Update on Current and Near Future Antiretroviral Therapy

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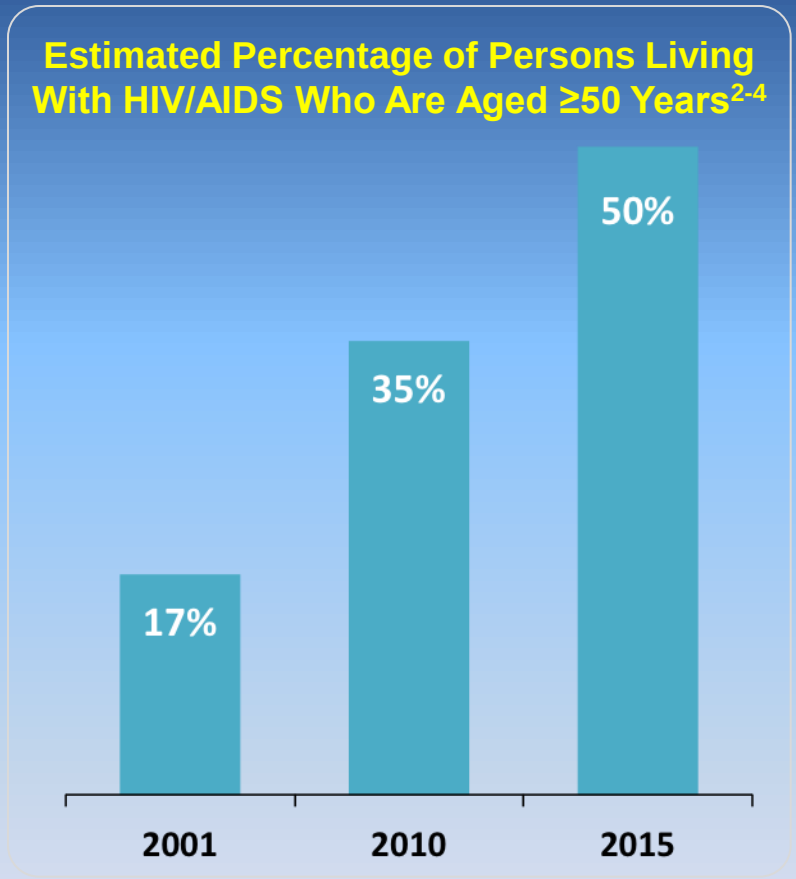
HIV+ Patients are living longer

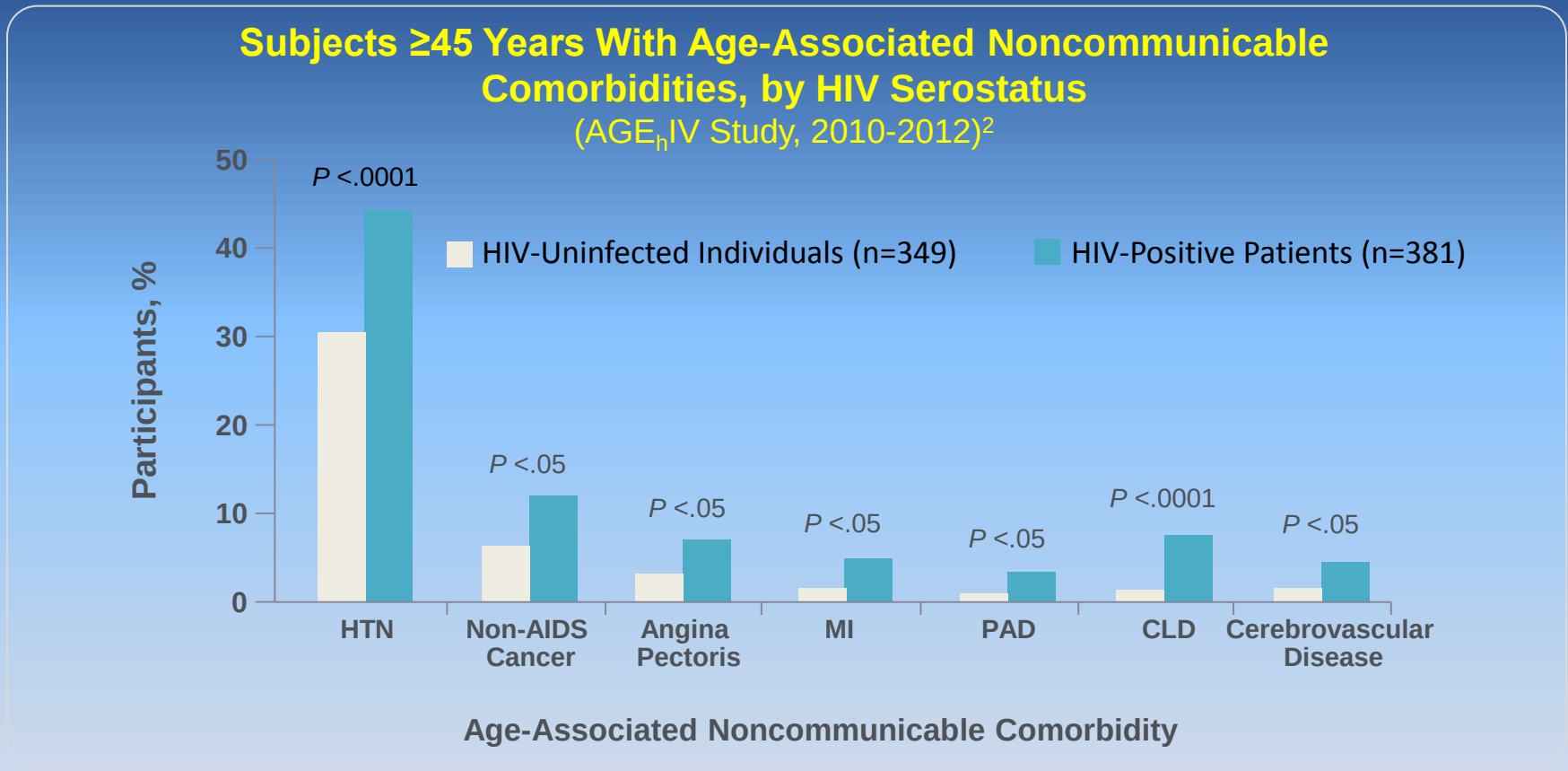


- In the United States, a 20-year-old HIV-positive patient can now expect to live into his/her early 70s[5]

ART, antiretroviral therapy; PY, person years.

[1] Palella FJ, et al. *J Acquir Immune Defic Syndr*. 2006;43:27-34; [2] Centers for Disease Control and Prevention (CDC). *HIV/AIDS Surveillance Report: Cases of HIV Infection and AIDS in the United States and Dependent Areas*. 2005; [3] CDC. *Diagnoses of HIV Infection in the United States and Dependent Areas*. 2011; [4] Effros RB, et al. *Clin Infect Dis*. 2008;47:542-553; [5] Samji H, et al. *PLoS ONE* 2013; 8e81355.

COMORBIDITIES ARE MORE PREVALENT IN HIV-POSITIVE PATIENTS



- Similarities between aging and the courses of HIV and AIDS suggest that HIV infection may compress certain aging processes, thereby accelerating comorbidities and frailty[1]
- Duration of ART use (OR 1.24 per 5 additional years of ART use) and lower nadir CD4 cell count (OR 1.12 per 100 fewer cells) were associated with an increased risk of a higher number of comorbidities

CLD, chronic liver disease; HTN, hypertension; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.

[1] Effros RB, et al. *Clin Infect Dis*. 2008;47:542-553; [2] Schouten J, et al. IAC 2012. Washington, DC. THAB0205.

Current Antiretroviral Medications

NRTI

- Abacavir
- Emtricitabine
- Lamivudine
- Tenofovir
- Zidovudine

NNRTI

- Efavirenz
- Rilpivirine
- Etravirine

PI

- Atazanavir
- Darunavir
- Lopinavir

Fusion Inhibitor

CCR5 Antagonist

- Maraviroc

Integrase Inhibitor

- Raltegravir
- Elvitegravir
- Dolutegravir

Combined Drugs

NRTI

- Lamivudine
- Zidovudine

COMBIVIR

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

Combined Drugs

NRTI

- Abacavir
- Lamivudine

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

EPZICOM

Combined Drugs

NRTI

- Abacavir
- Lamivudine
- Zidovudine

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

TRIZIVIR

NNRTI

Combined Drugs

NRTI

- Emtricitabine
- Tenofovir (TDF)

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

TRUVADA

Combined Drugs

NRTI

- Emtricitabine
- Tenofovir (TAF)

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

DESCOVY

Combined Drugs

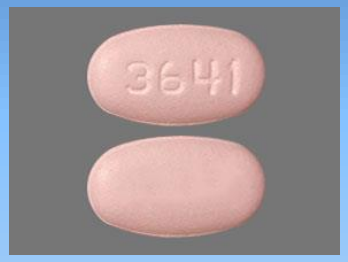
NRTI

PI

•Atazanavir

Fusion Inhibitor

CCR5 Antagonist



EVOTAZ

Integrase Inhibitor

+Cobicistat

NNRTI

Combined Drugs

NRTI

PI

•Darunavir

+ Cobicistat

PREZCOBIX

NNRTI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

Combined Drugs (STR)

NRTI

- Emtricitabine
- Tenofovir (TDF)

NNRTI

- Efavirenz

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

ATRIPLA

Combined Drugs (STR)

NRTI

- Emtricitabine
- Tenofovir (TDF)

NNRTI

- Rilpivirine

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

COMPLERA

Combined Drugs (STR)

NRTI

- Abacavir
- Lamivudine

NNRTI

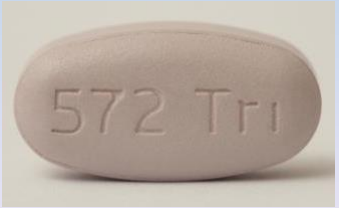
PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

- Dolutegravir



TRIUMEQ

Combined Drugs (STR)

NRTI

- Emtricitabine
- Tenofovir (TDF)

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

Elvitegravir

STRIBILD

Cobicistat

Combined Drugs (STR)

NRTI

- Emtricitabine
- Tenofovir (TAF)

NNRTI

- Rilpivirine

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

ODEFSEY

Combined Drugs (STR)

NRTI

•Emtricitabine

•Tenofovir (TAF)

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

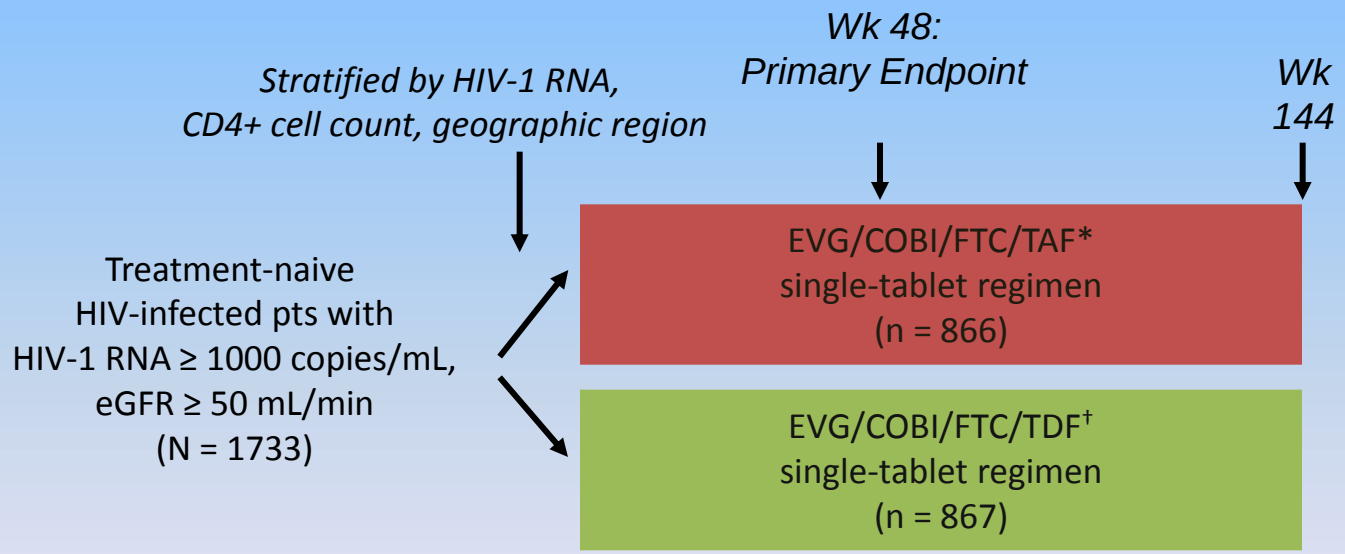
Elvitegravir

Cobicistat

GENVOYA

Studies 104/111: TAF vs TDF in Treatment-Naive Pts

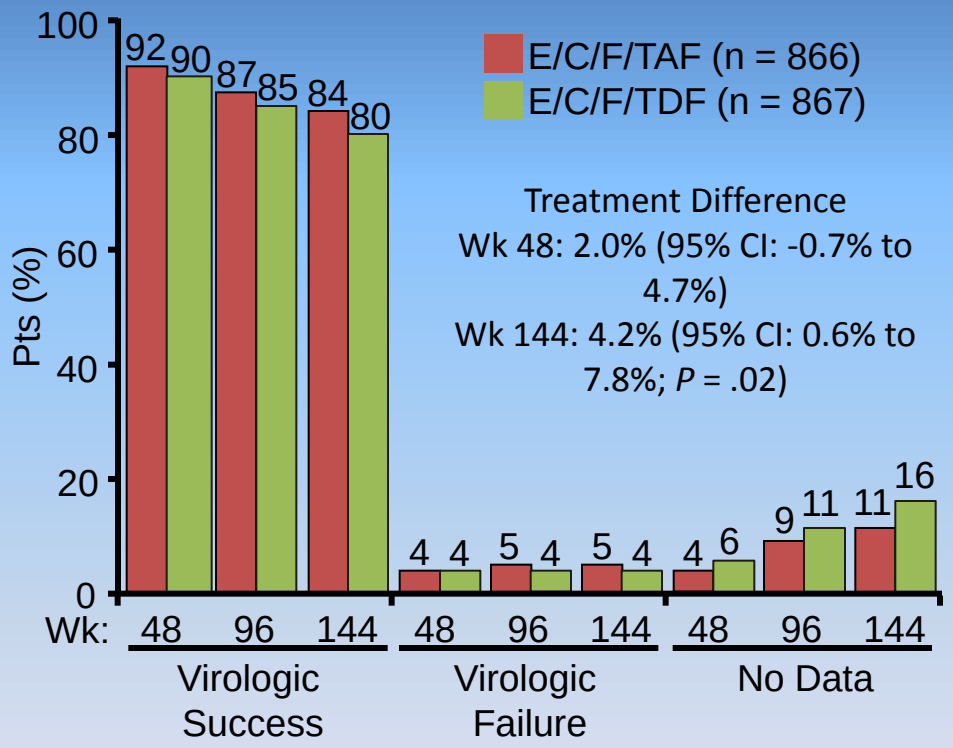
- Parallel, randomized, double-blind, active-controlled phase III studies
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48 (FDA Snapshot)



*150/150/200/10 mg once daily.
†150/150/200/300 mg once daily.

Arribas JR, et al. CROI 2017. Abstract 453. Sax PE, et al. Lancet. 2015;385:2606-2615.

Initial ART With E/C/F/TAF Superior to E/C/F/TDF at Wk 144



- Efficacy similar across pt subgroups, trending toward or significantly better with TAF in each group
  - By baseline HIV-1 RNA, baseline CD4+ cell count, adherence, age, sex, race, region
- Virologic failure with resistance by Wk 144: 1.4% in each arm

Arribas JR, et al. CROI 2017. Abstract 453. Sax PE, et al. Lancet. 2015;385:2606-2615.

Initial ART With E/C/F/TAF vs E/C/F/TDF: Wk 144 Safety Outcomes

- Rate of discontinuation for AEs higher with TDF vs TAF regimen
  - 3.3% vs 1.3% (*P* = .01)
- Spine and hip BMD loss greater with TDF vs TAF regimen
  - 6 discontinuations for bone AEs in TDF arm vs 0 in TAF arm
- TC, LDL, and HDL increases greater with TAF vs TDF regimen, but no difference in TC:HDL ratio
  - Rates of lipid-modifying therapy initiation similar: 5.5% vs 5.8%

Renal Events Leading to Discontinuation, n	E/C/F/TAF (n = 866)	E/C/F/TDF (n = 867)
Proximal renal tubulopathy	0	4
Cr elevation or eGFR decrease	0	3
Renal failure	0	2
Nephropathy	0	1
Proteinuria	0	1
Bladder spasm	0	1
Total	**0**	**12**

Arribas JR, et al. CROI 2017. Abstract 453.

Future Combined Drugs (STR)

NRTI

- Lamivudine

NNRTI

PI

?

Fusion Inhibitor

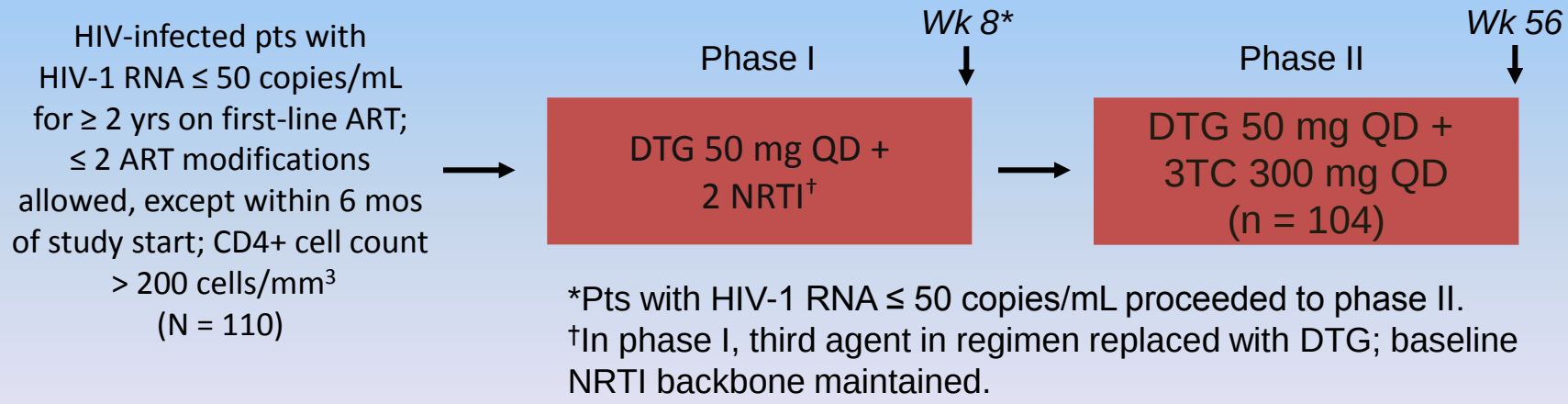
CCR5 Antagonist

Integrase Inhibitor

- Dolutegravir

Switch to DTG + 3TC From Virologically Suppressive 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.

Switch to DTG + 3TC Maintains 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.

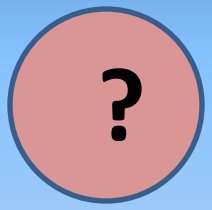
Future Combined Drugs (STR)

NRTI

NNRTI

•Rilpivirine

PI



Fusion Inhibitor

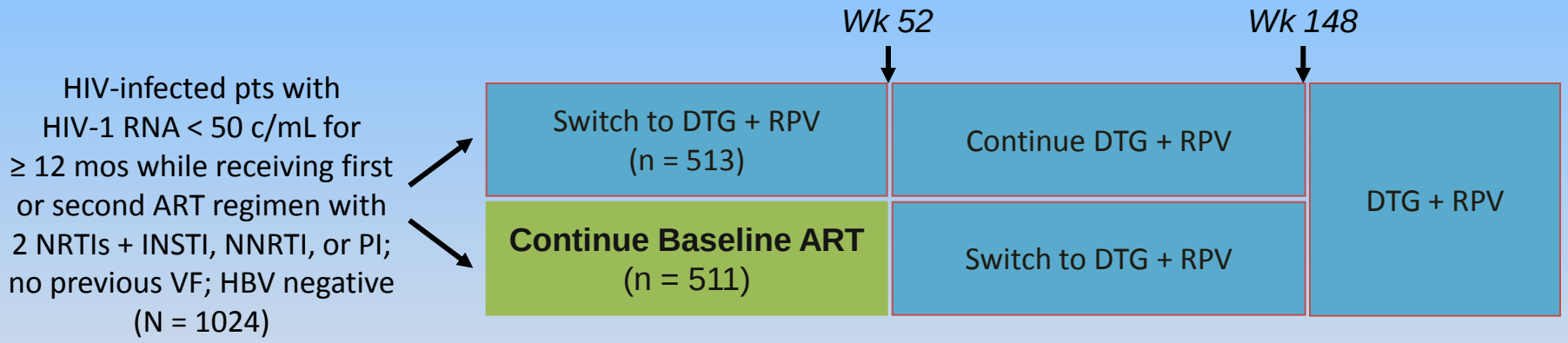
CCR5 Antagonist

Integrase Inhibitor

•Dolutegravir

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

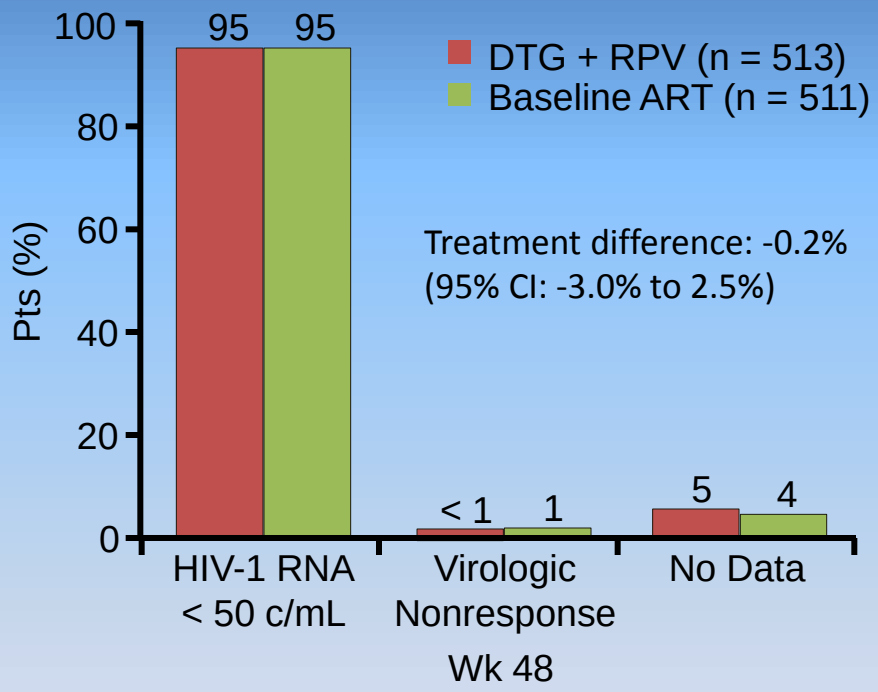
- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)



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

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

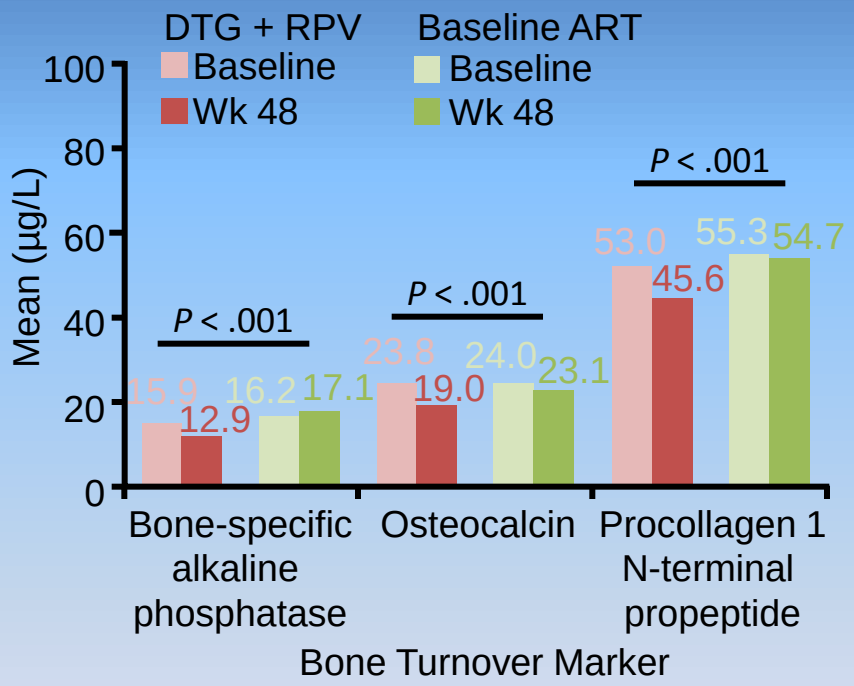
Switch From Suppressive ART to DTG + RPV Noninferior to Cont. BL ART at Wk 48



- 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.

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.

Future Combined Drugs (STR)

NRTI

- Emtricitabine
- Tenofovir (TAF)

NNRTI

PI

- Darunavir

?

+ Cobicistat

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

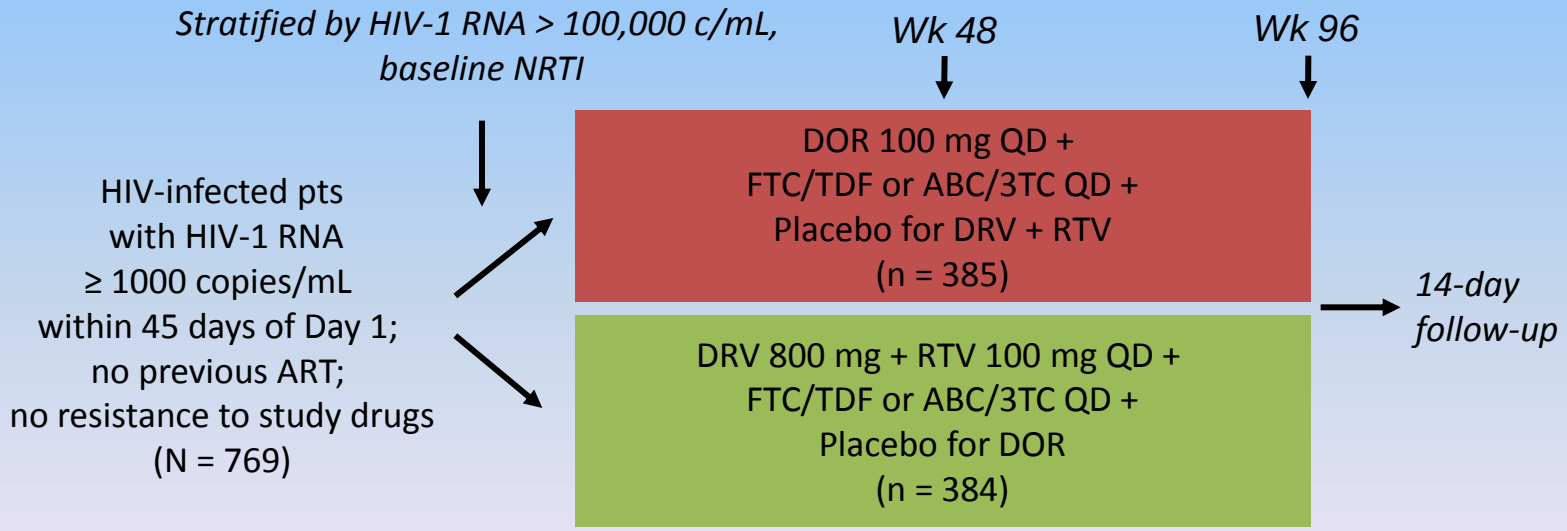
Future New Drugs in Existing Classes

- **NNRTI**: Doravirine.

- **INSTI** : Bictegravir

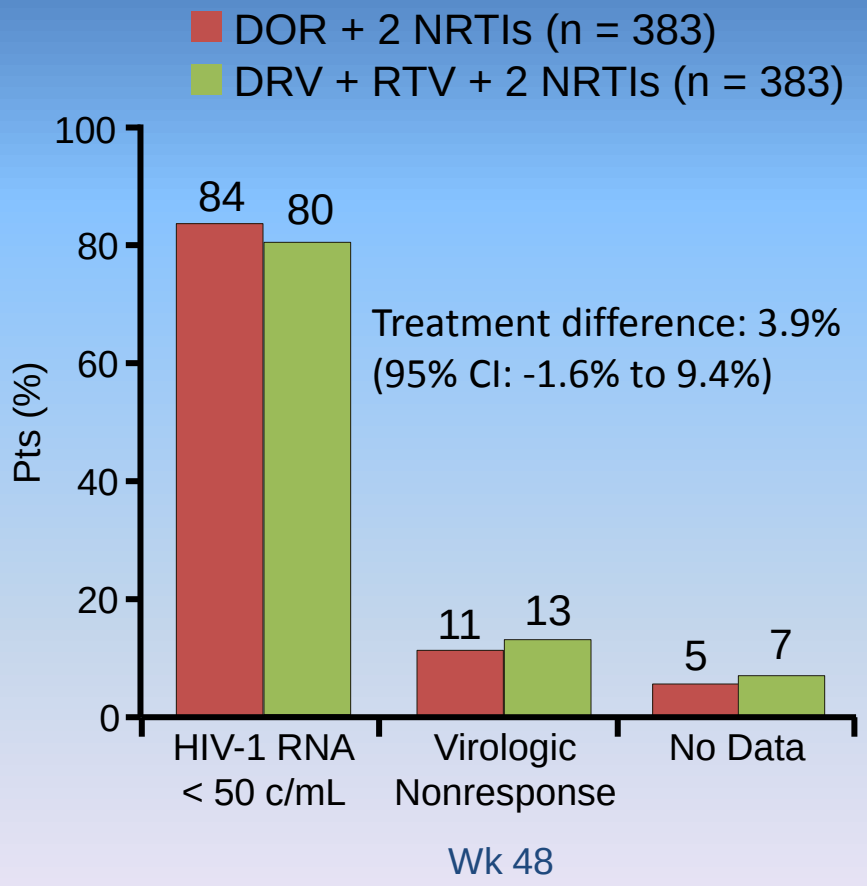
Doravirine or Darunavir + RTV Both With 2 NRTIs in Treatment-Naive Pts

- Doravirine: next-gen NNRTI, unique resistance profile, low DDI potential, no food or PPI effects
- 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



- 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.

Doravirine vs DRV + RTV: 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.

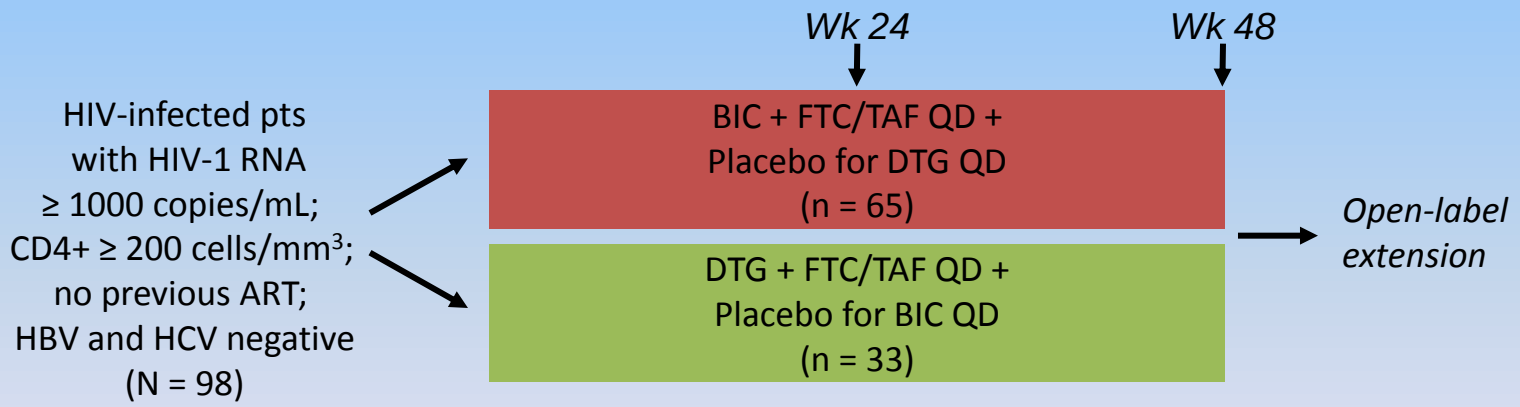
Fasting Lipid Δ From BL to Wk 48, mg/dL	DOR (n = 383)	DRV + RTV (n = 383)
LDL-c*	-4.51	9.92
Non-HDL-c*	-5.3	13.75
Cholesterol	-1.37	17.9
Triglyceride	-3.14	21.97
HDL-c	3.94	4.15

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

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

Bictegravir + FTC/TAF vs DTG + FTC/TAF in Treatment-Naive Pts

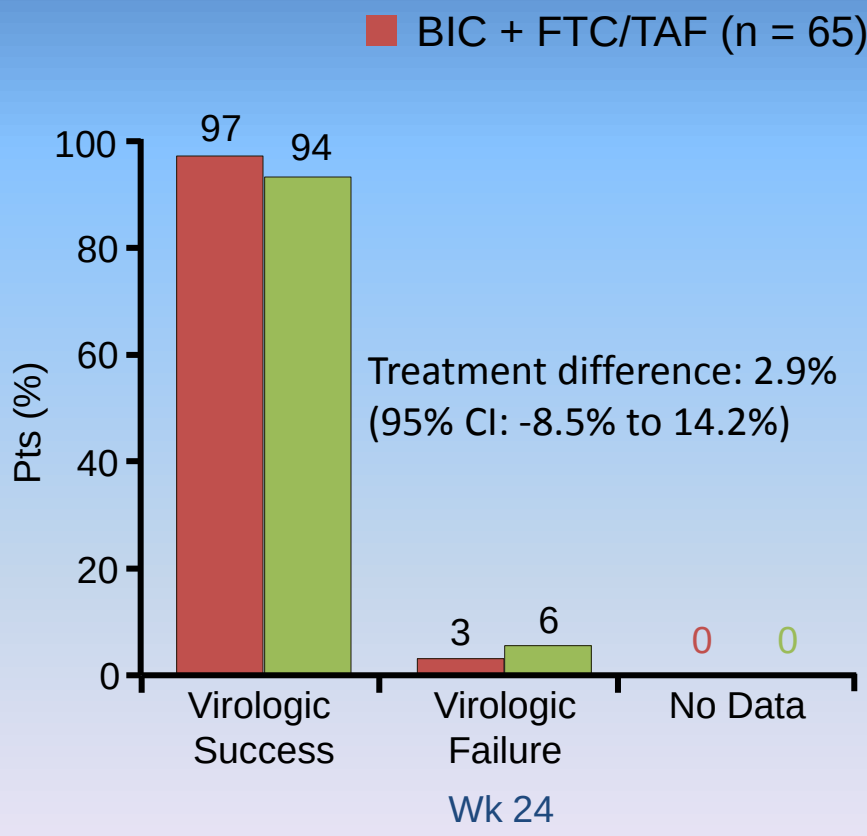
- Bictegravir: investigational QD INSTI, active against most INSTI RAVs, low DDI potential, half-life ~ 18 hrs, no food requirement with dosing, primarily metabolized by CYP3A4 and UGT1A1
- Randomized, double-blind, active-controlled phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

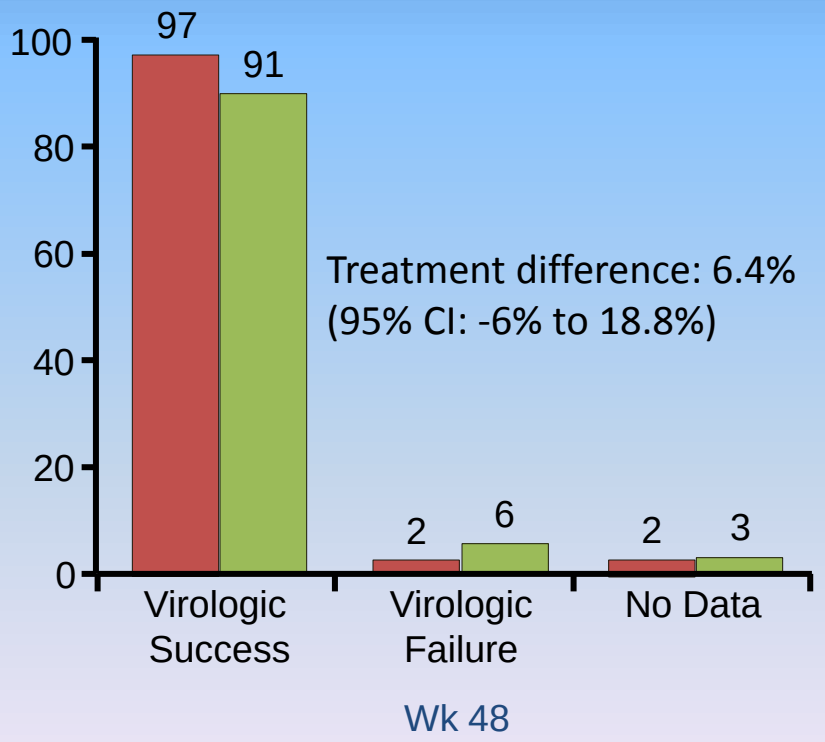


Sax PE, et al. CROI 2017. Abstract 41. Sax PE, et al. Lancet HIV. 2017;[Epub ahead of print]. Zhang H, et al. CROI 2017. Abstract 40.

Bictegravir + FTC/TAF vs DTG + FTC/TAF: Wk 24 and Wk 48 Efficacy (FDA Snapshot)

- No drug resistance detected in either arm through Wk 48





Sax PE, et al. CROI 2017. Abstract 41.

Bictegravir + FTC/TAF vs DTG + FTC/TAF: Safety

Any Grade AE Occurring in ≥ 5% in Either Arm, %	BIC + FTC/TAF (n = 65)	DTG + FTC/TAF (n = 33)
Diarrhea	12	12
Nausea	8	12
Headache	8	3
URTI	8	0
Fatigue	6	6
Arthralgia	6	6
Chlamydial infection	6	3
Back pain	6	0
Furuncle	5	6
Flatulence	2	6
Gastroenteritis	2	6
Costochondritis	0	6
Hemorrhoids	0	6
Pruritus	0	6

Grade 2-4 Lab Abnormality ≥ 5% in Either Arm, %	BIC + FTC/TAF (n = 64*)	DTG + FTC/TAF (n = 32*)
Creatine kinase	13	9
AST	9	3
Hyperglycemia	8	13
ALT	6	0
LDL	6	9
Amylase	5	6
Hematuria	3	6
Glycosuria	2	6

*Pts with ≥ 1 post-BL laboratory assessment, excluding those not specified for all pts.

- Difficult to conclude on safety from small study, but 4 fully enrolled phase III trials now evaluating efficacy, safety, tolerability of coformulated BIC/FTC/TAF

Sax PE, et al. CROI 2017. Abstract 41.

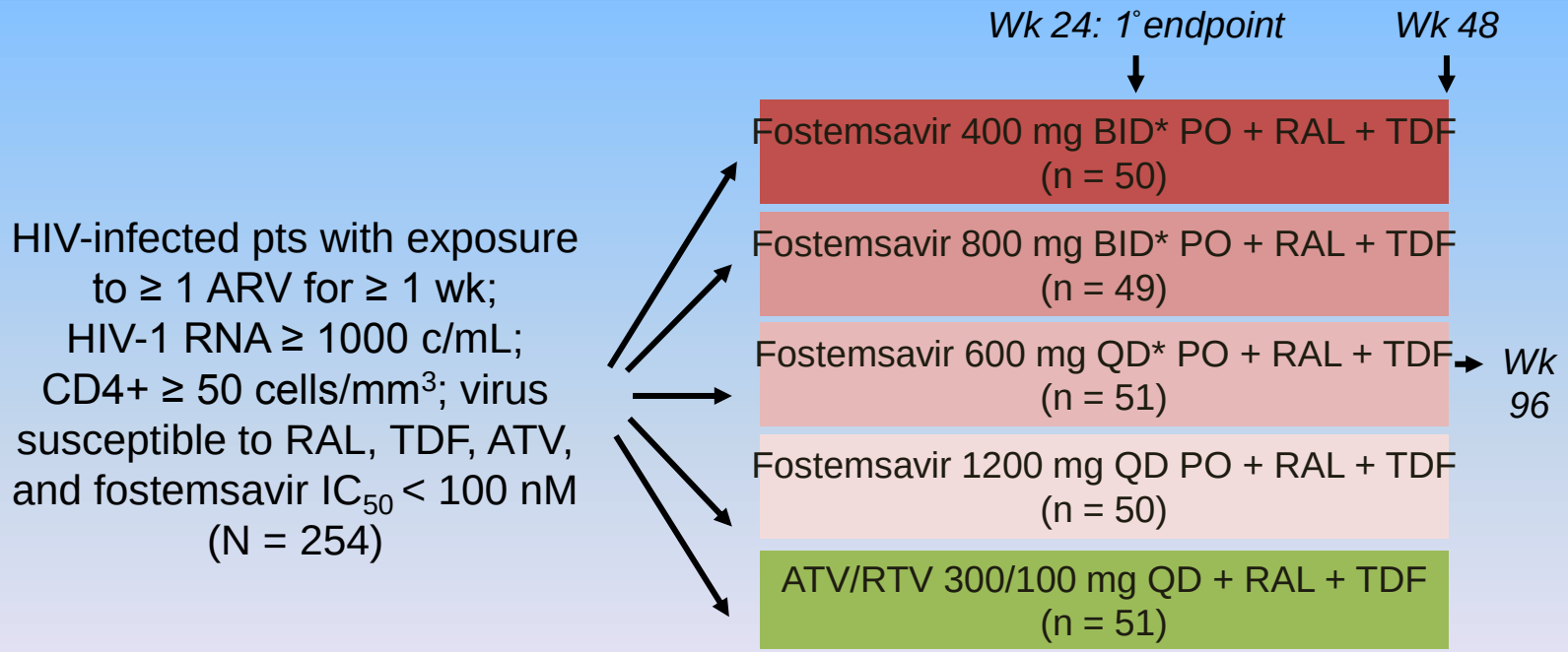
Emerging Investigational Agents for Pts With MDR HIV

Investigational Agent	Phase	MoA
Fostemsavir[1-3]	III	Prodrug; when metabolized **binds gp120 to prevent CD4+ cell attachment**, entry
Ibalizumab[4,5]	III	Humanized **anti-CD4 receptor mAb**

1. Lalezari JP, et al. Lancet HIV. 2015;2:e427-437. 2. Granados-Reyes ER, et al. HIV Glasgow 2016. Abstract O335A. 3. ClinicalTrials.gov. NCT02362503. 4. Lewis S, et al. CROI 2017. Abstract 449LB.
5. Lin H-H, et al. CROI 2017. Abstract 438.

AI438011: Fostemsavir + RAL + TDF in Treatment-Experienced Pts

- **Fostemsavir:** prodrug; proposed MoA: binding HIV-1 gp120 prevents viral attachment and entry into host CD4+ cells
- Randomized, active-controlled phase IIb study, blinded to dose
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 24



*Fostemsavir dose changed to 1200 mg QD from Wk 48 to Wk 96.

Granados-Reyes ER, et al. HIV Glasgow 2016. Abstract O335A.
Llamoso C, et al. HIV Glasgow 2016. Abstract O335B.

Efficacy, Safety of Fostemsavir + RAL + TDF

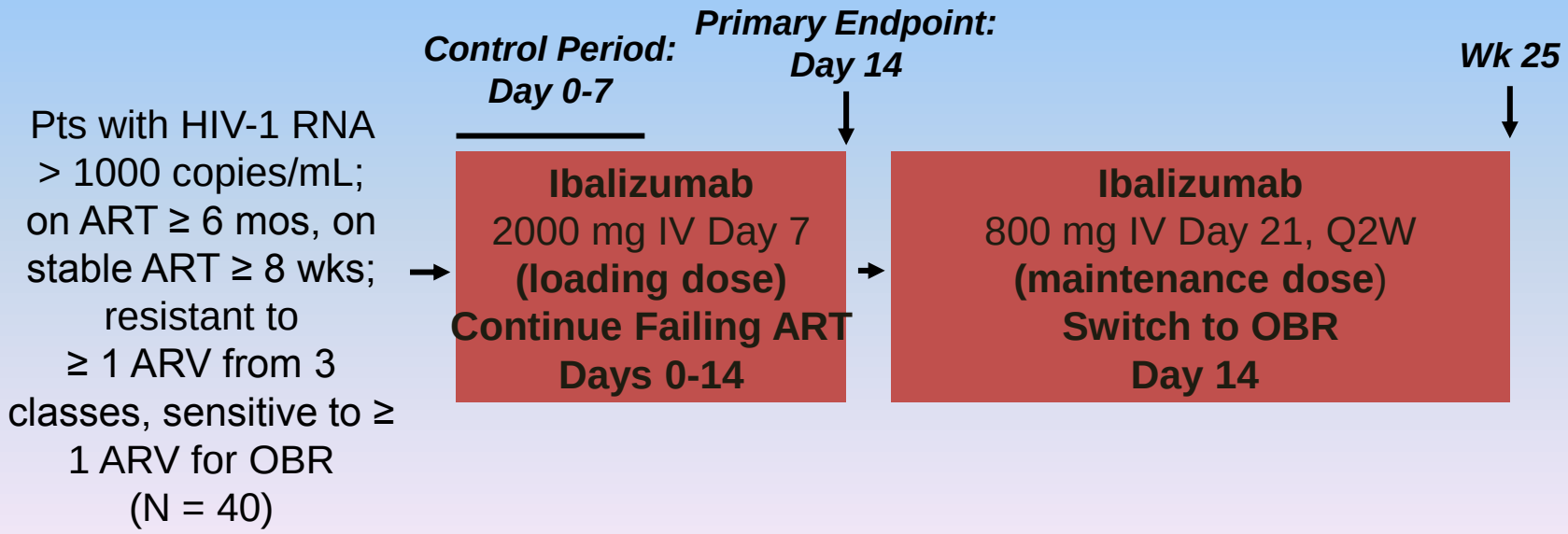
At Wk 96, 90% of pts had HIV-1 RNA < 50 copies/mL in both fostemsavir and ATV/RTV arms in observed analysis[1]

- No significant differences in virologic efficacy regardless of race, sex, age, BL HIV-1 RNA, BL CD4+ cell count, or IC_{50} subgroups[1]
- Fostemsavir generally well tolerated, with higher rates of grade 2-4 treatment-emergent AEs (37% vs 9%) and d/c for AEs (10% vs 3%) for ATV/RTV arm vs fostemsavir arm[2]

1. Granados-Reyes ER, et al. HIV Glasgow 2016. Abstract O335A.
2. Llamoso C, et al. HIV Glasgow 2016. Abstract O335B.

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

- **Ibalizumab:** humanized mAb to CD4 receptor that blocks HIV entry into CD4+ T-cells
  - FDA breakthrough and orphan drug designations
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14



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

TMB-301: Efficacy

Virologic Outcome	Ibalizumab + OBR
Day 14	
≥ 0.5 log_{10} HIV-1 RNA decrease, %	83*
≥ 1.0 log_{10} HIV-1 RNA decrease, %	60
Mean HIV-1 RNA decrease, log_{10}	1.1
Wk 24	
≥ 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 BL, log_{10}	1.6

Lewis S, et al. CROI 2015

*Primary endpoint; *P* < .0001 vs 3% at end of control period.

TMB-301: Safety

- 9 pts reported 17 serious AEs[1]
  - 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
- Phase III TMB-311 study ongoing; extension for pts from TMB-301; accepting new pts[2]
- IM dosing may be viable as administration route as compared with IV dosing[3]

1. Lewis S, et al. CROI 2017. Abstract 449LB. 2. ClinicalTrials.gov. NCT02707861. 3. Lin H, et al. CROI 2017. Abstract 438.

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)	I	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, QD 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

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.

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.