Antiretroviral Therapy for HIV Infection 2017

Novel and Investigational Strategies

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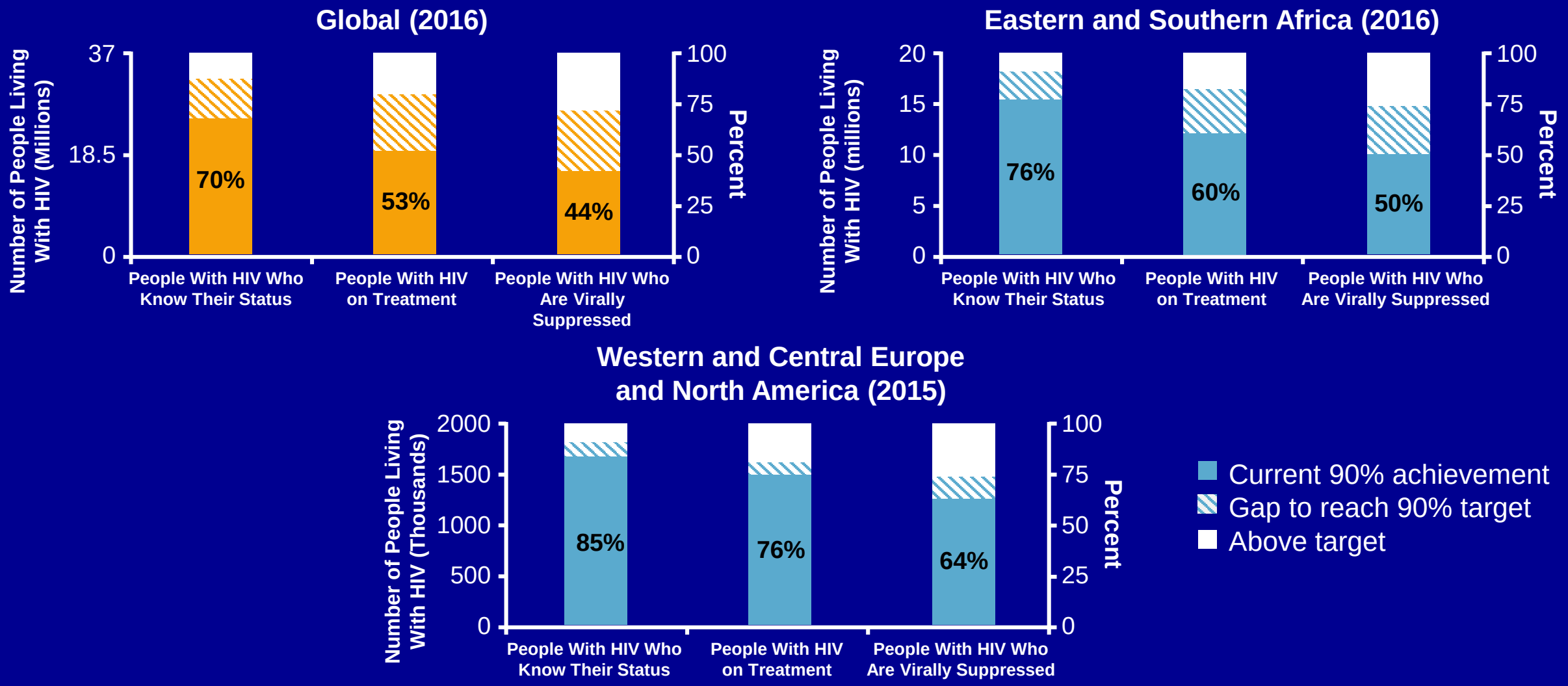
Current Status: 90-90-90 Targets



UNAIDS. Ending AIDS: Progress Towards The 90-90-90 Targets. July 2017.

When to Start ART: Global Consensus

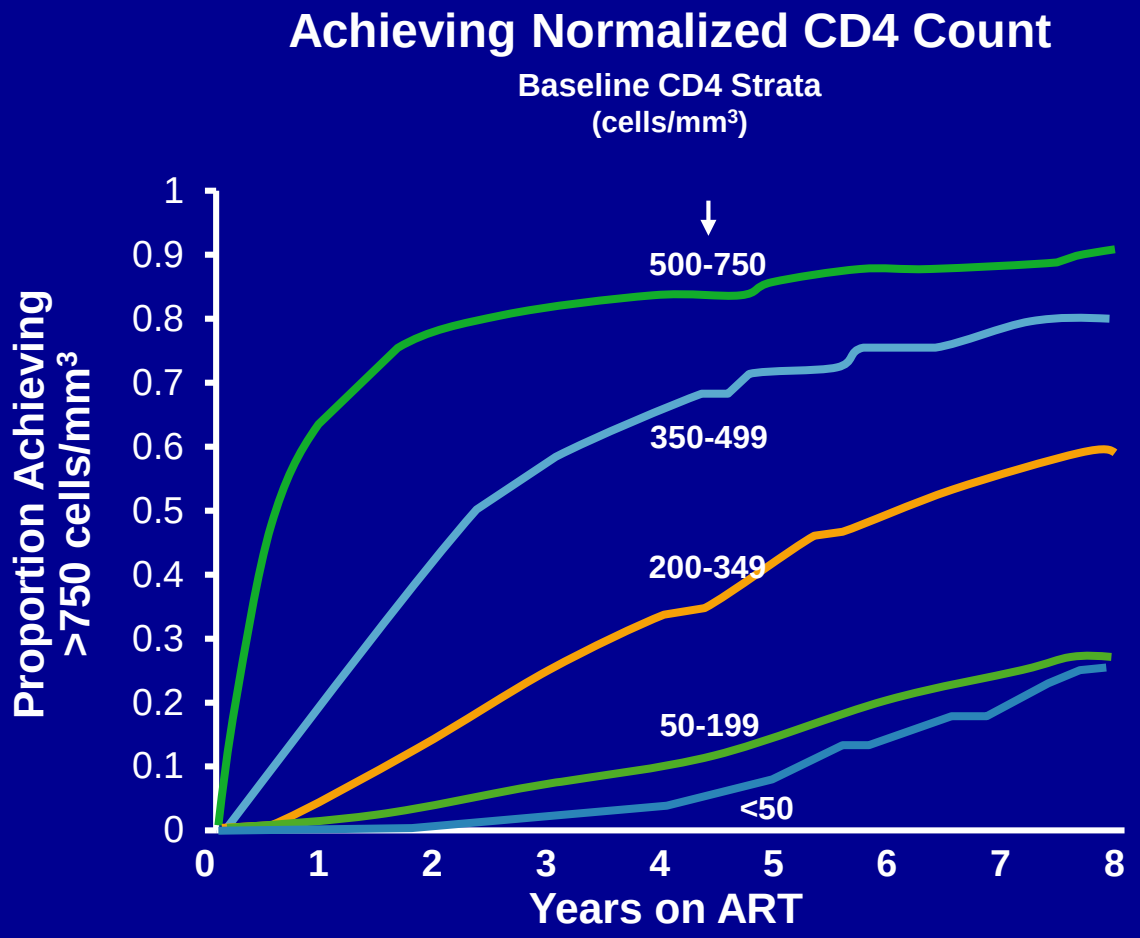
	AIDS or HIV-Related Symptoms	CD4 Count (cells/mm^3)			
		<200	200-350	350-500	>500
United States DHHS (2016)	Yes	Yes	Yes	Yes	Yes
IAS-USA (2016)	Yes	Yes	Yes	Yes	Yes
British HIV Association (2016)	Yes	Yes	Yes	Yes	Yes
European AIDS Clinical Society (2016)	Yes	Yes	Yes	Yes	Yes
WHO (2015)	Yes	Yes	Yes	Yes	Yes

DHHS. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision July 14, 2016.
Günthard HF, et al. *JAMA*. 2016;316:191-210.
EACS. http://www.eacsociety.org. Revision October 2016.
BHIVA. www.bhiva.org. Revision August 2016.
WHO. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Revision September 2015.

HOPS Cohort: ART Initiation and Achieving CD4 Normalization

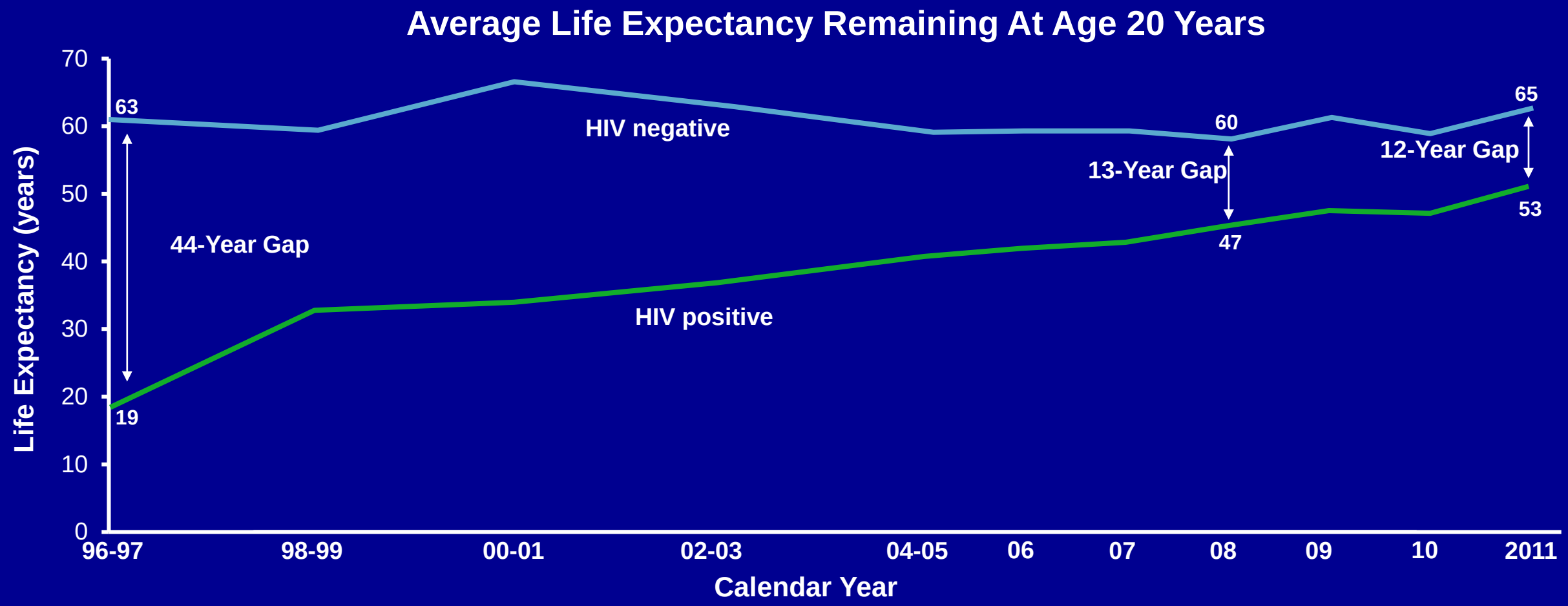
- CD4 trajectories in the HOPS Cohort after >3 years of ART (n=1327) (1996-2012)
  - CD4 normalization (>750 cells/mm^3)
- After 7.9 years of follow-up, progressively higher CD4 at ART initiation was associated with
  - Greater gains in CD4
  - Greater likelihood of CD4 normalization (baseline CD4 and hazard ratio for achieving CD4 normalization with ART)
    - 500-750 cells/mm^3: 12.78 (*P*<0.001)
    - 350-499 cells/mm^3: 7.02 (*P*<0.001)
    - 200-349 cells/mm^3: 3.16 (*P*<0.001)
    - Reference: 0-49 cells/mm^3: 1.0

    - Increased survival rates



Palella FJ, et al. *J Antimicrob Chemother*. 2016;71:2654-2662.

Narrowing the Gap in Life Expectancy Between HIV-Positive and Uninfected Persons (1996-2011)



Kaiser Permanente Northern California (1996 to 2011):
HIV-positive (n=25,768) and matched non-HIV-infected adults (n=257,600). Males (91%) and MSM (75%).

Marcus JL, et al. *JAIDS*. 2016;73:39-46.

DHHS Guidelines: Recommended Regimens

Regardless of Baseline HIV RNA Level or CD4 Count

INSTI	Raltegravir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF Elvitegravir/cobicistat/emtricitabine/tenofovir AF* Elvitegravir/cobicistat/emtricitabine/tenofovir DF* Dolutegravir/abacavir/lamivudine* Dolutegravir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF
PI	Darunavir + ritonavir (qd) + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF

***Available as a once-daily, single-tablet regimen.**

Notes:

- **Lamivudine may be substituted for emtricitabine or vice versa (if non-fixed dose NRTI combination is desired).**
- **The evidence supporting the use of emtricitabine/TAF with dolutegravir or raltegravir is based on relative bioavailability data plus data from randomized, controlled switch trials demonstrating the safety/efficacy of TAF-containing regimens.**
- **Tenofovir DF: use with caution in patients with renal insufficiency.**
- **Elvitegravir/cobicistat/emtricitabine/tenofovir AF: only for patients with pre-ART creatinine clearance ≥30 mL/min.**
- **Elvitegravir/cobicistat/emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance ≥70 mL/min.**
- **Dolutegravir/abacavir/lamivudine: only for patients who are HLA-B*5701 negative.**

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision July 14, 2016.

DHHS Guidelines: Alternative Regimens

May Be the Preferred Regimen for Some Patients

NNRTI	Efavirenz/emtricitabine/tenofovir DF* Efavirenz + emtricitabine/tenofovir AF Rilpivirine/emtricitabine/tenofovir DF* Rilpivirine/emtricitabine/tenofovir AF*
PI	Atazanavir/cobicistat + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF Atazanavir + ritonavir + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF Darunavir/cobicistat + emtricitabine/tenofovir DF or emtricitabine/tenofovir AF Darunavir/cobicistat or darunavir/ritonavir + abacavir/lamivudine

***Available as a once-daily, single-tablet regimen.**

Notes:

- **Lamivudine may be substituted for emtricitabine or vice versa (if non-fixed dose NRTI combination is desired).**
- **The evidence supporting the use of emtricitabine/TAF with efavirenz, rilpivirine, atazanavir, or darunavir is based on relative bioavailability data plus data from randomized, controlled switch trials demonstrating the safety/efficacy of TAF-containing regimens.**
- **Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.**
- **Tenofovir DF: use with caution in patients with renal insufficiency.**
- **Rilpivirine/emtricitabine/tenofovir DF: only for patients with pre-ART HIV RNA <100K copies/mL and CD4 >200 cells/mm^3.**
- **Atazanavir/cobicistat or darunavir/cobicistat + emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance ≥70 mL/min.**
- **Atazanavir + RTV: absorption depends on food and low gastric pH.**
- **Darunavir/cobicistat or darunavir/ritonavir + abacavir/lamivudine: only for patients who are HLA-B*5701 negative.**

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision July 14, 2016.

IAS-USA Guidelines: Recommended Regimens

INSTI	Elvitegravir/cobicistat/emtricitabine/tenofovir AF* Dolutegravir/abacavir/lamivudine† Dolutegravir + emtricitabine/tenofovir AF* Raltegravir + emtricitabine/tenofovir AF*

***Tenofovir DF may be substituted for tenofovir AF if tenofovir AF is not available.**
†HLA-B*5701-negative patients.

Notes:
Tenofovir DF is not recommended for individuals with creatinine clearance <50 mL/min or at high risk of kidney or bone disease (eg, osteopenia/osteoporosis).
Abacavir should be used with caution in patients who have or are at high risk of cardiovascular disease.
Tenofovir AF is not recommended in patients with creatinine clearance <30 mL/min.

Günthard HF, et al. *JAMA*. 2016;316:191-210.

IAS-USA Guidelines: Alternative Regimens in Whom an INSTI is not an Option

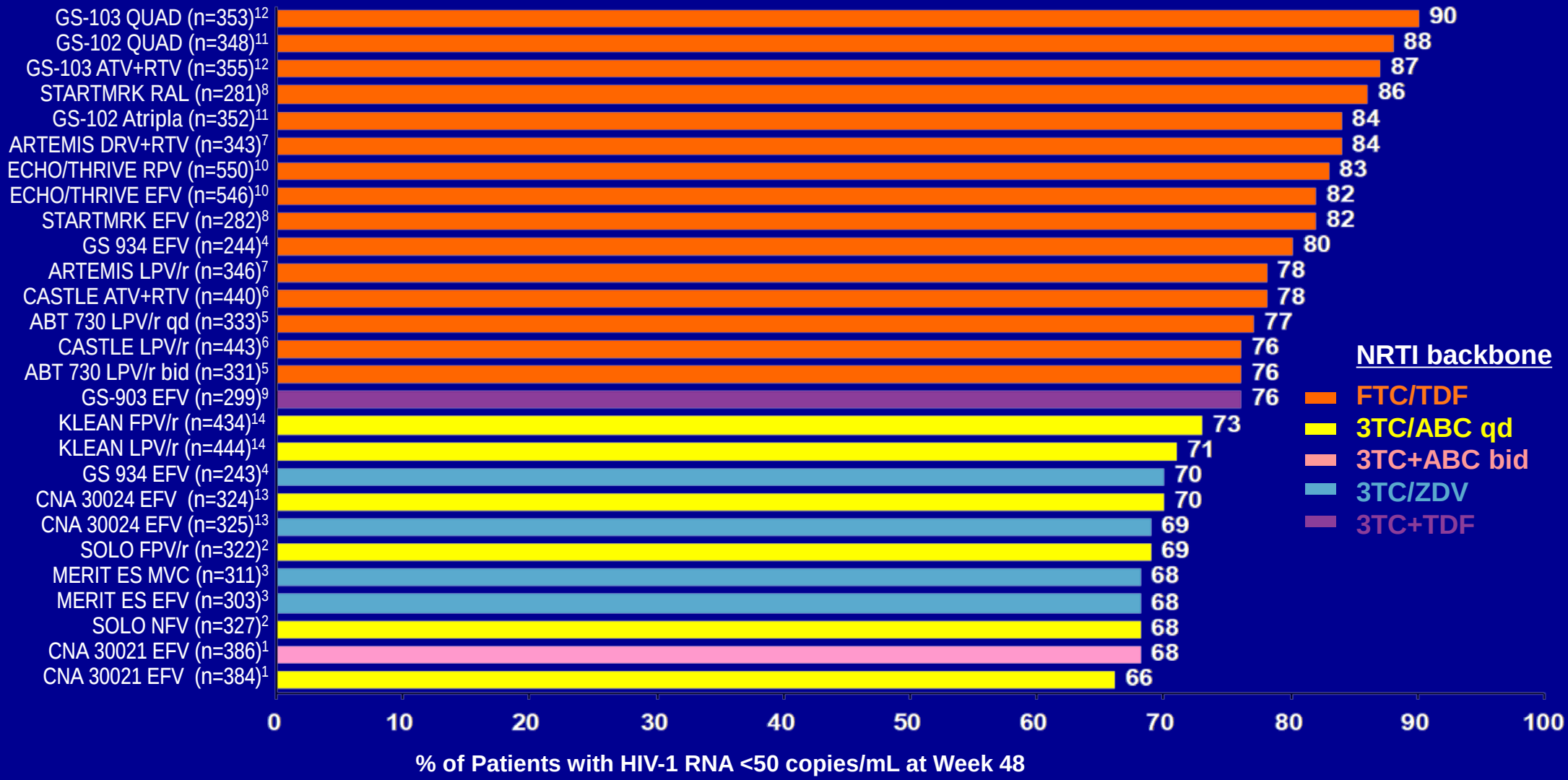
PI	Darunavir/cobicistat + emtricitabine/tenofovir AF Darunavir + ritonavir + emtricitabine/tenofovir DF
NNRTI	Rilpivirine/emtricitabine/tenofovir AF Rilpivirine/emtricitabine/tenofovir DF Efavirenz/emtricitabine/tenofovir DF

Notes:
Tenofovir DF is not recommended for individuals with or at high risk of kidney or bone disease (osteopenia or osteoporosis).
Tenofovir AF is not recommended in patients with a creatinine clearance <30 mL/min.

Günthard HF, et al. *JAMA*. 2016;316:191-210.

Registrational Treatment-Naive Clinical Trials: Cross-Study Comparison*

HIV RNA <50 c/mL at Week 48



**This slide depicts data from multiple studies published from 2004-2012. Not all regimens have been compared head-to-head in a clinical trial*

Current Status of INSTI Resistance in the United States

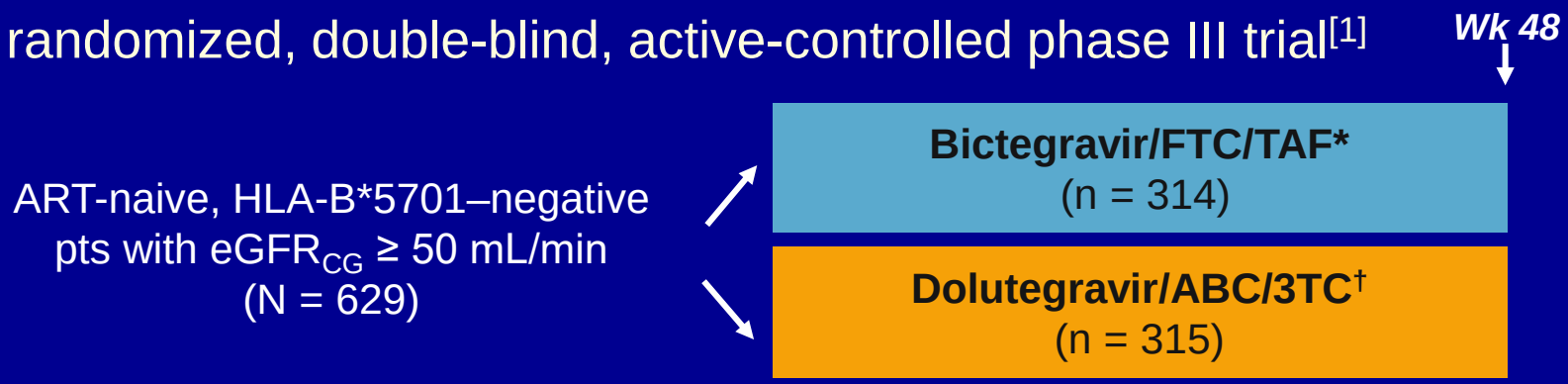
- **Transmitted INSTI resistance remains rare and rates of on-treatment INSTI resistance continue to be low[1-3]**
- CDC National HIV Surveillance System[1]:
  - Prevalence of INSTI resistance for HIV diagnoses through 2014: 65/14,468 **(0.4%)**
  - Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)
- UNC CFAR HIV Clinical Cohort[2]:
  - 2015 INSTI resistance prevalence in 685 pts who began ART in 2007 or later: **1%**
- **In modeling study assuming 0.1% rate of transmitted INSTI resistance and $250 cost per test: pre-ART INSTI resistance testing correlated with worse outcomes, higher costs vs no test[3]**

1. Hernandez AL, et al. CROI 2017. Abstract 478. 2. Davy T, et al. CROI 2017. Abstract 483.
3. Koullias Y, et al. CROI 2017. Abstract 493.

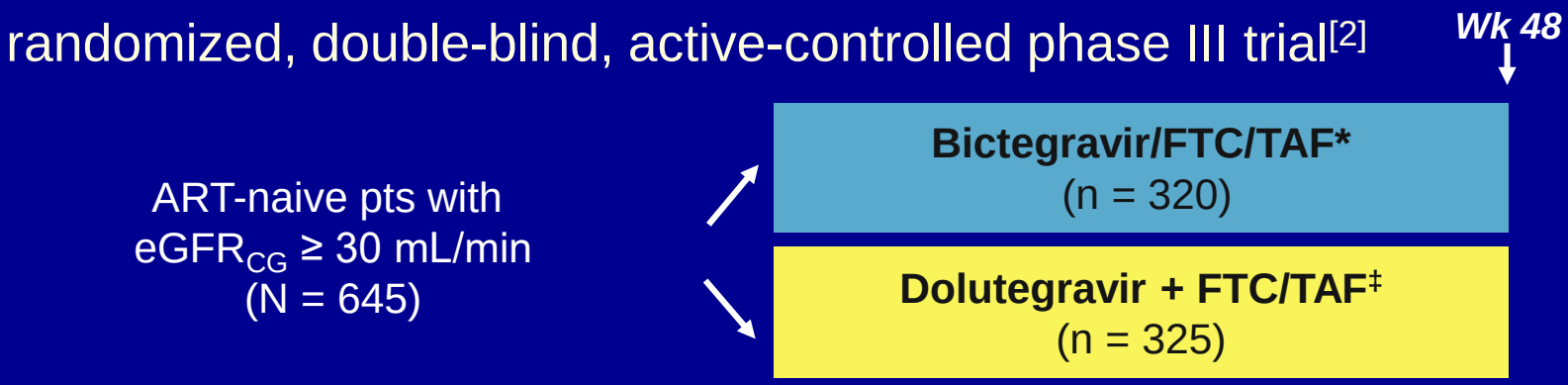
Investigational ART Regimens

Bictegravir/FTC/TAF vs Dolutegravir-Containing Regimens for Treatment-Naive Pts

- **Bictegravir**: novel QD unboosted INSTI coformulated with FTC/TAF
- GS-1489: randomized, double-blind, active-controlled phase III trial[1]



- GS-1490: randomized, double-blind, active-controlled phase III trial[2]



All pts also received placebo tablets for comparator regimen (eg, pts in GS-1489 who received BIC/FTC/TAF also received DTG/ABC/3TC placebo). *BIC/FTC/TAF, 50/200/25 mg PO QD. †DTG/ABC/3TC, 50/600/300 mg PO QD. ‡DTG + FTC/TAF, 50 + 200/25 mg PO QD

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

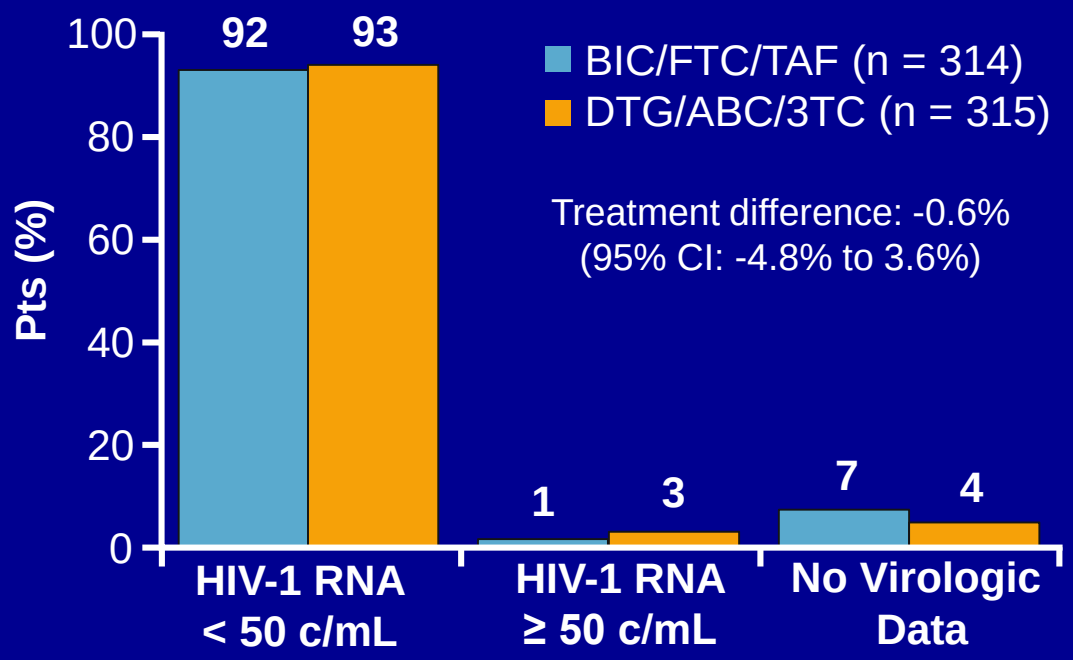
BIC/FTC/TAF vs DTG-Containing Regimens: Selected Baseline Characteristics

Baseline Characteristic	GS-1489[1]		GS-1490[2]	
	BIC/FTC/TAF (n = 314)	DTG/ABC/3TC (n = 315)	BIC/FTC/TAF (n = 320)	DTG + FTC/TAF (n = 325)
Median age, yrs (range)	31 (18-71)	32 (18-68)	33 (18-71)	34 (18-77)
Male, %	91	90	88	89
Median HIV-1 RNA, log_{10} copies/mL (IQR)	4.42 (4.03-4.87)	4.51 (4.04-4.87)	4.43 (3.95-4.90)	4.45 (4.03-4.84)
▪ HIV-1 RNA > 100,000 copies/mL, %	17	16	21	17
Median CD4+ cell count, cells/mm^3 (IQR)	443 (299-590)	450 (324-608)	440 (289-591)	441 (297-597)
▪ CD4+ cell count < 200 cells/mm^3, %	11	10	14	10

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

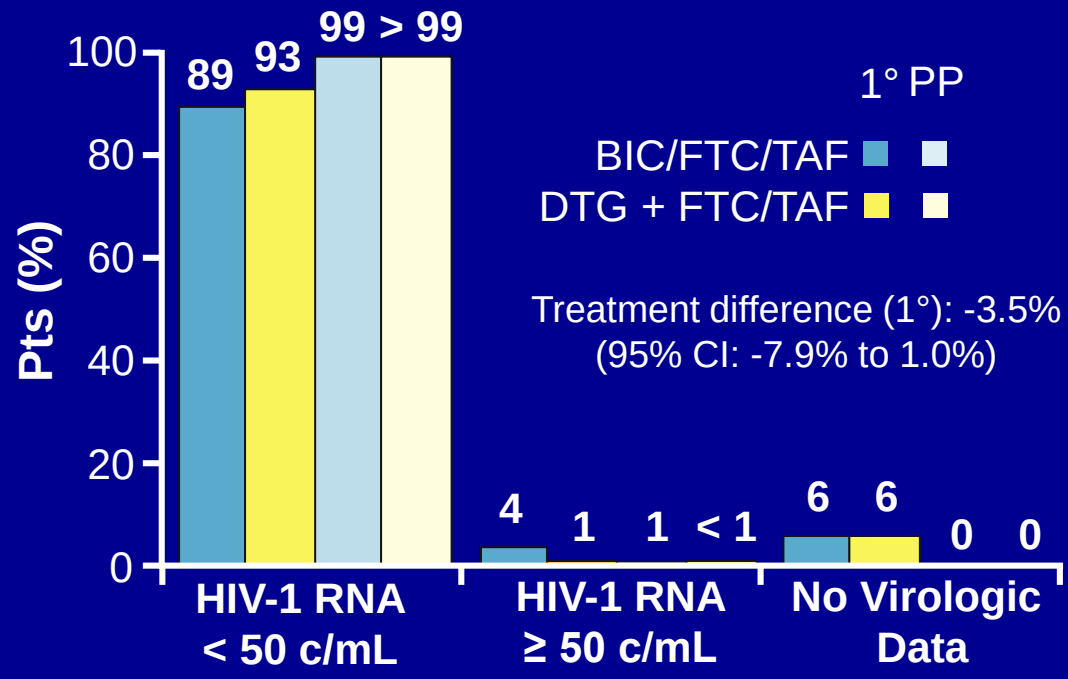
BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

GS-1489: Wk 48 Virologic Efficacy[1]



- No resistance for any regimen components detected for either group

GS-1490: Wk 48 Virologic Efficacy[2]



- No resistance for any regimen components detected for either group

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. Reproduced with permission.
2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB. Reproduced with permission.

BIC/FTC/TAF vs DTG-Containing Regimens: Key Safety Findings

Outcome Through Wk 48	GS-1489[1]		GS-1490[2]	
	BIC/FTC/TAF (n = 314)	DTG/ABC/3TC (n = 315)	BIC/FTC/TAF (n = 320)	DTG + FTC/TAF (n = 325)
Diarrhea, %	12.7	13.0	11.6	12.0
Headache, %	11.5	13.7	12.5	12.3
Nausea, %	**10.2**	**22.9***	7.8	8.9
Upper respiratory tract infection, %	6.4	10.8	4.7	7.1
Median $eGFR_{CG}$ Δ from BL, mL/min	-10.5	-10.8†	-7.3	-10.8‡
Mean BMD Δ from BL, % spine/hip	-0.83/-0.78	-0.60/-1.02†	NR	NR
D/c for AE, n (%)	0	4 (1.3)	5 (1.6)	1 (0.3)

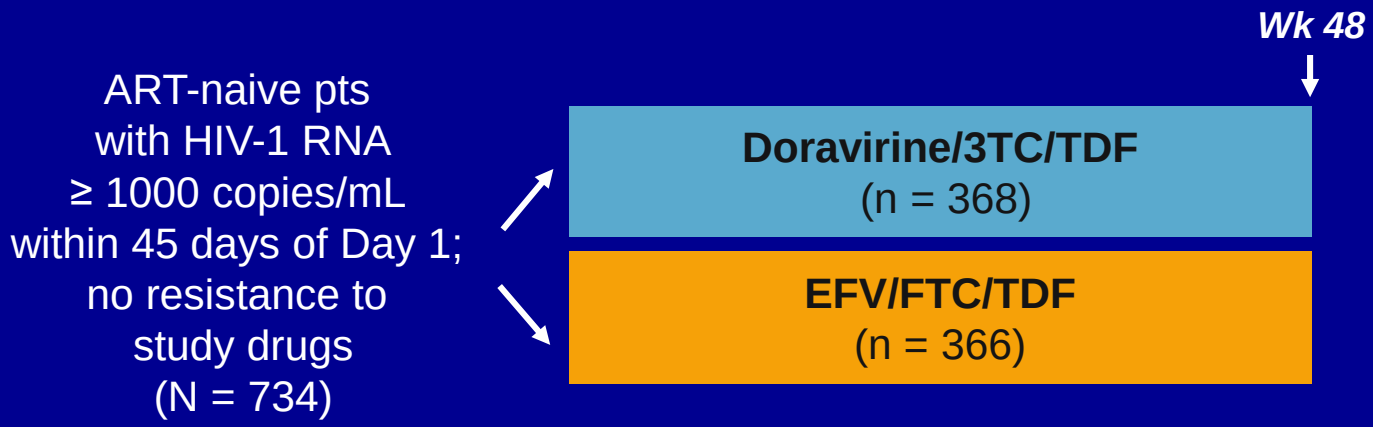
*P < .001. †P = NS. ‡P = .02.

- **GS-1489: similar changes in lipids and proteinuria between groups; some pt-reported neuropsychiatric (eg, anxiety, depression) and sleep-related symptoms (eg, disturbance) more frequent with DTG/ABC/3TC**
- No d/c for renal AEs and no proximal tubulopathy for any regimen

1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. 2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB.

DRIVE-AHEAD: Doravirine/3TC/TDF vs EFV/FTC/TDF for Treatment-Naive Pts

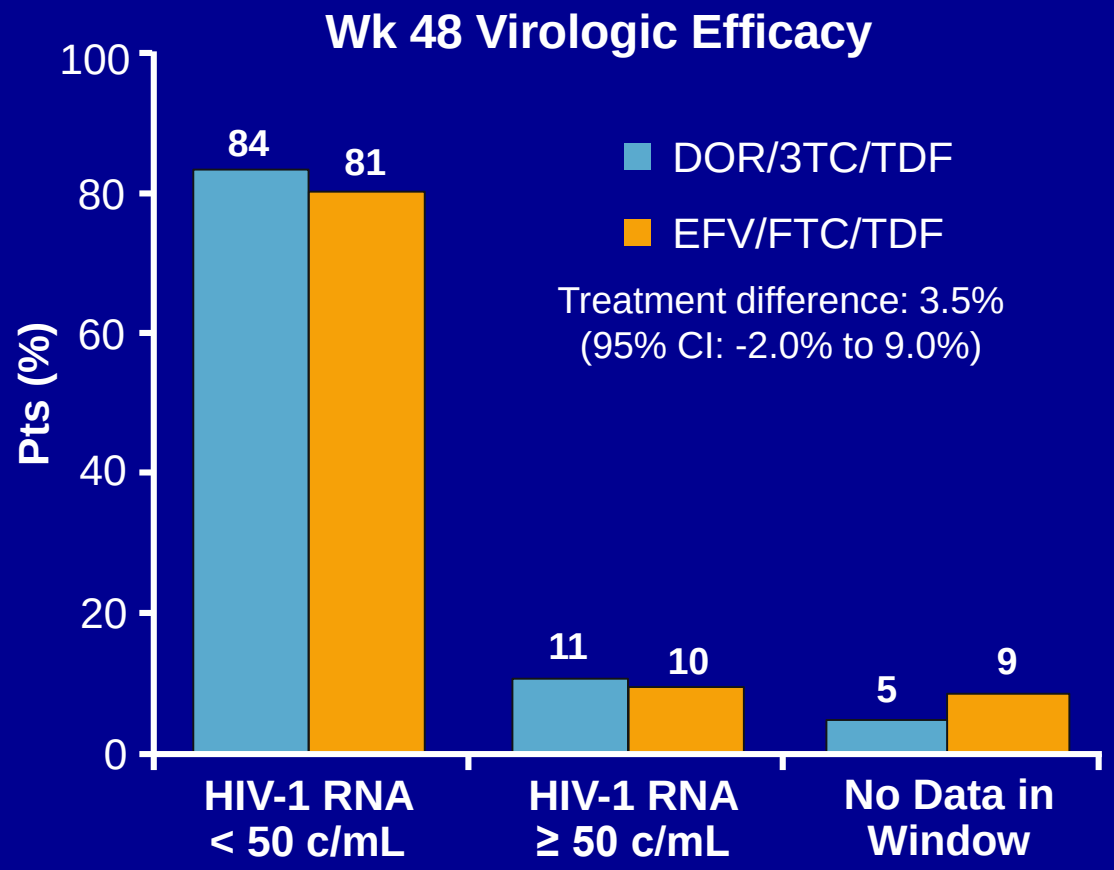
- **Doravirine:** NNRTI with unique resistance profile, low drug–drug interaction potential; doravirine + 2 NRTIs noninferior to DRV/RTV + 2 NRTIs with improved lipid profile in phase III DRIVE-FORWARD[1]
- DRIVE-AHEAD: randomized, double-blind, active-controlled phase III trial[1]



- Baseline: male, 84% to 85%; mean CD4+ cell count, 416-435 cells/mm^3 (12% to 13% ≤ 200 cells/mm^3)

1. Molina JM, et al. CROI 2017. Abstract 45LB. 2. Squires KE, et al. IAS 2017. Abstract TUAB0104LB.

DRIVE-AHEAD: Key Efficacy Findings



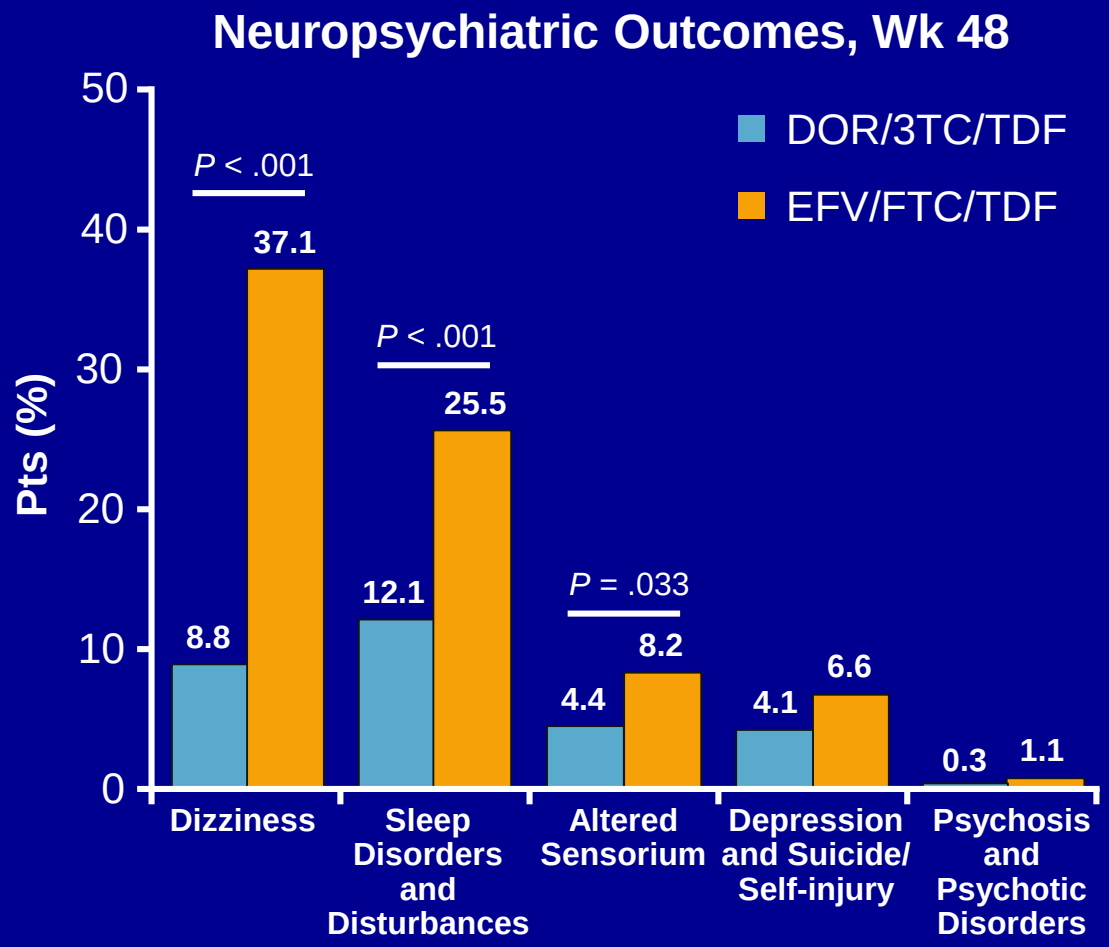
Outcome at Wk 48, n (%)	DOR/3TC/TDF (n = 364)	EFV/FTC/TDF (n = 364)
PDVF	22 (6.0)	14 (3.8)
Genotyped	23	24
Primary NNRTI* resistance	6 (1.6)	12 (3.3)
Primary NRTI* resistance	5 (1.4)	5 (1.4)

*See slidenotes for specific mutations.

- No unanticipated mutations observed

Squires KE, et al. IAS 2017. Abstract TUAB0104LB. Reproduced with permission.

DRIVE-AHEAD: Key Safety Findings

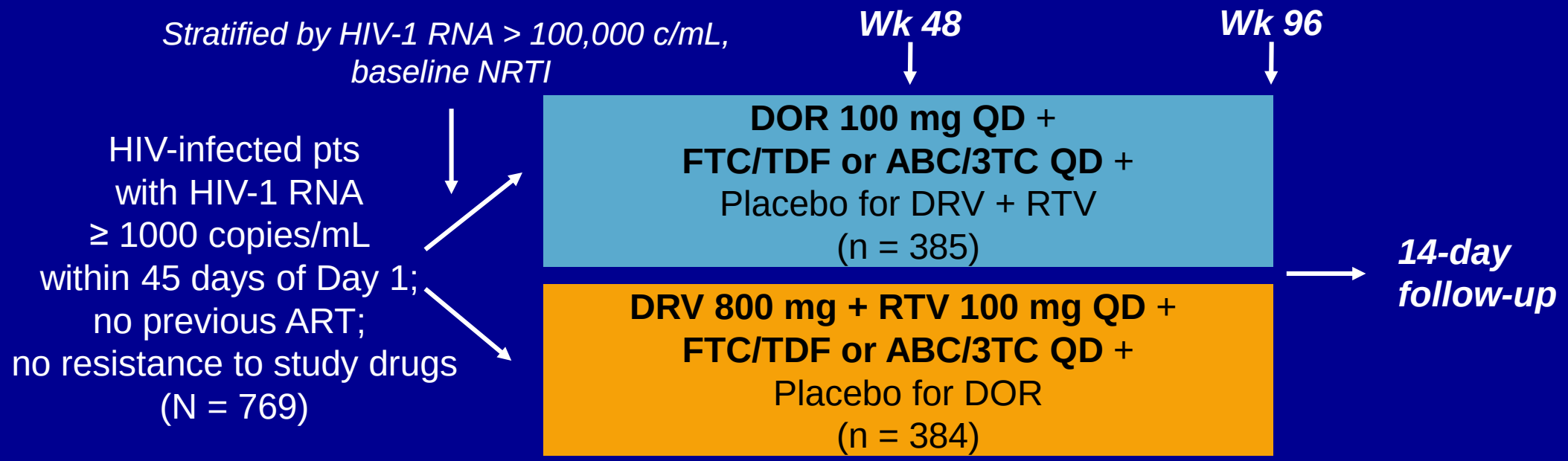


AEs at Wk 48,%	DOR/3TC/TDF (n = 364)	EFV/FTC/TDF (n = 364)	Difference (95% CI)
Drug-related AE, %	31	63	-31.9 (-38.6, -24.8)
D/c for AEs, %	3	7	-3.6 (-6.9, -0.5)
Lipid Δ From BL at Wk 48, mg/dL	**DOR/3TC/TDF (n = 364)**	**EFV/FTC/TDF (n = 364)**	***P* Value**
LDL-C	-1.6	8.7	< .0001
Non–HDL-C	-3.8	13.3	< .0001
Cholesterol	-2.0	21.8	NR
Triglycerides	-12.4	22.0	NR
HDL-C	1.9	8.5	NR

Squires KE, et al. IAS 2017. Abstract TUAB0104LB. Reproduced with permission.

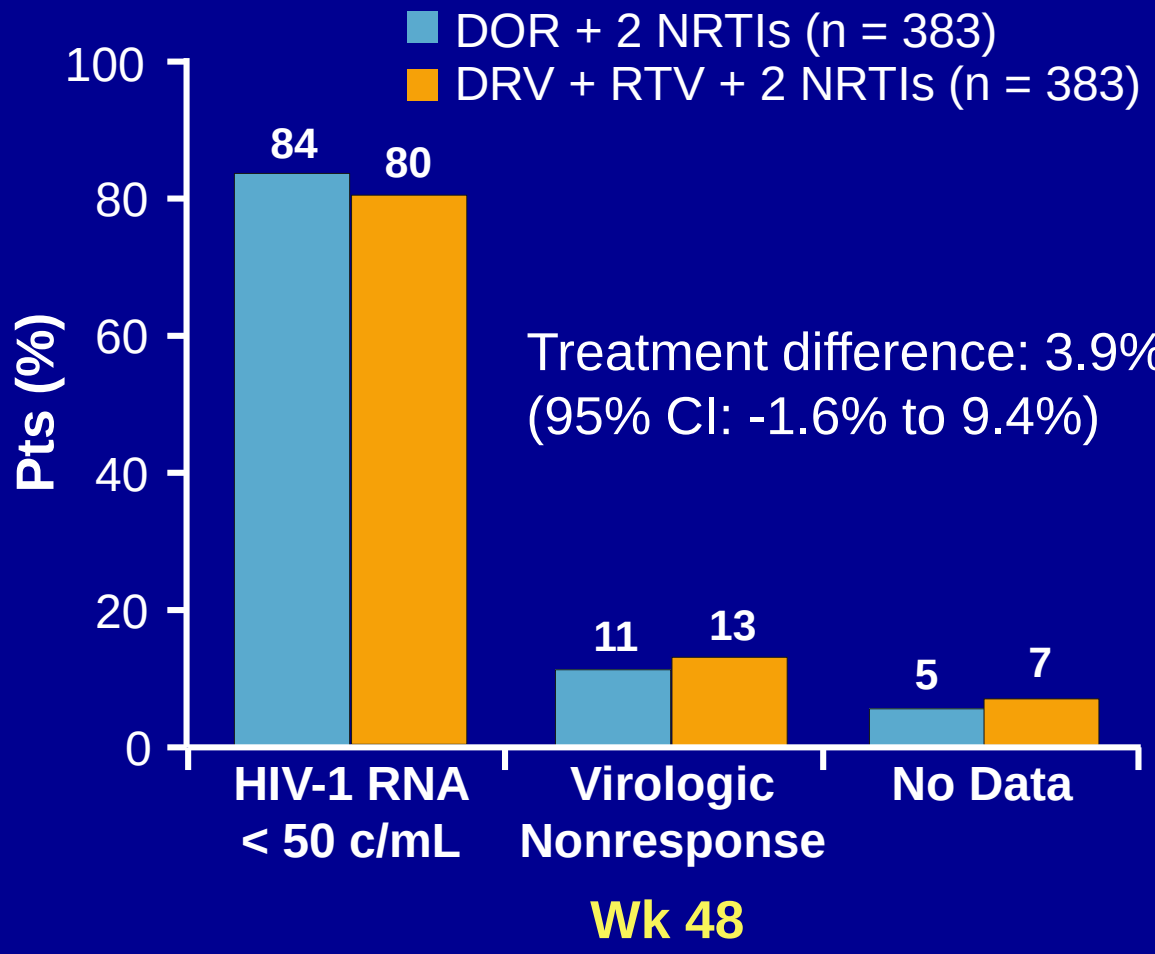
Doravirine or Darunavir + RTV Both With FTC/TDF or ABC/3TC in Treatment-Naive Pts

- Doravirine: next-gen NNRTI, unique resistance profile, low DDI potential
- Multicenter, randomized, double-blind phase III trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



Molina JM, et al. CROI 2017. Abstract 45LB.

Doravirine Is Noninferior to DRV + RTV at Wk 48 (FDA Snapshot)



- Efficacy similar in both arms regardless of baseline HIV-1 RNA or CD4+ cell count
- No drug resistance detected in pts with PDVF through Wk 48 in either arm
  - n = 1 pt with noncompliance discontinued at Wk 24, developed DOR and FTC resistance

Molina JM, et al. CROI 2017. Abstract 45LB. Reproduced with permission.

Doravirine vs DRV + RTV in Combination With FTC/TDF or ABC/3TC: Safety

AE, %	DOR (n = 383)	DRV + RTV (n = 383)
≥ 1 AE	80	78
Treatment-related AE	31	32
Serious AE	5	6
Discontinuation for AE	2	3
AEs of clinical interest		
▪Rash*	7	8
▪Neuropsychiatric†	11	13

*Discontinued due to rash: n = 2 in DOR arm; n = 1 in DRV + RTV arm.
†No discontinuation for neuropsychiatric conditions.

Fasting Lipid Δ From BL to Wk 48, mg/dL	DOR (n = 383)	DRV + RTV (n = 383)
LDL-c*	**-4.51**	**9.92**
Non-HDL-c*	**-5.3**	**13.75**
Cholesterol	**-1.37**	**17.9**
Triglyceride	**-3.14**	**21.97**
HDL-c	3.94	4.15

**P* < .0001 for DOR vs DRV + RTV.

Molina JM, et al. CROI 2017. Abstract 45LB. Reproduced with permission.

Dual-Therapy Regimens for Initial ART

- **ANDES:** randomized phase IV study of DRV/RTV + 3TC vs DRV/RTV + TDF/3TC in ART-naive pts (N = 145)[1]
  - Baseline: 24% HIV-1 RNA > 100,000 c/mL

HIV-1 RNA < 400 c/mL (ITT) at Wk 24, n/N (%)	DRV/RTV + 3TC	DRV/RTV + TDF/3TC
Overall	71/75 (95)	68/70 (97)
BL HIV-1 RNA > 100,000 c/mL	20/20 (100)	15/15 (100)

- 1 virologic failure with DRV/RTV + TDF/3TC

- **ACTG A5353:** single-arm phase II study of DTG + 3TC in ART-naive pts (N = 120)[2]
  - Baseline: 31% HIV-1 RNA > 100,000 c/mL

Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, c/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

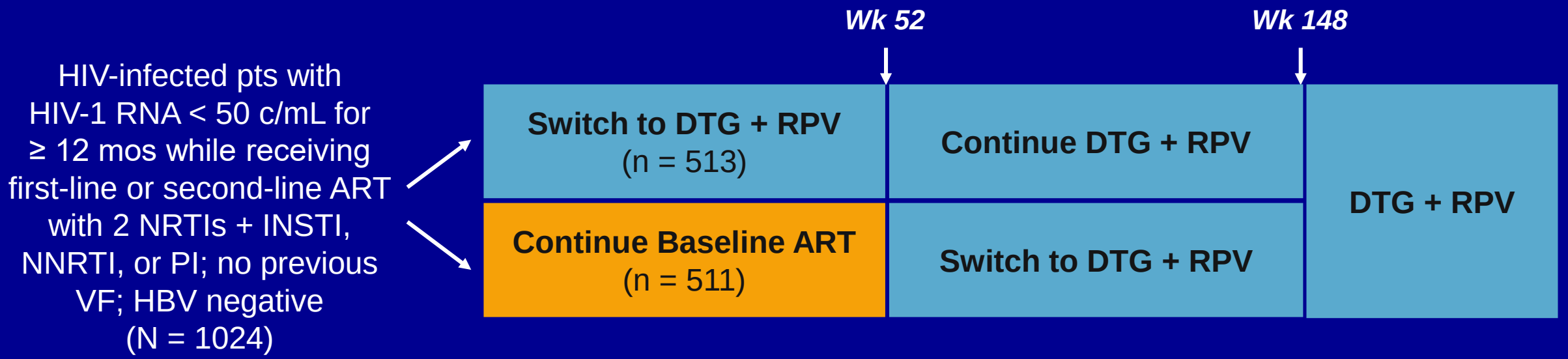
- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
- GEMINI 1/2 randomized phase III trials of DTG + 3TC ongoing[3,4]

1. Sued O, et al. IAS 2017. Abstract MOAB0106LB. 2. Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB. 3. ClinicalTrials.gov. NCT02831673. 4. ClinicalTrials.gov. NCT02831764.

Switch/Simplification

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

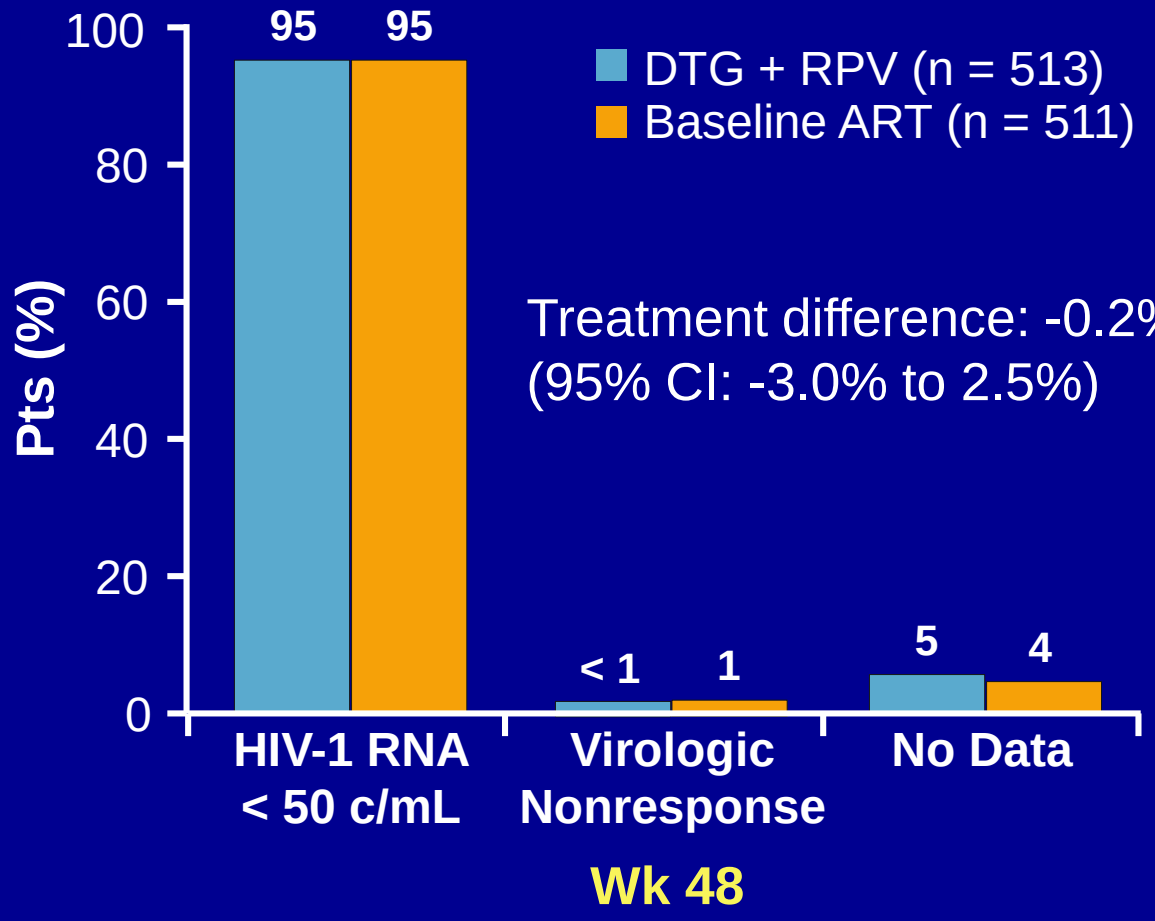
- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)



- 70% to 73% of pts receiving TDF at baseline

Llibre JM, et al. CROI 2017. Abstract 44LB.

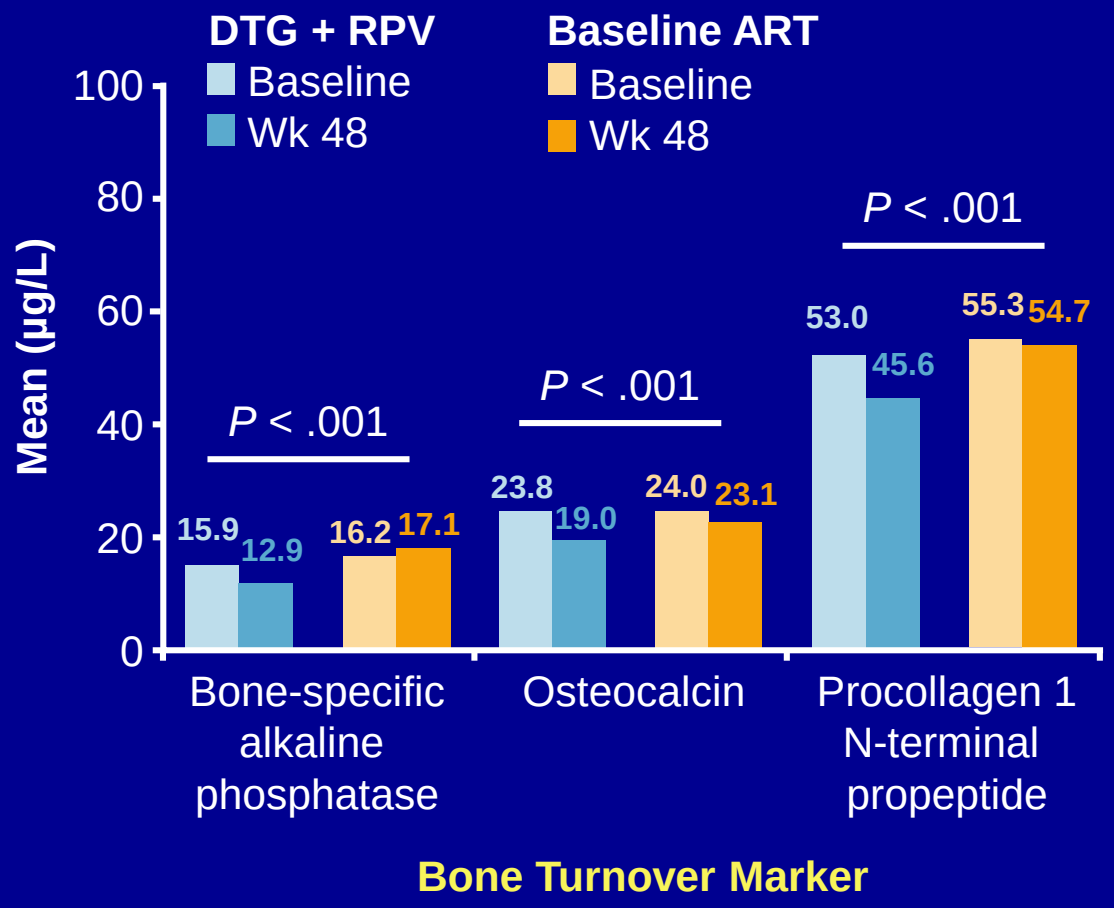
Switch From Suppressive ART to DTG + RPV Noninferior to Continued Baseline ART at Wk 48



- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E
  - Documented nonadherence at VF
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Llibre JM, et al. CROI 2017. Abstract 44LB. Reproduced with permission.

Switch From Suppressive ART to DTG + RPV: Safety Outcomes

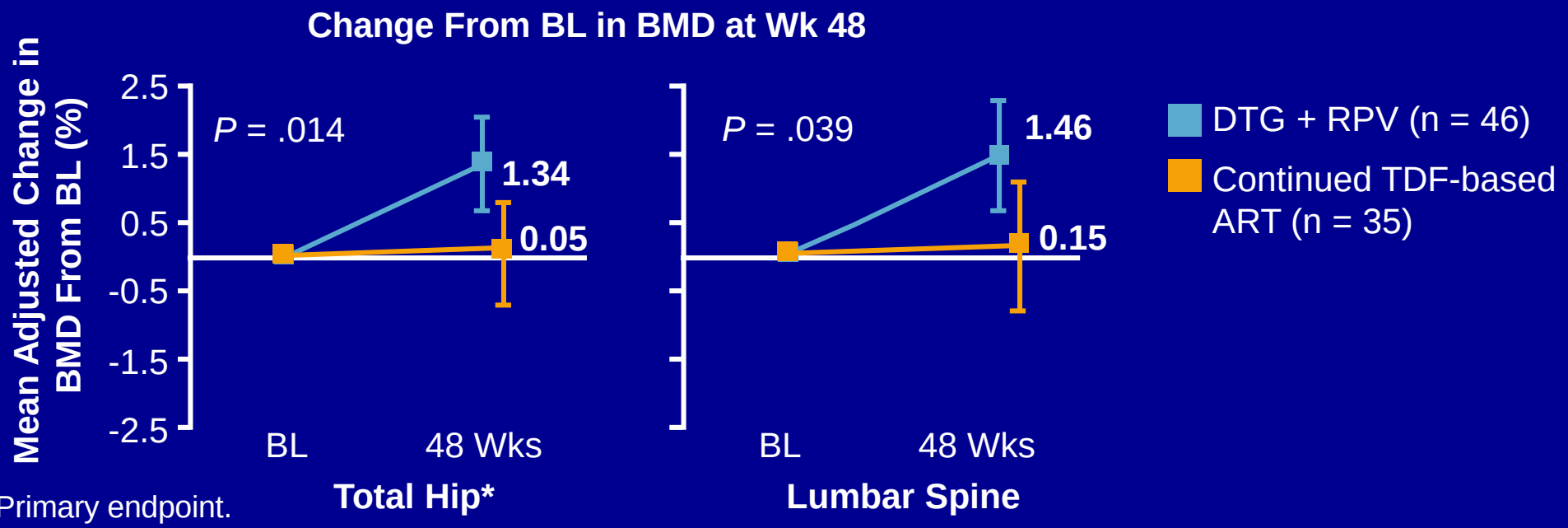


- AE rates generally similar between treatment arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%
- No notable change in serum lipid values from baseline to Wk 48 in either treatment arm

Llibre JM, et al. CROI 2017. Abstract 44LB. Reproduced with permission.

SWORD 1 & 2 Substudy: BMD Impact of Switch From TDF-Based ART to DTG + RPV

- Randomized, open-label, multicenter phase III trials demonstrated that switch to DTG + RPV noninferior to remaining on baseline ART at Wk 48 in virologically suppressed pts[1]
- Current analysis assessed BMD in pts who continued on TDF-containing triple ART regimen or switched from TDF-containing triple ART to DTG + RPV (N = 102)[2]



*Primary endpoint.

1. Llibre JM, et al. CROI 2017. Abstract 44LB. 2. McComsey G, et al. IAS 2017. Abstract TUPDB0205LB.
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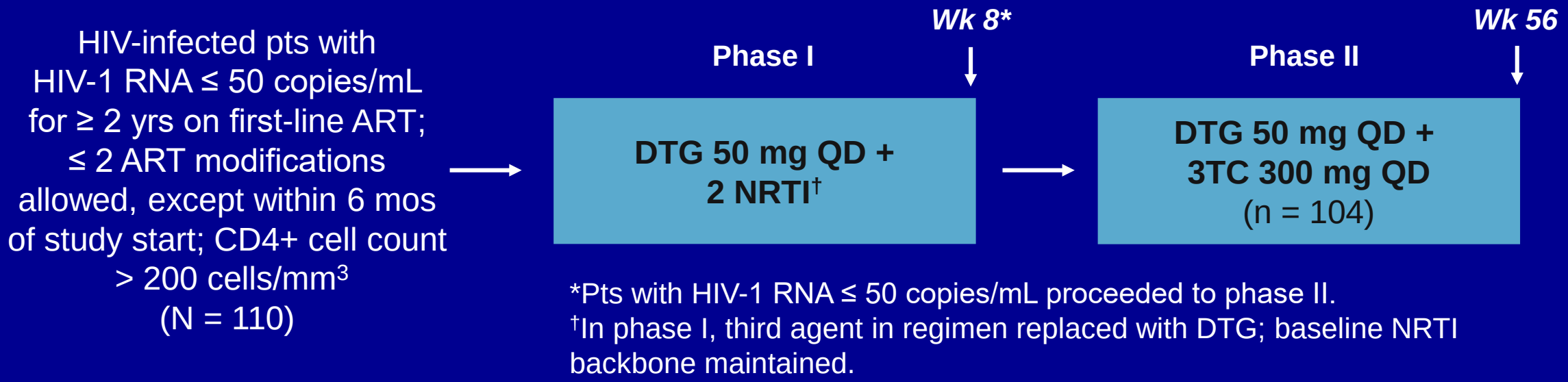
ANRS 167 LAMIDOL: Switch to DTG + 3TC in Virologically Suppressed Pts on Triple ART

- Noncomparative, open-label, single-arm multicenter trial
  - Primary endpoint: therapeutic success at Wk 56 (ie, after 48 wks of dual therapy)
    - Therapeutic failure: HIV-1 RNA > 50 copies/mL, interruption, lost to f/u, death



*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase II.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

Joly V, et al. CROI 2017. Abstract 458.

LAMIDOL Interim Analysis: Switch to DTG + 3TC Effective in Maintaining Viral Suppression

- 97% (101/104) pts maintained therapeutic success through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy
- DTG + 3TC dual therapy currently under phase III evaluation as both initial ART[2,3] and as a switch strategy for virologically suppressed pts[4]

Therapeutic Success, n/N* (%)	DTG + 3TC
Wk 0 (entry; on BL triple therapy)	110/110 (100)
Wk 8 (end of phase I, start of phase II)	104/104 (100)
Wk 12	104/104 (100)
Wk 16	103/104 (99)
Wk 24	103/104 (99)
Wk 32	103/104 (99)
Wk 40	102/104 (98)
Wk 48	101/104 (97)

*Pts enrolled in phase I, N = 110; pts enrolled in phase II, N = 104.

1. Joly V, et al. CROI 2017. Abstract 458. 2. ClinicalTrials.gov. NCT02831673. 3. ClinicalTrials.gov. NCT02831764 4. ClinicalTrials.gov. NCT02263326.

DOMONO: Switch to DTG Monotherapy in Virologically Suppressed Pts Not Sufficient

- Randomized comparison of switch to DTG 50 mg QD monotherapy vs continued baseline ART for 24 wks in virologically suppressed pts with no previous VF[2]
- At Wk 24, DTG monotherapy noninferior to continued baseline ART for maintained HIV-1 RNA < 200 c/mL
  - After 24 wks, all pts allowed to switch to DTG QD monotherapy
- Study d/c early because of high VF rate after 48 wks of DTG monotherapy
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group (*P* = .03)
  - Among 6 VF cases with resistance data in DTG monotherapy group, 3 developed INSTI resistance

Wijting I, et al. CROI 2017. Abstract 451LB.

Emergent INSTI Resistance After Switch to DTG Monotherapy

- International, multicenter retrospective study evaluated virologically suppressed pts who were switched from combination ART to DTG 50 mg QD monotherapy
  - Pts with history of VF on INSTI and INSTI resistance excluded
- 11 of 122 pts switched to DTG monotherapy experienced VF
  - 9 of 11 had genotypic INSTI resistance at VF
  - INSTI resistance pathways varied: 92Q/155H (n = 1); 97A/155H (n = 1); 155H/148R (n = 1); 118R (n = 2); 148K (n = 1); 148H (n = 2); 148R (n = 1)

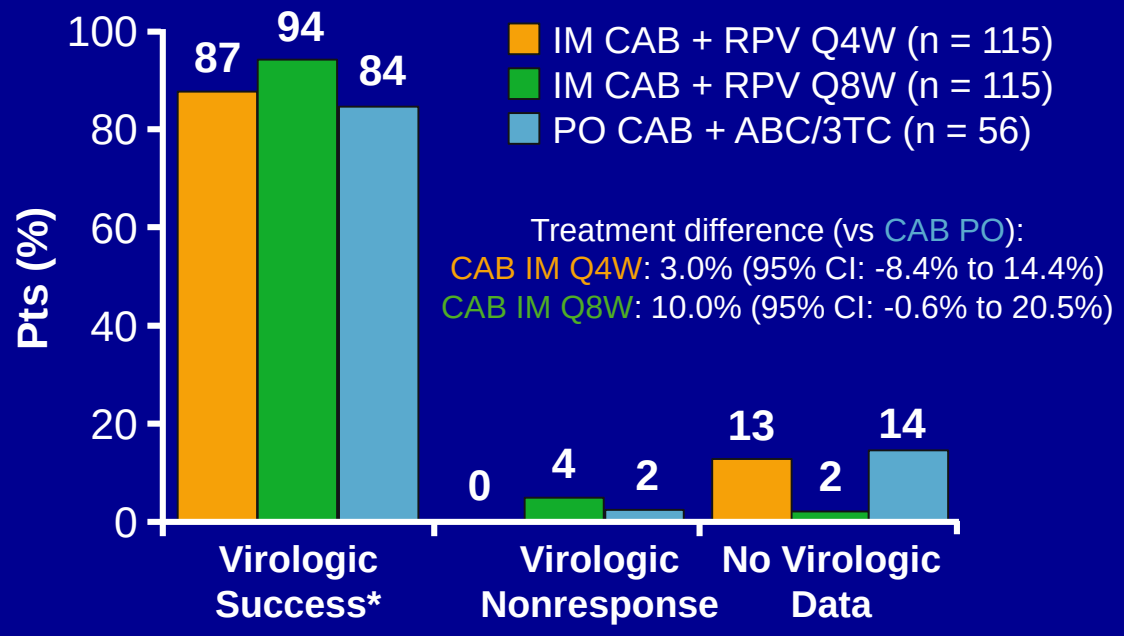
Blanco JL, et al. CROI 2017. Abstract 42.

Slide credit: clinicaloptions.com

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART

- **Cabotegravir:** INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to CAB 400 mg + RPV 600 mg IM Q4W, CAB 600 mg + RPV 900 mg IM Q8W, or CAB 30 mg + ABC/3TC 600/300 mg PO QD after induction/virologic suppression with oral CAB + ABC/3TC (N = 309)

Wk 96 Virologic Efficacy



*HIV-1 RNA < 50 copies/mL.

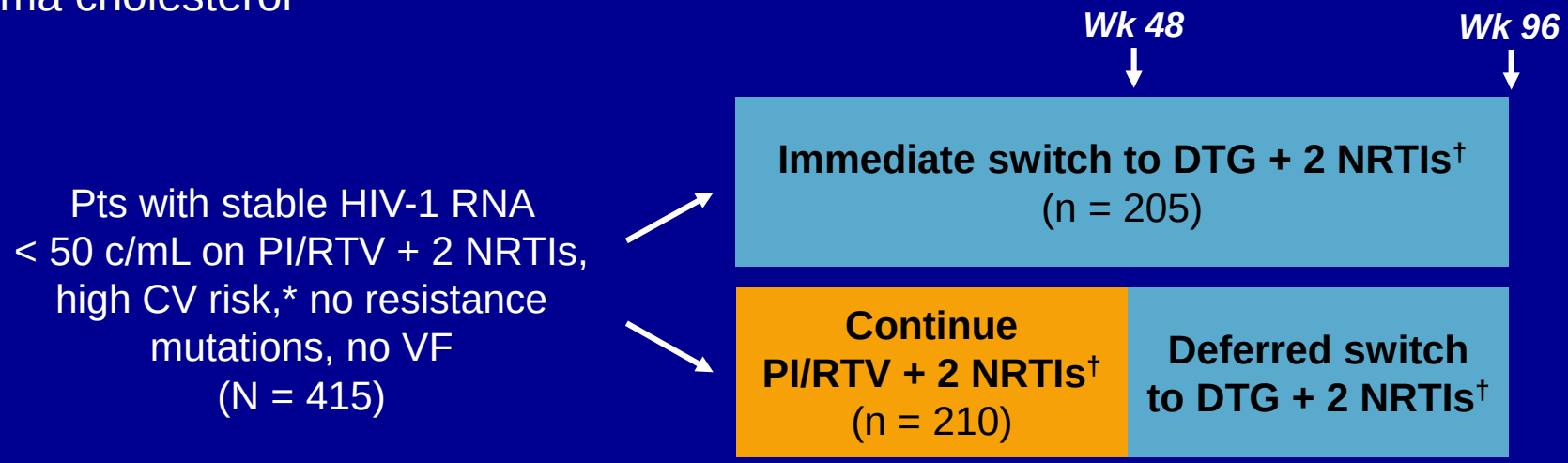
- At 96 wks, ~ 30% pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%; PO arm, 2%
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB

Eron J, et al. IAS 2017. Abstract MOAX0205LB. Margolis DA, et al. Lancet. 2017;[Epub ahead of print].

Slide credit: clinicaloptions.com

NEAT 022: Switch From Boosted PI to DTG in Suppressed Pts With High CV Risk

- International, randomized, open-label phase IV study
  - Primary endpoints at Wk 48: proportion with HIV RNA < 50 copies/mL (ITT), change in total plasma cholesterol



*> 50 yrs of age and/or Framingham risk score > 10% at 10 yrs. †NRTIs to remain the same throughout study.

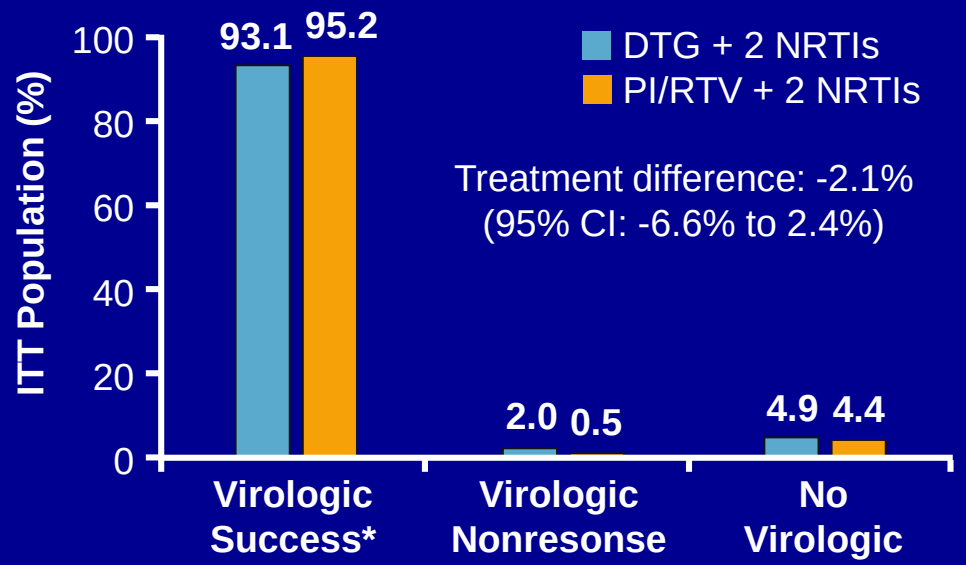
- Baseline NRTI backbones: FTC/TDF, 64.8%; ABC/3TC, 31.3%

Gatell JM et al. IAS 2017. Abstract TUAB0102. ClinicalTrials.gov. NCT02098837.

Slide credit: clinicaloptions.com

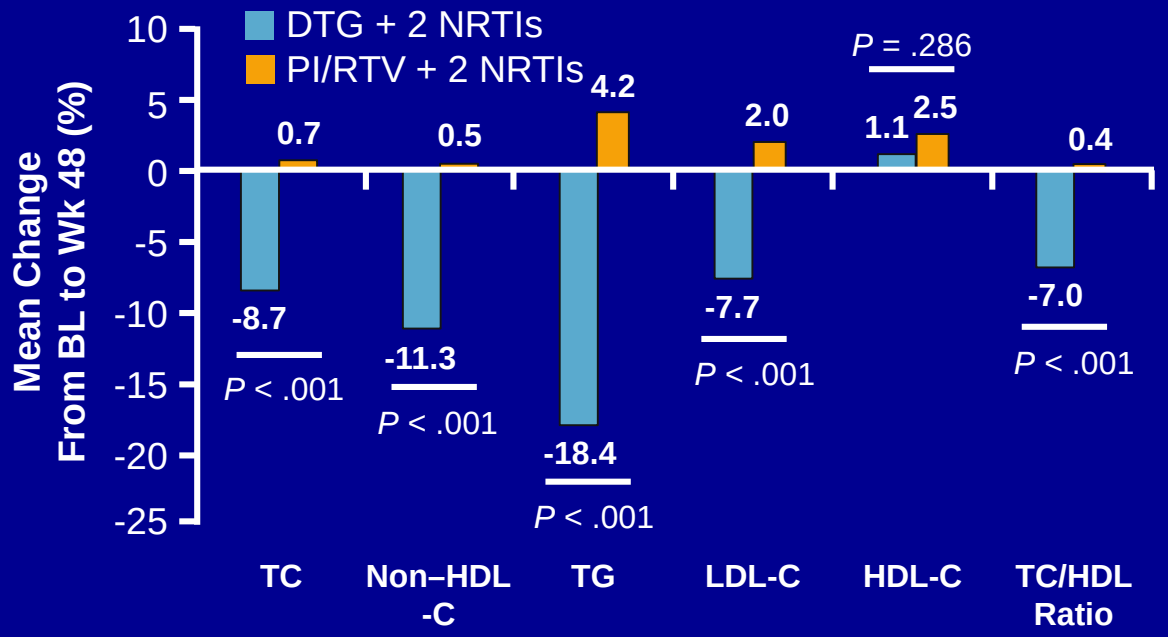
NEAT 022: Key Findings

- Switching to DTG noninferior to continuing boosted PI through Wk 48



*HIV-1 RNA < 50 copies/mL.

- Switching to DTG associated with improved lipid profile vs continuing boosted PI through Wk 48



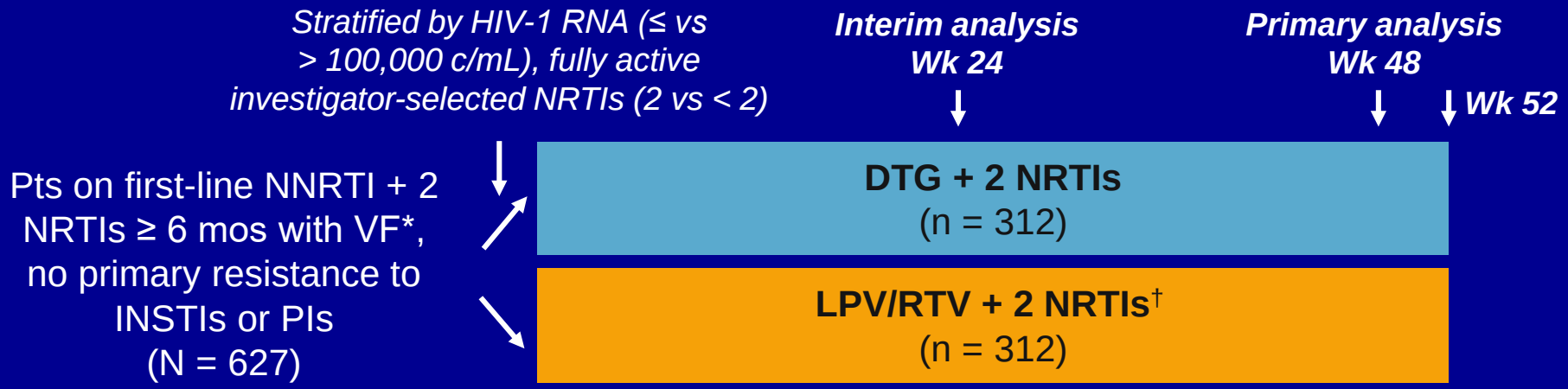
- No emergent resistance in pts with VF
- No significant differences in grade 3/4 AEs, serious AEs, AE-related d/c

Gatell JM, et al. IAS 2017. Abstract TUAB0102. Reproduced with permission.

Slide credit: clinicaloptions.com

DAWNING: Second-line DTG vs LPV/RTV + 2 NRTIs in Pts With Virologic Failure

- Interim results of an international, randomized, open-label phase IIIb study (N = 627)
  - Most frequent enrolment sites: South Africa (27%), Peru, Ukraine, Brazil, Thailand, China (8% to 10% each)



*HIV-1 RNA ≥ 400 copies/mL on 2 occasions. †After preplanned analysis (all Wk 24 and subsets of Wks 36/48 data), it was recommended that LPV/RTV be discontinued due to differences in virologic nonresponse and PDVF favoring DTG arm. Protocol amendment allowed pts on LPV/RTV to switch to DTG.

- Baseline characteristics (DTG vs LPV/RTV): female, 37% vs 33%; African heritage, 42% vs 36%; HIV-1 RNA > 100,000 copies/mL, 22% vs 20%

Aboud M, et al. IAS 2017. Abstract TUAB0105LB. ClinicalTrials.gov. NCT02227238.

DAWNING: Key Findings

Virologic Outcome at Wk 24, n (%)	DTG + 2 NRTIs (n = 312)	LPV/RTV + 2 NRTIs (n = 312)	Treatment Difference, % (95% CI)
Success*	257 (82)	215 (69)	13.8 (7.3-20.3; *P* < .001)
Nonresponse	37 (12)	77 (25)	NR
No data	18 (6)	20 (6)	NR

ITT-E population. *HIV-1 RNA < 50 copies/mL.

- Virologic withdrawal†: DTG arm, n = 10 (3%); LPV/RTV arm, n = 28 (9%)
- In pts with virologic withdrawal:
  - No pts in DTG arm developed INSTI or NRTI RAMs
  - n = 3 in LPV/RTV arm developed NRTI RAMs
- AEs, DTG vs LPV/RTV
  - Drug related, 15% vs 36%
  - Serious/death, 5% vs 6%
  - Leading to withdrawal, 2% vs 5%

†HIV-1 RNA decrease of < 1 $\log_{10}$ c/mL by Wk 16, increase to ≥ 400 c/mL after suppression, ≥ 400 c/mL at or after Wk 24.

Aboud M, et al. IAS 2017. Abstract TUAB0105LB.

Efficacy, Safety of Ibalizumab Through 24 Wks

- Non-immunosuppressive monoclonal antibody that binds CD4 and inhibits viral entry
- Able to block both CCR5- and CXCR4 tropic viruses.

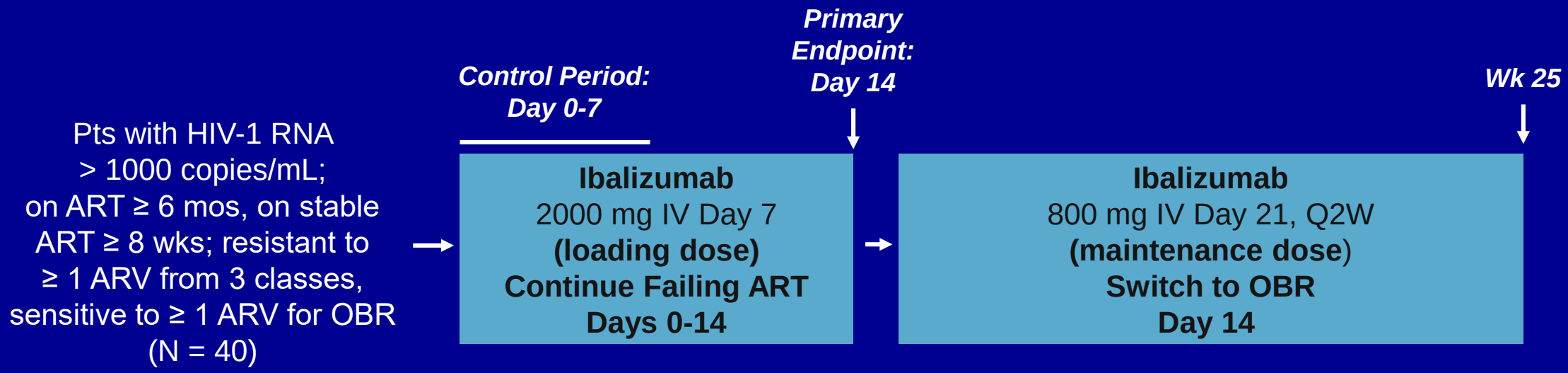
Wk 24 Virologic Outcome	Ibalizumab + OBR
≥ 1.0 $\log_{10}$ HIV-1 RNA decrease, %	55
≥ 2.0 $\log_{10}$ HIV-1 RNA decrease, %	48
HIV-1 RNA < 50 copies/mL, %	43
HIV-1 RNA < 200 copies/mL, %	50
Mean HIV-1 RNA decrease from baseline, $\log_{10}$	1.6

- Primary endpoint: 83% with ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs 3% at end of control period (P < .0001)
  - 60% with ≥ 1.0 $\log_{10}$ HIV-1 RNA decrease
  - Mean decrease by Day 14: 1.1 $\log_{10}$
- 9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation
- 9 other pts discontinued
  - Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal (n = 3)
  - Lost to follow-up (n = 2)
- **No cases of anti-ibalizumab antibodies**

Lewis S, et al. CROI 2017. Abstract 449LB.

TMB-301: Long-Acting Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14



- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance

Lewis S, et al. CROI 2017. Abstract 449LB.

CD01 Extension: Long-term, Maintenance PRO 140 Monotherapy Following Initial ART

- PRO 140: humanized IgG4 CCR5 mAb
- Single-arm, open-label phase IIb extension study[1]
  - Maintenance PRO 140 given at 350 mg SC/wk for ≤ 3 yrs in pts stable on initial ART from CD01 study (N = 16)
- Wkly PRO 140 maintenance SC injection generally well tolerated
  - No drug-related severe AEs or d/c for AEs
  - Infrequent, mild, transient administration-site reactions in < 10% of pts
- HIV-1 RNA < 40 copies/mL maintained in majority of pts
  - > 40 wks: 13/16 pts (81.3%)
  - > 2 yrs: 10/16 pts (62.5%)
  - 1 pt d/c due to relocation; 5 pts had VF
- CD4+ cell counts stable through study
- No anti-PRO 140 antibodies detected
- Ongoing phase IIb/III studies of PRO 140 monotherapy[2] and in combination with ART[3]

1. Lalezari J, et al. CROI 2017. Abstract 437. 2. ClinicalTrials.gov. NCT02859961.
3. ClinicalTrials.gov. NCT02483078.

Additional Investigational Agents Reported at CROI 2017: Preclinical and Phase I

Agent	MoA or Formulation	Phase	Dosing/ Administration	Implications
GS-CA1[1]	HIV capsid inhibitor	Pre-clinical	Extended release, suitable for SC of solid depot formulation	▪ Potent ART with orthoganol resistance profile to existing ART; potential for long-acting formulation due to low aqueous solubility, high stability
GS-9131[2]	NRTI	Pre-clinical	Potential for once daily dosing	▪ Potent ART active against NRTI RAMs K65R, L74V, M184V alone or in combination; minimal loss of susceptibility with 4 or more TAMs
MK-8591[3]	Nucleoside Reverse Transcriptase **Translocation** Inhibitor (NRTTI)	Pre-clinical	10 mg QW PO; potential for extended duration	▪ Comparable MK-8591 levels in animal rectal, vaginal tissue to TDF levels in tissues of human subjects highlights potential prophylaxis utility
GS-PI1[4]	PI	Pre-clinical	Potential for unboosted, once daily dosing	▪ Potent ART with high barrier to resistance, including < 2-fold loss in potency against major PI RAMs, and 10-fold to 40-fold longer in vivo half life vs ATV or DRV
NANO-EFV, NANO-LPV[5]	Oral, lower dose SDN	I	nEFV: 50 mg QD, 21 d nLPV/RTV: 200/100 mg BID, 7 d	▪ Enhanced oral bioavailability suggests can reduce EFV, LPV dose by ~ 50% while maintaining PK

1. Tse WC, et al. CROI 2017. Abstract 38. 2. White KL, et al. CROI 2017. Abstract 436.
3. Grobler J, et al. CROI 2017. Abstract 435. 4. Link JO, et al. CROI 2017. Abstract 433. 5. Owen A, et al. CROI 2017. Abstract 39.

Additional Investigational Agents Reported at CROI 2017: Phase II

Agent	MoA or Formulation	Phase	Dosing/ Administration	Implications
TMC278 LA[1]	LA injectable RPV (IM)	II	1200 mg IM Q8W	▪ Potential as injectable, long-acting PrEP
Elsulfavirine[2]	Prodrug of new NNRTI VM1500A	IIb	Combined therapy: 20 mg elsulfavirine + FTC/TDF PO QD	▪ Less toxic alternative to EFV for initial ART
UB-421[3]	Anti-CD4 receptor mAb	II	10 mg/kg QW IV or 25 mg/kg Q2W IV	▪ Possible ART alternative for maintenance therapy in virologically suppressed pts

1. Bekker L-G, et al. CROI 2017. Abstract 421LB. 2. Murphy R, et al. CROI 2017. Abstract 452LB.
3. Wang C-Y, et al. CROI 2017. Abstract 450LB.

ART and Pregnancy

Current DHHS Recommendations: Initial ART in Pregnant Women

Guideline Status	NRTIs	PIs	INSTIs	NNRTIs
Preferred	**3TC/ABC** **FTC/TDF** **3TC + TDF**	**ATV/RTV*** **DRV/RTV*†**	**RAL*§**	
Alternative	3TC/ZDV	LPV/RTV*†		EFV* RPV*‡
Insufficient data to recommend	FTC/TAF	FPV	DTG EVG/COBI	

*In addition to preferred 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if pretreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm^3. § If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

DHHS Perinatal Guidelines. October 2016.

Slide credit: clinicaloptions.com

Tsepamo: Birth Outcomes When Initiating First-line DTG vs EFV in Pregnancy

- Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

Adverse Birth Outcomes, n (%)	DTG (n = 845)	EFV (n = 4593)	aRR* (95% CI)
Any	291 (34.4)	1606 (35.0)	1.0 (0.9-1.1)
▪ Severe	92 (10.9)	519 (11.3)	1.0 (0.8-1.2)
Stillbirth	18 (2.1)	105 (2.3)	0.9 (0.6-1.5)
Neonatal death (< 28 d)	11 (1.3)	60 (1.3)	1.0 (0.5-1.9)
Preterm birth (< 37 wks)	149 (17.8)	844 (18.5)	1.0 (0.8-1.1)
▪ Very preterm (< 32 wks)	35 (4.2)	160 (3.5)	1.2 (0.8-1.7)
SGA (< 10th percentile weight)	156 (18.7)	838 (18.5)	1.0 (0.9-1.2)
▪ Very SGA (< 3rd percentile weight)	51 (6.1)	302 (6.7)	0.9 (0.7-1.2)

*For DTG vs EFV; adjusted for maternal age, education, gravida.

- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396); most second/third trimester
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- Adverse birth outcome risks similar when initiating first-line DTG vs EFV in pregnancy

Zash R, et al. IAS 2017. Abstract MOAX0202LB.

Slide credit: clinicaloptions.com

Selected Prevention Studies

- **Opposites Attract:** international, prospective cohort study assessing the incidence of linked HIV transmission in MSM serodiscordant couples when HIV-infected partner on ART and virologically suppressed (N = 343 couples; 591 CYFU; 16,889 acts of CLAI)[1]
  - For HIV-infected partner, HIV-1 RNA undetectable for 95% of CYFU
  - **No linked infections; 3 infections occurring during study contracted from outside partners**
- **Pluspills:** open-label demonstration study of FTC/TDF PO QD + support for HIV prevention in uninfected, sexually active adolescents 15-19 yrs of age in South Africa (N = 148)[2]
  - **Adherence decreased over time and with less frequent study visits**; at Wk 12 (monthly visits), 54% had plasma TDF levels of ≥ 10 ng/mL; at Wk 48 (visits every 3 mos), 38% had plasma TDF levels of ≥ 10 ng/mL
- **MTN023/IPM 030:** randomized, double-blind, placebo-controlled phase IIa trial of a dapivirine vaginal ring for HIV prevention in uninfected, sexually active US adolescents 15-17 yrs of age (N = 96)[3]
  - At Wk 24, similar rates of grade ≥ 2 AE between study groups; **87% of plasma samples (taken at 2, 4, 12, 24 wks) showed dapivirine levels suggestive of adherence; 95% of returned rings had residual dapivirine levels suggestive of adherence**

1. Bavinton BR, et al. IAS 2017. Abstract TUAC0506LB. 2. Gill K, et al. IAS 2017. Abstract TUAC0207LB. 3. Bunge K, et al. IAS 2017. Abstract TUAC0206LB.

Slide credit: clinicaloptions.com

Selected Prevention Studies

- **IPERGAY:** randomized, double-blind, placebo-controlled study of event-driven FTC/TDF PO PrEP for uninfected, high-risk MSM in France and Canada (N = 400)
  - Previous findings: HIV incidence/100 PY, FTC/TDF vs placebo groups 0.91 vs 6.60 (*P* = .002; 86% reduction in HIV incidence with event-driven FTC/TDF); median pills/mo 15[1]
  - **Substudy of 269 pts using ≤ 15 pills/mo with reported PrEP use systematically/often during intercourse: HIV incidence/100 PY, FTC/TDF vs placebo groups 0 vs 9.3 (*P* = .013)[2]**
- **PROUD:** randomized, open-label study of immediate vs deferred FTC/TDF PO QD PrEP for uninfected, high-risk MSM in England (N = 544)[3]
  - Current analysis: post deferred phase, in which all pts offered PrEP

HIV Incidence/100 PY (Infections/PY)[4]	Immediate PrEP	Deferred PrEP	*P* Value
Deferred phase (Yr 1)	1.6 (4/254)	9.4 (21/223)	NR
Post deferred phase (Yrs 2-4)	1.2 (5/424)	0.3 (1/356)*	.18

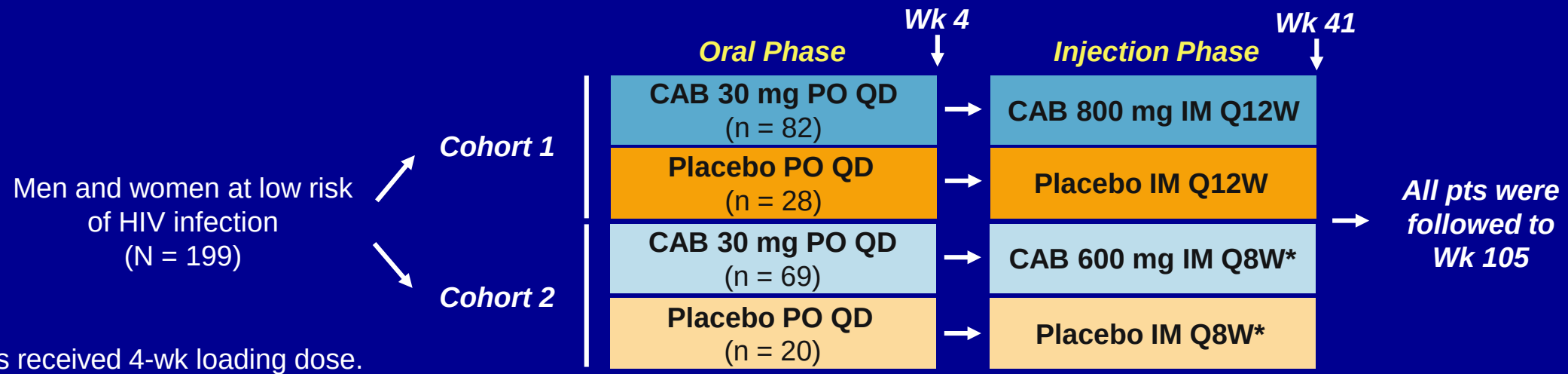
*Significant difference in HIV incidence observed for deferred group pts in deferred vs post deferred phases (*P* < .0001).

1. Molina JM, et al. N Engl J Med. 2015;373:2237-2246. 2. Antoni G, et al. IAS 2017. Abstract TUAC0102.
3. McCormack S, et al. Lancet. 2016;387:53-60. 4. White E, et al. IAS 2017. Abstract TUAC0101.

Slide credit: clinicaloptions.com

HPTN 077: Cabotegravir for PrEP in Low-Risk Persons

- International, randomized, double-blind, placebo-controlled phase IIa study (N = 199)



- **Grade ≥ 2 AEs significantly different between CAB and PBO during injection phase: injection-site pain (34% vs 2%; *P* < .0001), headache (15% vs 2%; *P* = .03)**
  - Most injection-site reactions mild/moderate; 1 discontinuation due to injection-related AE
- 1 seroconversion (CAB cohort 1): detected 48 wks after final injection; CAB levels undetectable
- Participants in cohort 2 (600 mg IM Q8W) consistently met prespecified PK targets; this dose will be assessed in phase III studies

Landovitz R, et al. IAS 2017. Abstract TUAC0106LB. ClinicalTrials.gov. NCT02178800.

Slide credit: clinicaloptions.com

HIV Cure Strategies Currently in Human Trials

Minimize Reservoir

Early Treatment to Limit Reservoir

ART

Broadly neutralizing antibodies

Shock

Reactivate Latently Infected Cells

HDAC inhibition

Bromodomain and extra-terminal inhibition

Activate toll-like receptors

Activate protein kinase

Kill

Viral Clearance by Immune System

Broadly neutralizing antibodies

Therapeutic vaccines

Anti-programmed death (PD) 1

Anti-PD ligand 1

HIV-Resistant Cells

Transfuse Cells Without CCR5 Gene

Gene-editing therapy

Bone marrow or cord blood transplantation

Timing of ART Initiation in Primary Infection and HIV Reservoirs: Key Lessons

- HIV persistence
  - Established early in primary HIV infection in long-lived memory CD4+ T cells and not eliminated by immune surveillance or ART
- ART initiated during primary HIV infection
  - Can reduce the HIV reservoir size to a greater extent than when treatment is given in chronic HIV
  - However, infection persists in memory CD4+ T cells in most early treated individuals
- Treatment initiated in the earliest primary HIV infection stage (Fiebig I)
  - May protect central memory CD4+ T cells from infection and skew the distribution of latently infected cells to the shorter-lived memory CD4+ T cells (eg, elite controllers and post-treatment controllers)
- Containing HIV reservoir seeding with ART in primary HIV infection (before use of other interventions aimed at eliminating all latently infected cells)
  - May be a first critical step in achieving HIV remission

Ananworanich J, et al. *Curr Opin HIV AIDS*. 2015;10:18-28.