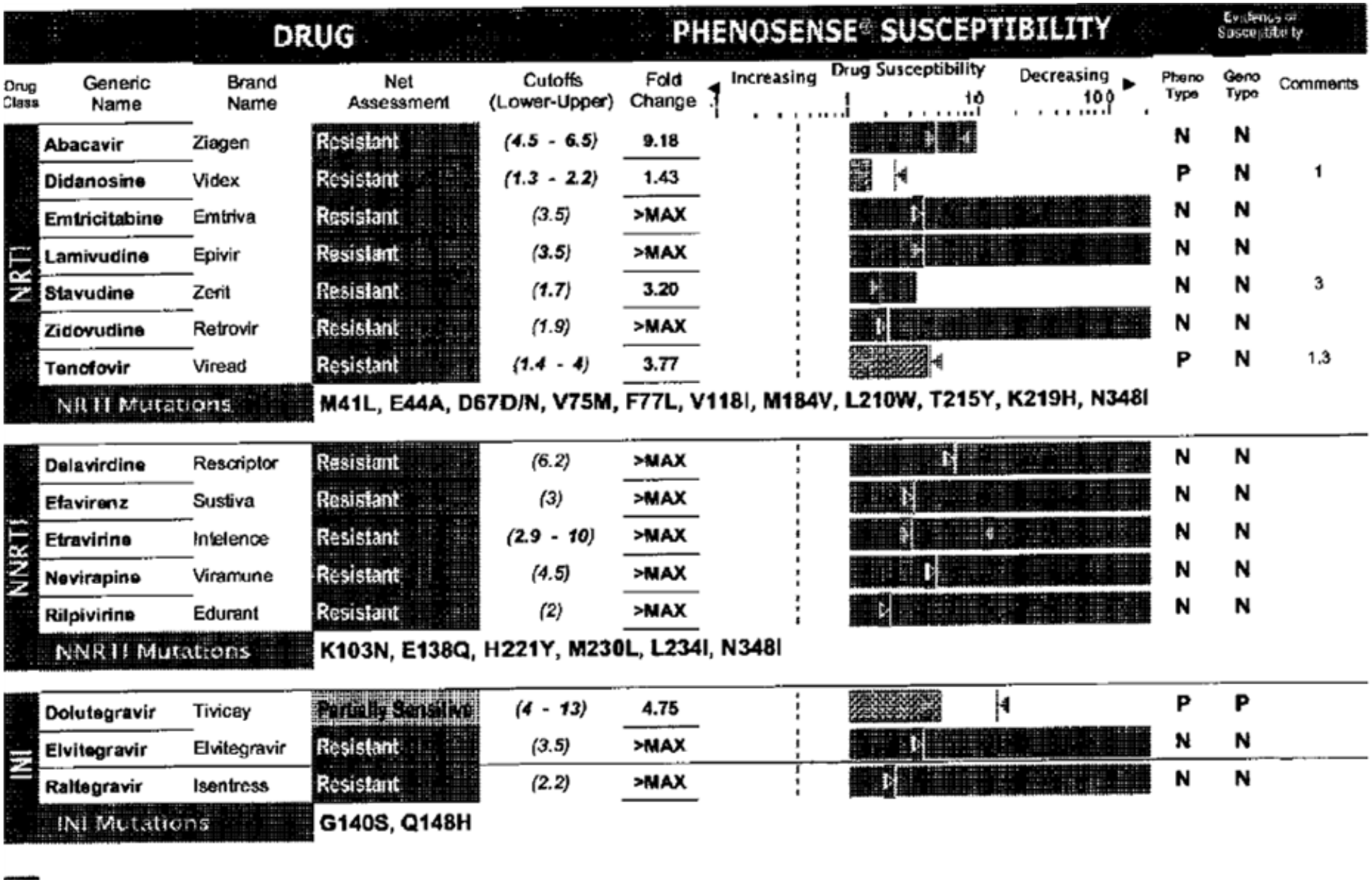


Maximum reduction of HIV RNA: -1.8 to 2.0 log10 c/mL

Daar E IAS 2019 LBPEB13

Case #6

- 67-year-old man, diagnosed with HIV infection in 1989.
- Treated initially with single and dual NRTIs; subsequently received agents in all available drug classes.
- Although clinically stable with a relatively preserved CD4 cell count, he has had viral suppression only transiently when receiving LPV/r, ZDV/3TC, TDF in early 2000s; that regimen was stopped for injection site reactions.
- Most recent regimen: DTG, ETR, twice-daily DRV/r.
- Resistance testing sent for viral load of 2100.


DRUG
PHENOSENSE® SUSCEPTIBILITY
Evidence of Susceptibility
Drug Class
Generic Name
Brand Name
Net Assessment
Cutoffs (Lower-Upper)
Fold Change
Increasing
Drug Susceptibility
Decreasing
1
10
100
Pheno Type
Geno Type
Comments
NRTI
Abacavir Ziagen Resistant (4.5 - 6.5) 9.18 N N
Didanosine Videx Resistant (1.3 - 2.2) 1.43 P N 1
Emtricitabine Emtriva Resistant (3.5) >MAX N N
Lamivudine Epivir Resistant (3.5) >MAX N N
Stavudine Zerit Resistant (1.7) 3.20 N N 3
Zidovudine Retrovir Resistant (1.9) >MAX N N
Tenofovir Viread Resistant (1.4 - 4) 3.77 P N 1,3
NRTI Mutations
M41L, E44A, D67D/N, V75M, F77L, V118I, M184V, L210W, T215Y, K219H, N348I
NNRTI
Delavirdine Rescriptor Resistant (6.2) >MAX N N
Efavirenz Sustiva Resistant (3) >MAX N N
Etravirine Intelence Resistant (2.9 - 10) >MAX N N
Nevirapine Viramune Resistant (4.5) >MAX N N
Rilpivirine Edurant Resistant (2) >MAX N N
NNRTI Mutations
K103N, E138Q, H221Y, M230L, L234I, N348I
INI
Dolutegravir Tivicay Partially Sensitive (4 - 13) 4.75 P P
Elvitegravir Elvitegravir Resistant (3.5) >MAX N N
Raltegravir Isentress Resistant (2.2) >MAX N N
INI Mutations
G140S, Q148H

DRUG — PHENOSENSE® SUSCEPTIBILITY

Drug Class	Generic Name	Brand Name	Net Assessment	Cutoffs (Lower-Upper)	Fold Change	Pheno Type	Geno Type	Comments
PI	Atazanavir	Reyataz	Resistant	(2.2)	14	N	N	
	Atazanavir	Reyataz / r*	Resistant	(5.2)	14	N	N	
	Darunavir	Prezista / r*	Partially Sensitive	(10 - 90)	60	P	N	
	Fosamprenavir	Lexiva / r*	Resistant	(4 - 11)	>MAX	N	N	
	Indinavir	Crixivan / r*	Resistant	(10)	19	N	N	
	Lopinavir	Kaletra*	Partially Sensitive	(9 - 55)	14	P	N	
	Nelfinavir	Viracept	Resistant	(3.6)	35	N	N	
	Ritonavir	Norvir	Resistant	(2.5)	>MAX	N	N	
	Saquinavir	Invirase / r*	Resistant	(2.3 - 12)	36	N	N	
	Tipranavir	Aptivus / r*	Partially Sensitive	(2 - 8)	4.79	P	N	
	PI Mutations		L10I, V11I, V32I, L33F, M36I, M46L, I54L, Q58E, I62V, A71V, G73S, I84V, I85V, L89V, L90M					

Drug Susceptibility: Increasing ← 1 — 10 — 100 → Decreasing

Phenotype / Genotype Comments (clinical significance may vary)

1 - **Mixture:** Mixtures detected at resistance-associated position(s); minor populations with decreased susceptibility may be present and may increase in the presence of drug pressure.

3 - **IC50 reduced:** Phenotypic measurement reflects possible enhanced susceptibility due to M184I or V.

Paul Sax
@PaulSaxMD

Hey HIV treaters out there--in the past 2 years, do you follow, or have you seen, any people with viral failure and resistance to ALL major HIV drug classes? (Enfuvirtide and ibalizumab excluded.) If yes, share how many in the replies. (I've seen 2.)

Yes.	12%
No.	**53%**
Not an HIV treater.	35%

449 votes · Final results

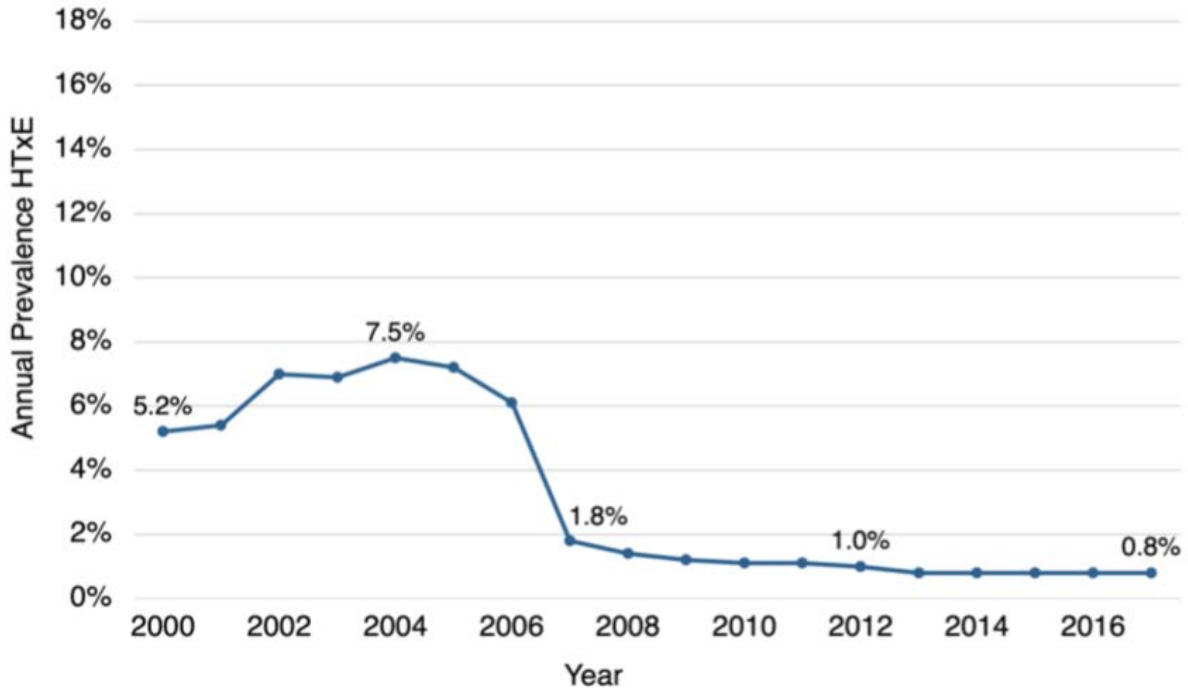
Unmet Need? Heavily Treatment–Experienced People With HIV

- ART with novel mechanisms of action play a critical role for a small proportion of people with HIV: those with **resistance to multiple classes and no treatment options**
- Two primary target populations
  1) Older people with HIV treated in early days of ART with less potent regimens that had low resistance barriers
  2) Younger people with congenital infection, now young adults
- Currently, **ibalizumab and enfuvirtide** are the only options
  - Both injectable and expensive
  - Some people already have resistance to enfuvirtide

1. Struble. AIDS Lond Engl. 2005;19:747. 2. Richman. AIDS Lond Engl. 2004;18:1393. 3. Weinstock. J Infect Dis. 2004;189:2174.
4. Yazdanpanah. Clin Infect Dis. 2009;49:1441. 5. Emu. NEJM. 2018;379:645. 6. Reeves. J Virol. 2005;79:4991.

Prevalence of Heavily Treatment Experienced (HTxE) with Multi-class Resistance

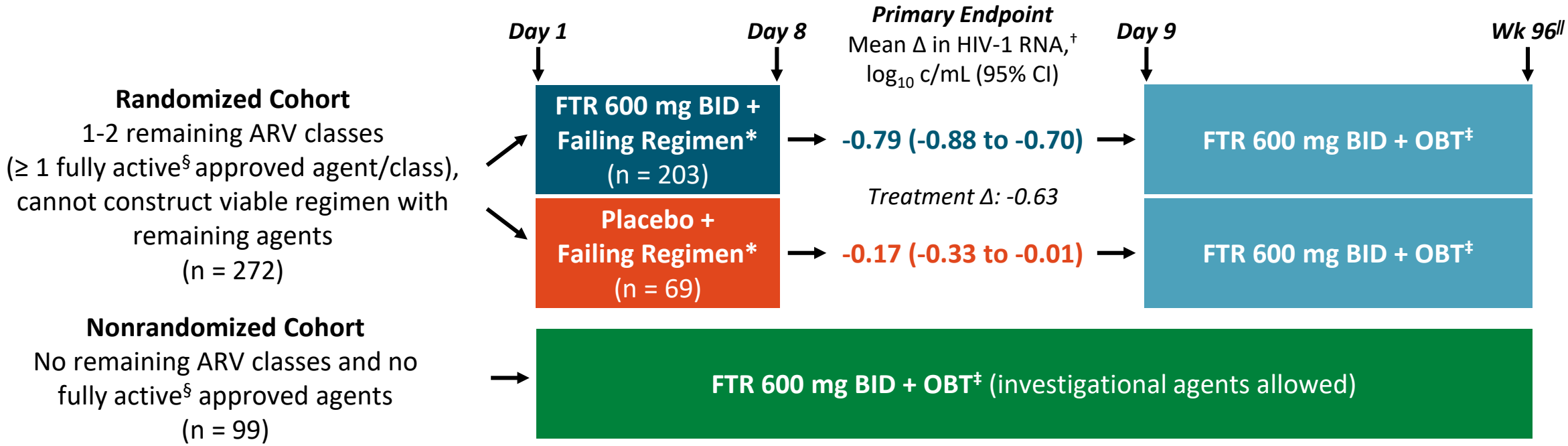
- CNICS cohort of > 32,000 ART-experienced people with HIV receiving care in USA
- HTxE defined as <= 2 available classes by resistance testing



Bajema K et al. IAS 2019 MOPEB246.

BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug Resistant HIV

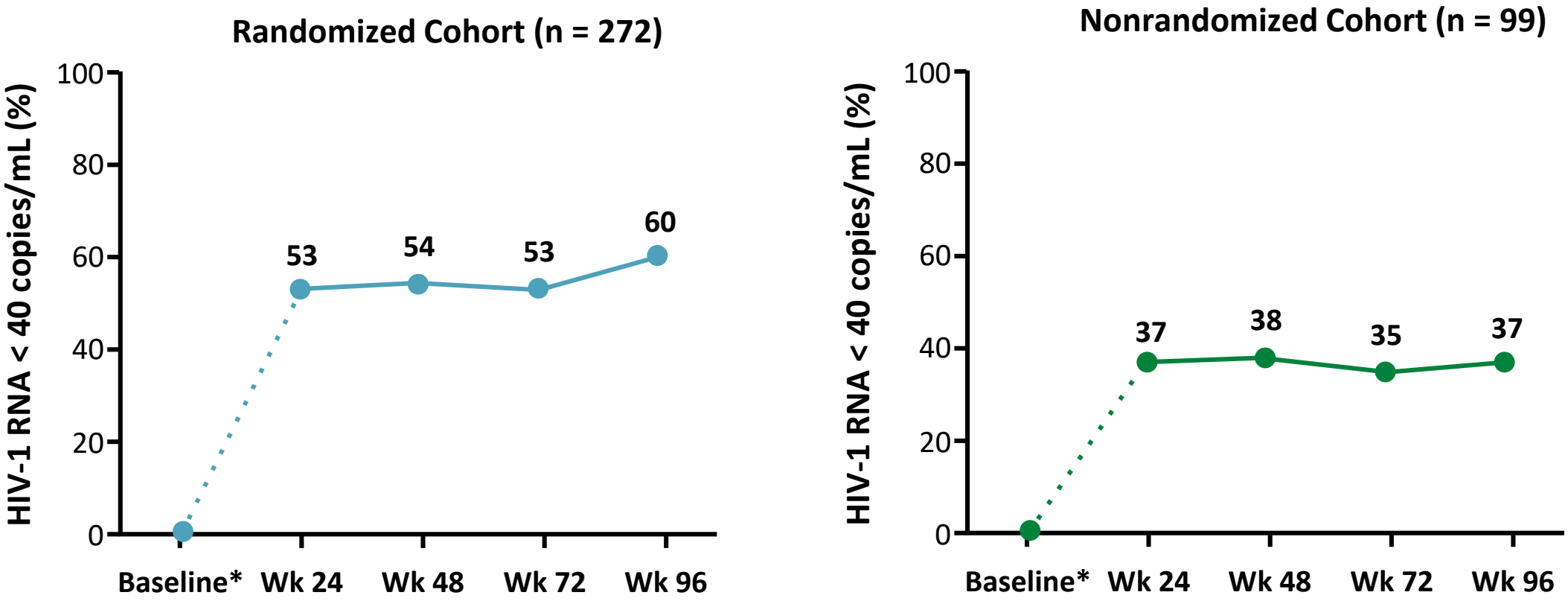
- Wk 96 analysis of randomized, double-blind phase III trial in heavily treatment–experienced adults failing current ART with confirmed HIV-1 RNA ≥ 400 c/mL
  - At BL: median HIV-1 RNA, 4.6 $\log_{10}$ c/mL; median CD4+ cell count, 80 cells/mm^3; AIDS history, 86%



*Blinded. †Day 8 adjusted by Day 1. ‡Open-label. §No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV. ‖Measured from start of open-label tx. Study conducted until another option, rollover study, or approved ARV available.

Lataillade. IAS 2019. Abstr MOAB0102. Pialoux. IAS 2018. Abstr THPEB045.

BRIGHTE: ITT-E Virologic Response Through Wk 96



*Snapshot analysis excluded baseline data. 1 patient had BL HIV-1 RNA < 40 copies/mL.

Lataillade. IAS 2019. Abstr MOAB0102. Reproduced with permission.

Question

- How many patients do you follow who could be eligible for fostemsavir therapy?

A. Zero
B. 1-3
C. More than 3

Case #6 -- Outcome

- Placed on ibalizumab, enfuvirtide, DTG BID, and TAF/FTC.
- HIV RNA < 20!
- Uncertain whether fostemsavir (when approved) should replace ibalizumab, or enfuvirtide, or both!

Case #7

- 50 year-old man, diagnosed with HIV infection in 2013.
- Initial CD4 770, HIV RNA 1000, no resistance. Asymptomatic.
- Refuses to go on ART initially due to insurance concerns and confidentiality.
- Ultimately agrees in 2015 when he realizes he can purchase ART in South Africa during his business trips – buys TDF/3TC, RAL ($110/month), tolerates well.
- HIV since then < 20 copies/mL.
- Recently researched an even cheaper treatment, and switches to DTG + 3TC, which costs him $65/month.

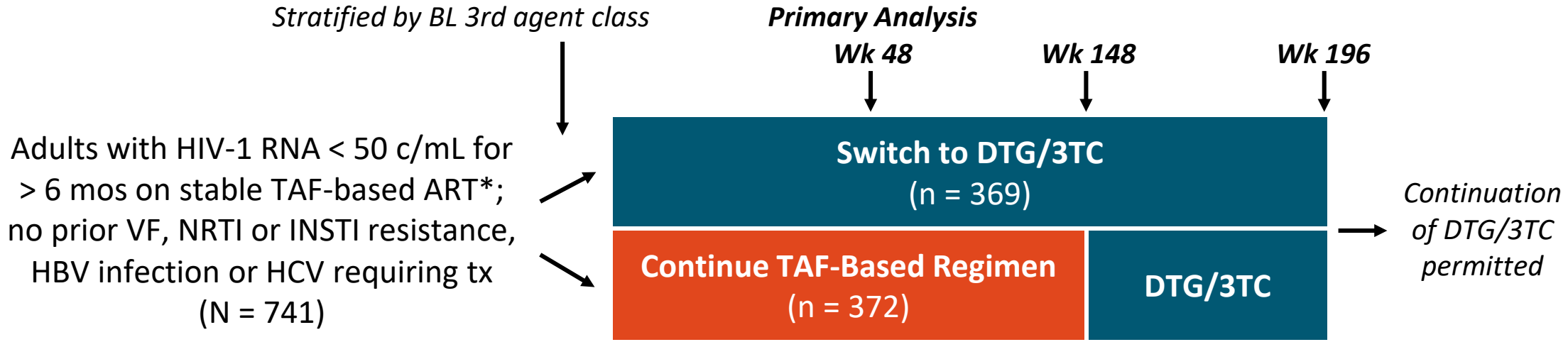
Question

- Should we support this strategy?

A. Yes
B. No
C. Sort of, but it makes me nervous

TANGO: Switch to DTG/3TC vs Continuing TAF-Based 3-Drug Regimen

- International, randomized, open-label phase III noninferiority study

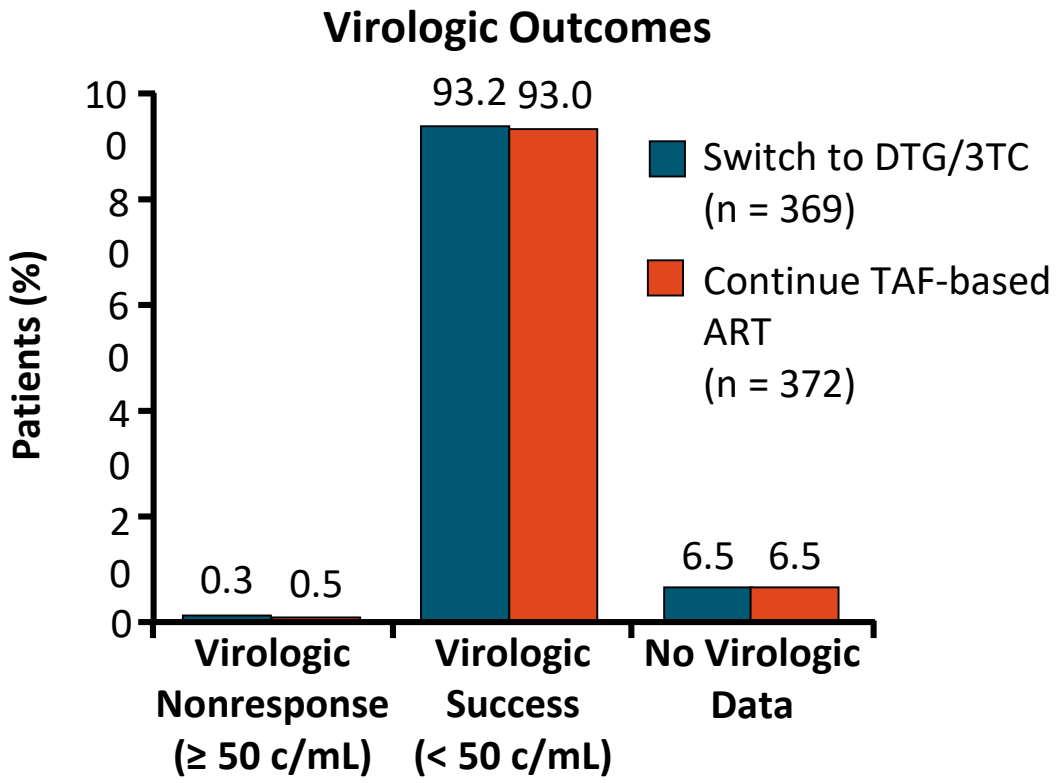


*Initial regimen of FTC/TAF + PI, NNRTI, or INSTI, or TDF switched to TAF ≥ 3 mos prior to screening with no other regimen changes.

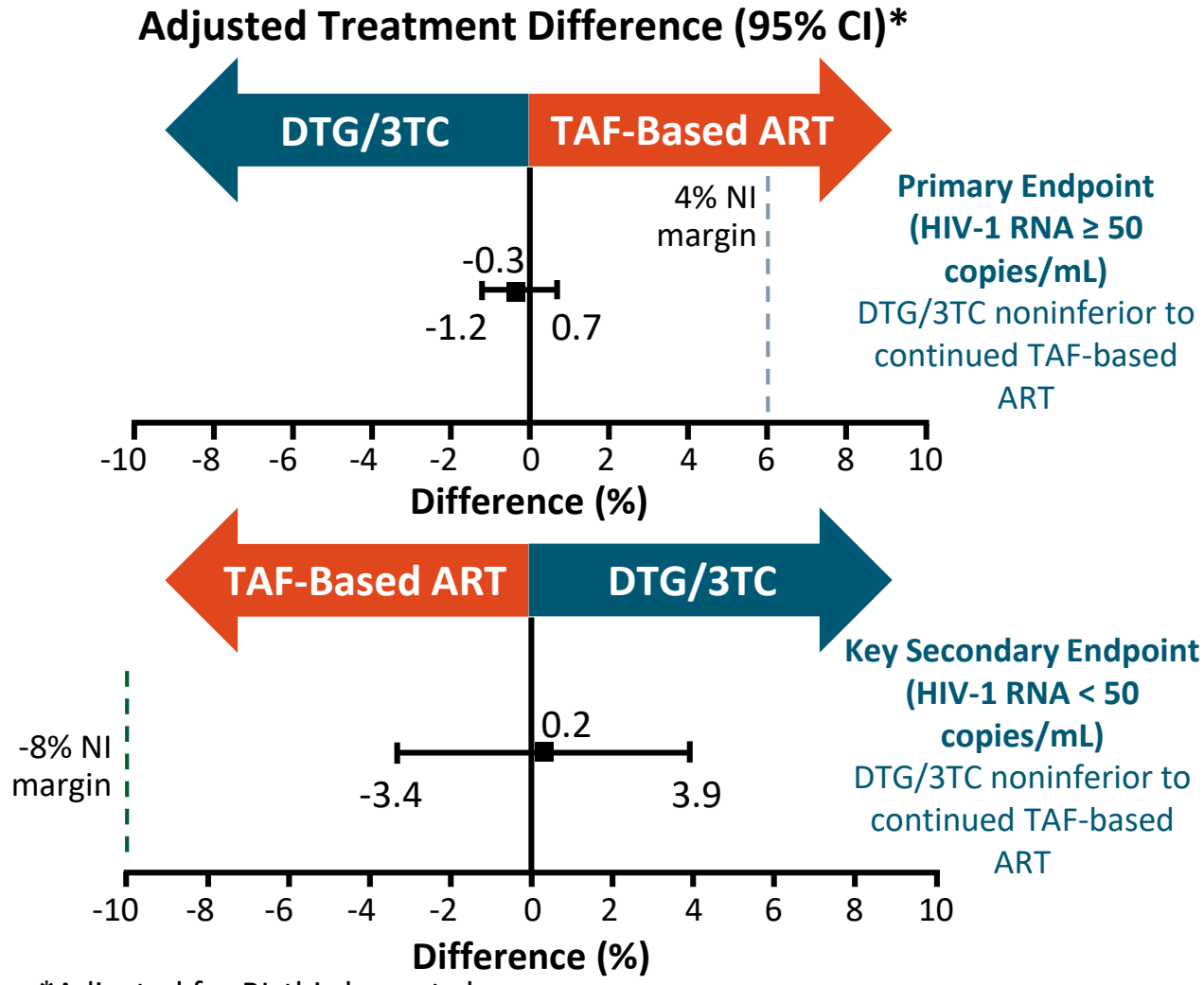
- Primary endpoint: virologic failure at Wk 48 by FDA Snapshot analysis (ITT-E)
  - Noninferiority margin: 4%
- Secondary endpoint: safety

Van Wyk. IAS 2019. Abstr WEAB0403LB. NCT03446573.

TANGO: Virologic Outcomes by FDA Snapshot at Wk 48 (ITT-E)



- No CVW in DTG/3TC arm, CVW in 1 (< 1%) patient in TAF-ART arm; no resistance detected at failure
- All 7 patients (4 in DTG/3TC group and 3 in TAF-based ART group) with proviral M184V/I mutation at BL maintained HIV-1 RNA < 50 copies/mL at Wk 48

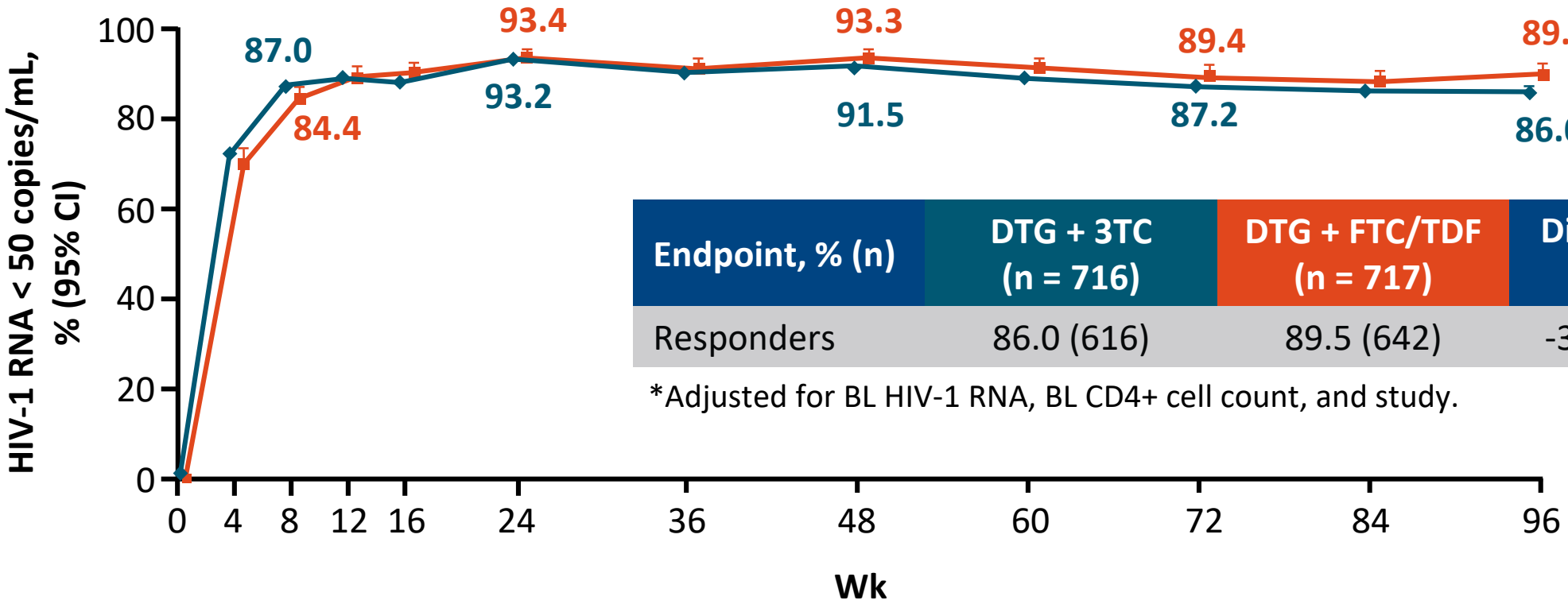


*Adjusted for BL third agent class.

Van Wyk J. IAS 2019. Abstr WEAB0403LB.

GEMINI-1 and -2: Virologic Response at Wk 96

- Rates of HIV-1 RNA ≥ 50 copies/mL unchanged from Wk 48; d/c for reasons other than AEs or death higher with DTG + 3TC at Wk 96 (8% vs 5% with 3-drug ART)



Endpoint, % (n)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	Difference,* % (95% CI)
Responders	86.0 (616)	89.5 (642)	-3.4 (-6.7 to 0)

*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

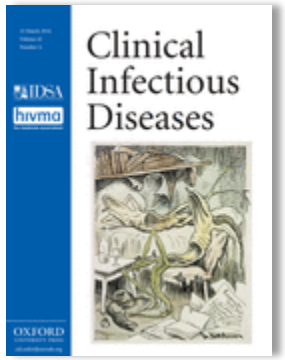
Cahn. IAS 2019. Abstr WEAB0404LB. Reproduced with permission.

Question

- Where do you think DTG/3TC will have the greatest impact?

A. As initial therapy
B. As switch therapy

Cost-effectiveness of 2-drug DTG-3TC



- Modeling study projecting cost effectiveness and budget impact of 2-drug DTG-3TC as an “induction-maintenance” strategy
- Results
  - DTG-3TC after virologic suppression highly cost-effective (ICER $22,500/QALY)
  - US cost savings could be $500-800 million/year for new diagnoses – even higher ($3 billion/year) if existing suppressed patients switch
- Limitation: Study done with price estimates

Girouard MP, et al, Clinical Infectious Diseases 2016.

Perspective

Treating and Preventing HIV with Generic Drugs — Barriers in the United States

Erika G. Martin, Ph.D., M.P.H., and Bruce R. Schackman, Ph.D.

- Loss of coformulations due to different patent expiry dates
- Variable payment models for HIV care mean variable incentives to use generics
- Will there be sufficient generic manufacturers to decrease costs?
- Will cost savings be passed along to patients? What about co-pays?
- What about 340b pharmacy revenue?

Martin EG and Schackman BR. N Engl J Med 2018; 378:316-319

DTG/3TC: Questions Raised by GEMINI and TANGO Results

- Should DTG/3TC now be a recommended first-line regimen?
- Will there be a higher risk of resistance in clinical practice not seen in clinical trials?
- In GEMINI, how can the lower response rate in those with CD4 < 200 be explained?
- What specific drug toxicity are we avoiding when TAF/FTC is the NRTI pair?
- Right now 3TC separately is generic – is the premium for the coformulated tablet worthwhile?

Future ART – Conclusions

- Current treatments are extraordinarily safe and effective, but future ART will need to address
  - Pregnancy
  - Advanced HIV disease (low CD4, high HIV RNA)
  - Emerging toxicities (weight gain)
  - Non-adherent patients
  - People with limited treatment options
  - Cost
- Dual-therapy, long-acting ART, and novel drug classes will all play a role – as will additional clinical and translational research!

Thank you to my wonderful mentors and supporters!

- Marty Hirsch
- Deborah Cotton
- Judy Currier
- Scott Hammer
- Dan Kuritzkes
- Carolyn Sax, Joseph Sax, Mimi Sax, Louie (the dog) Sax