Antiretroviral Therapy – What's New

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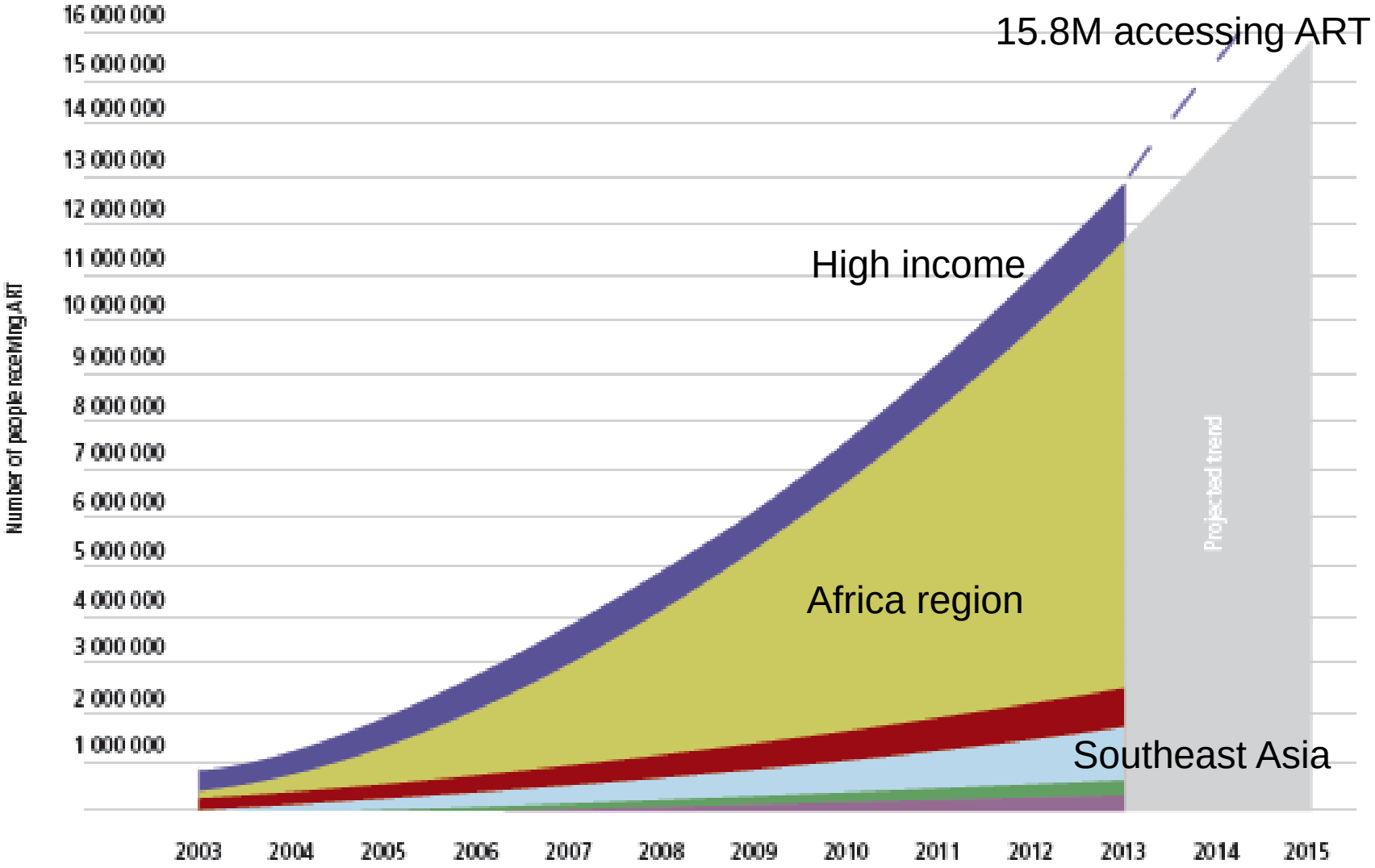
Outline

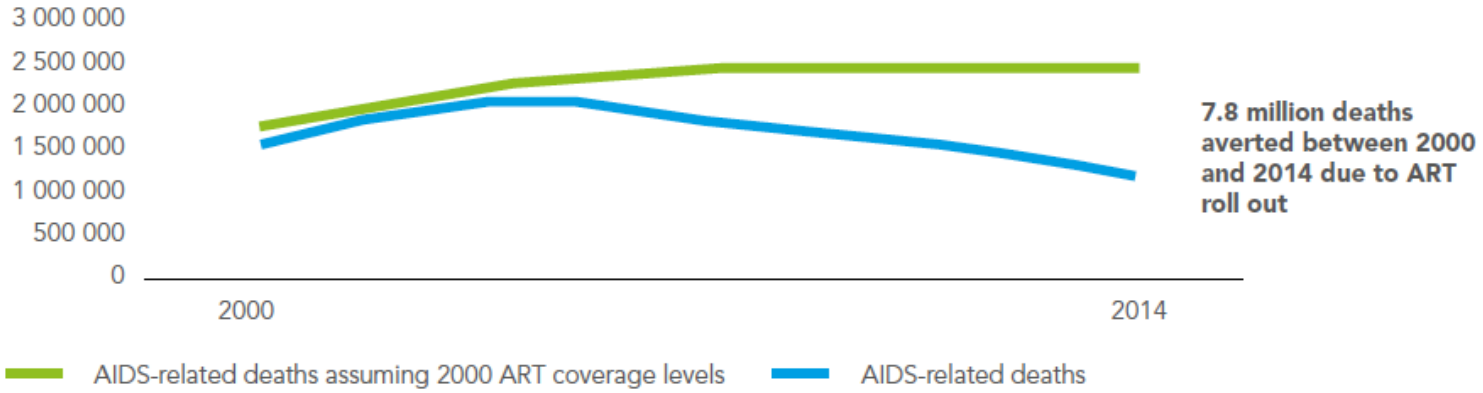
- Evolving global epidemiology
- What's new in the guidelines
- What's new with "newer" drugs and regimens
- What's new with investigational drugs and regimens
  - Clinical trial data supporting their activity
- Antiretroviral therapy for the future

Actual and projected numbers of people receiving antiretroviral therapy in low-and middle-income countries, and by WHO Region, 2003–2015



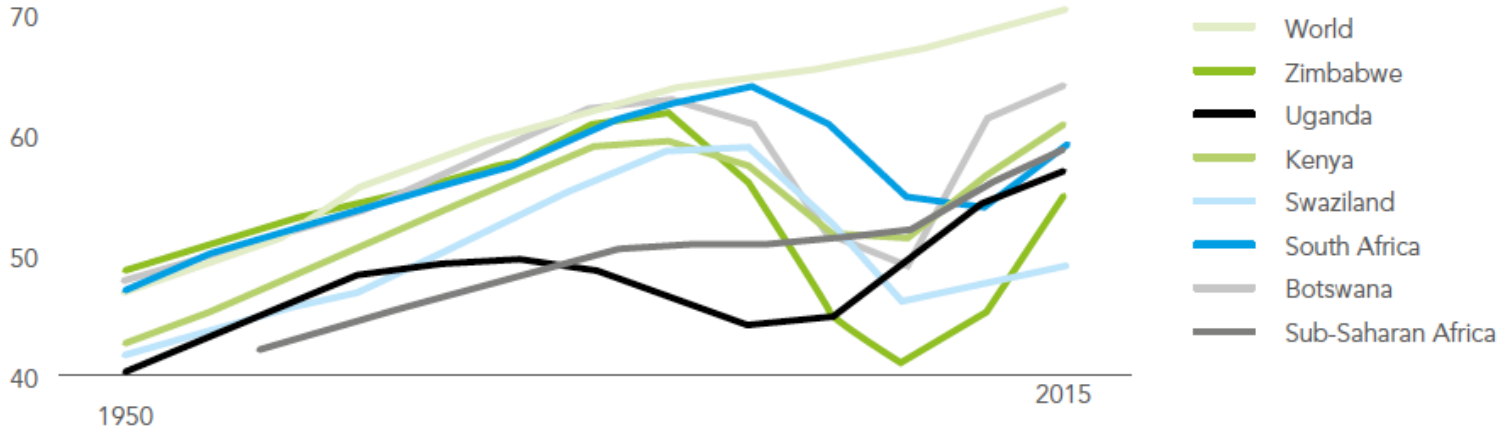
Impact of ART on Life Expectancy

Fig. 3. **AIDS deaths, global, 2000–2014**



Source: UNAIDS, How AIDS changed everything — MDG6: 15 years, 15 lessons of hope from the AIDS response, Geneva 2015.

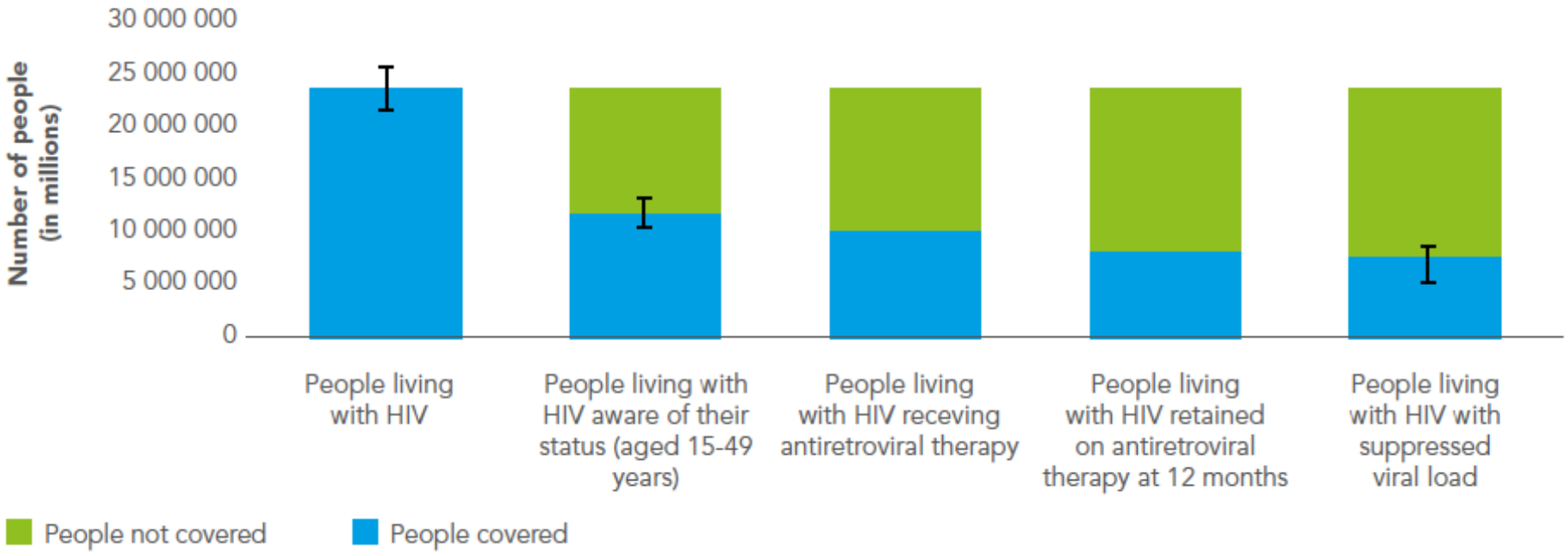
Fig. 4. **Dramatic impact of HIV response on life expectancy, 1950–2015**



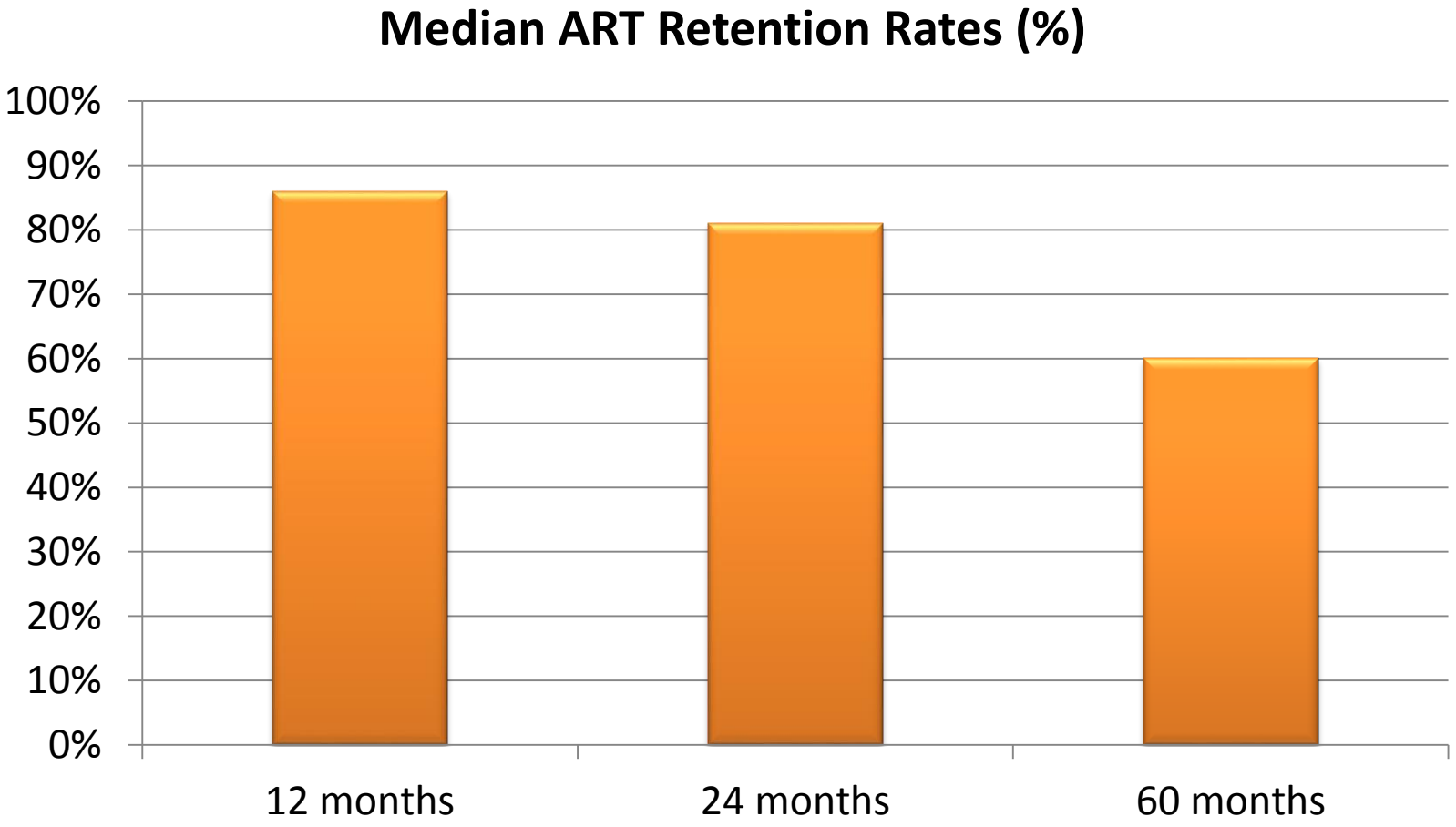
Source: United Nations Population Division, World Population Prospects, 2015 revision.

The Treatment Cascade

Fig. 13. **HIV treatment cascade for people aged 15 years and over in sub-Saharan Africa, 2014**



ART Retention Rates Reported by Selected Low- & Middle-Income Countries



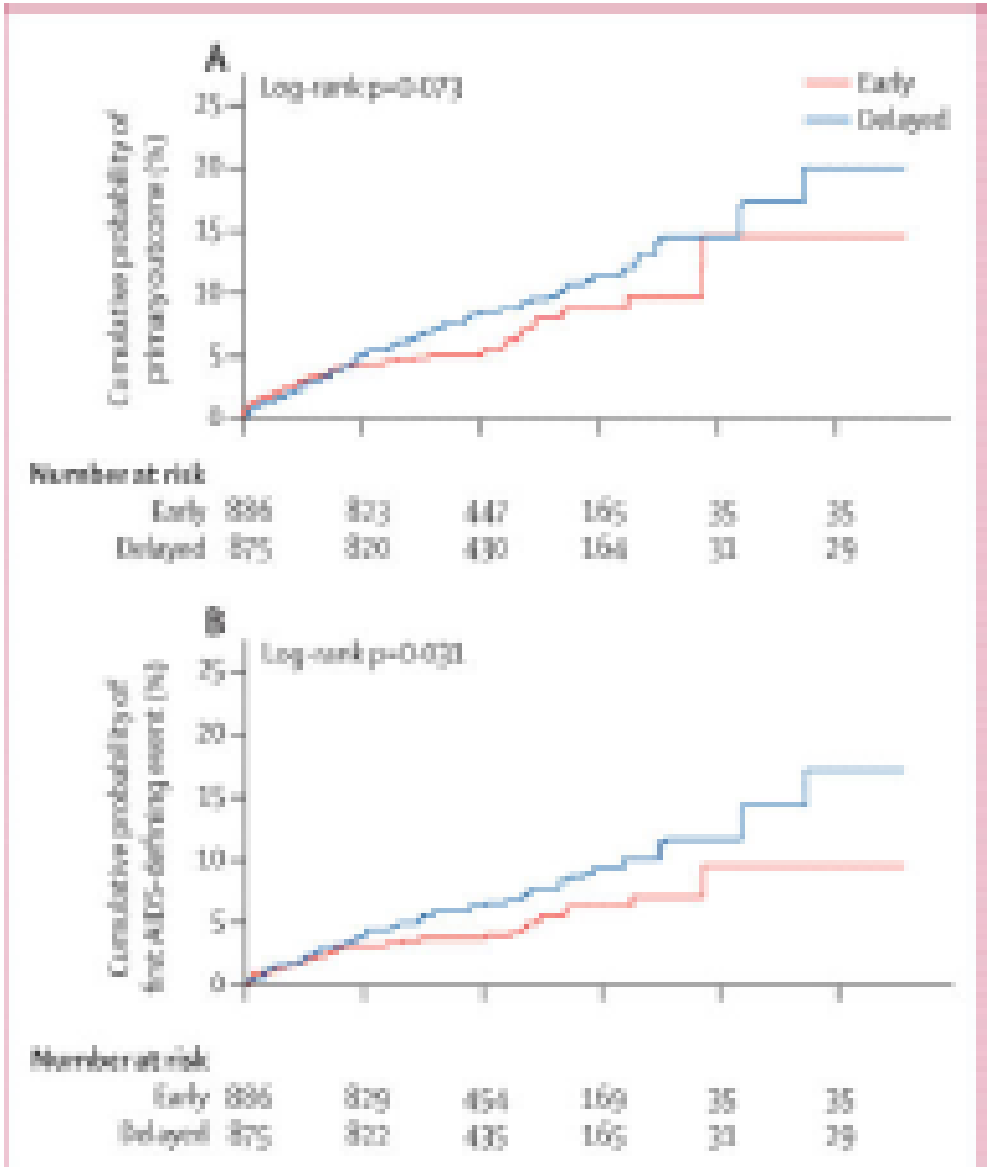
WHO/Unicef/UNAIDS 2015

New in the WHO ART Guidelines

Recommendation 1: When to start ART among people living with HIV			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED
Adolescents (10–19 years old)	ART should be initiated in all adolescents living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*

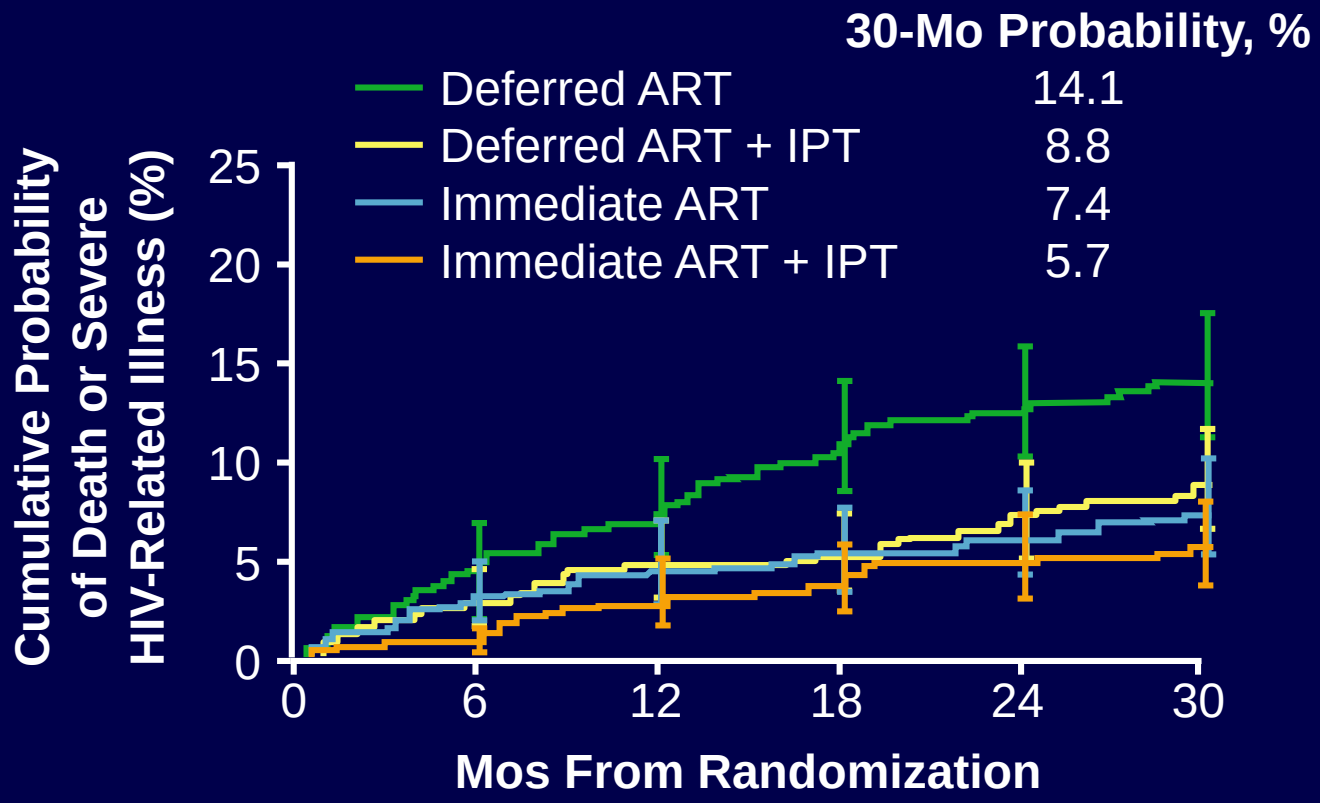
HPTN 052 Clinical Endpoint Analyses

- 1763 pts and serodiscordant partners
- Median CD4 count 442 cells/mm^3 early vs. 230 cells/mm^3 delayed ART
- New onset AIDS events 40 early vs. 61 delayed ART (HR 0.64, 95% CI 0.43-0.96; p=0.031)
- TB 17 early vs. 34 delayed (HR 0.49, 95% CI 0.28-0.89; p=0.018)



Grinsztejn B, et al. Lancet Inf Dis 2014

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts



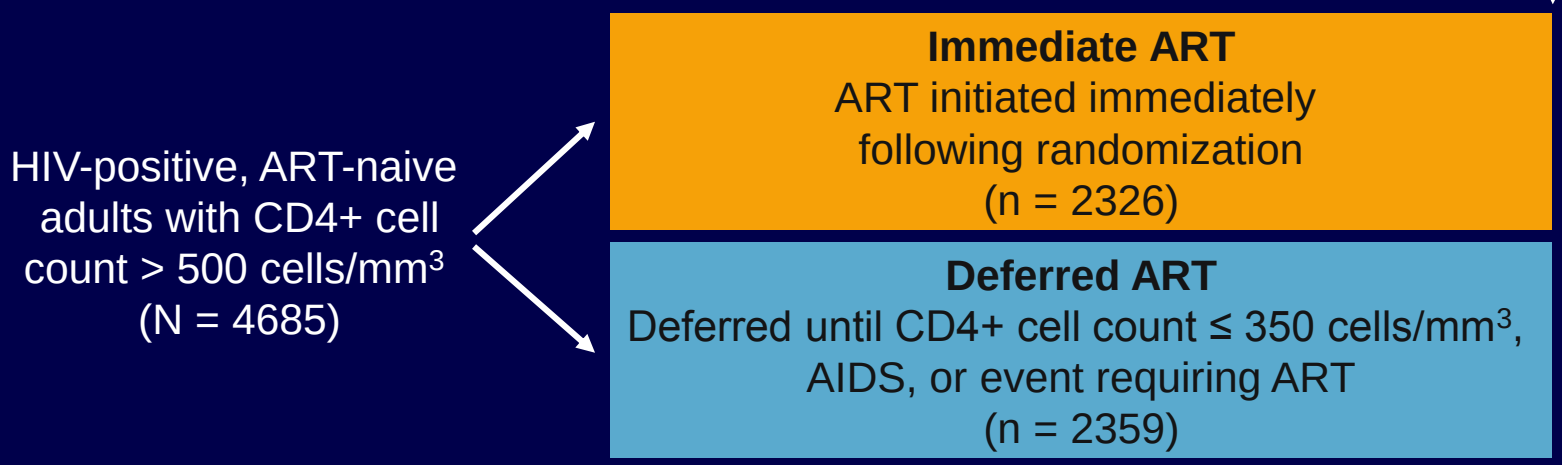
TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;373:808-822.

Slide credit: clinicaloptions.com

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

Study closed by DSMB following interim analysis

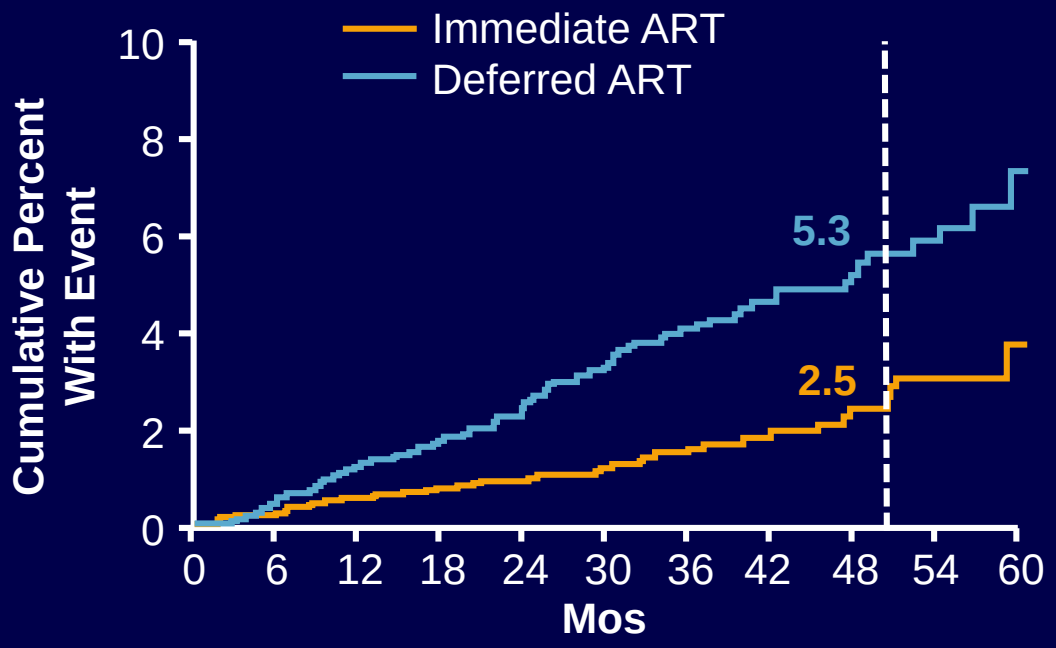


- Primary composite endpoint (target = 213)
  - Serious AIDS or death from AIDS
  - Serious non-AIDS events and death not attributable to AIDS
    - CVD, ESRD, decompensated liver disease, non-AIDS–defining cancers

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Slide credit: clinicaloptions.com

START: Primary Outcome



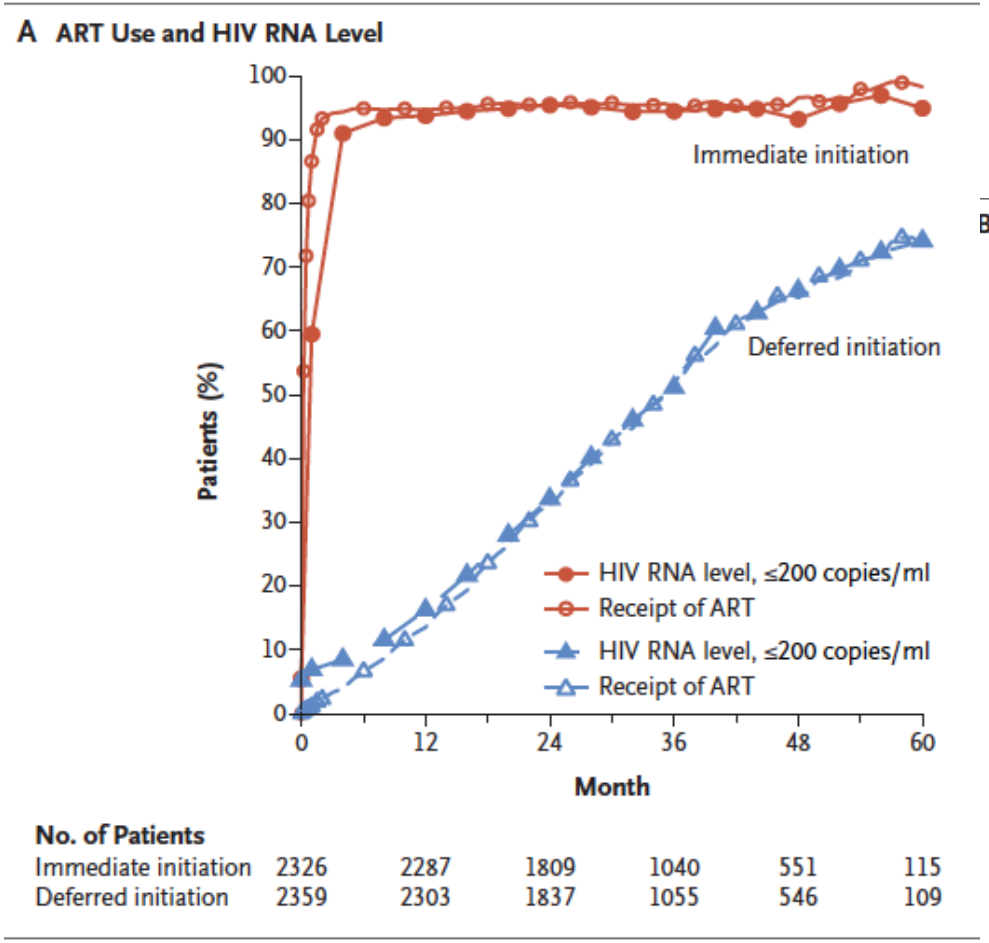
- 57% reduced risk of serious events or death with immediate ART
- 68% of primary endpoints occurred in pts with CD4+ cell counts > 500 cells/mm^3

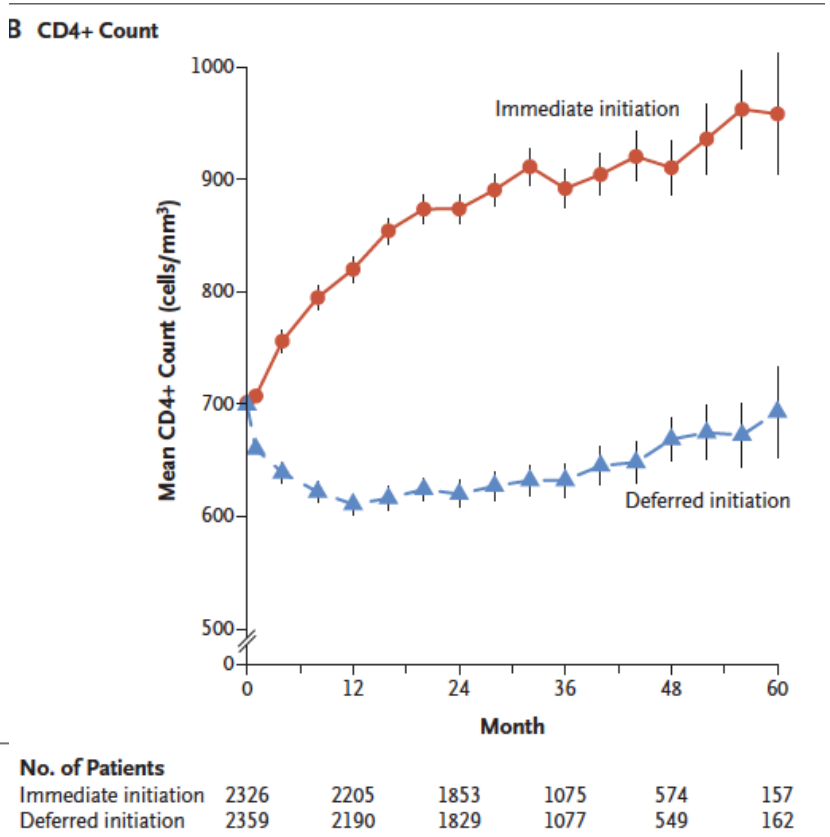
Primary Endpoint	Immediate ART	Deferred ART
No. with event (%)	42 (1.8)	96 (4.1)
Rate/100 PY	0.60	1.38
HR (immediate/deferred)	0.43 (95% CI: 0.30-0.62; *P* < .001)	

INSIGHT START Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Slide credit: clinicaloptions.com

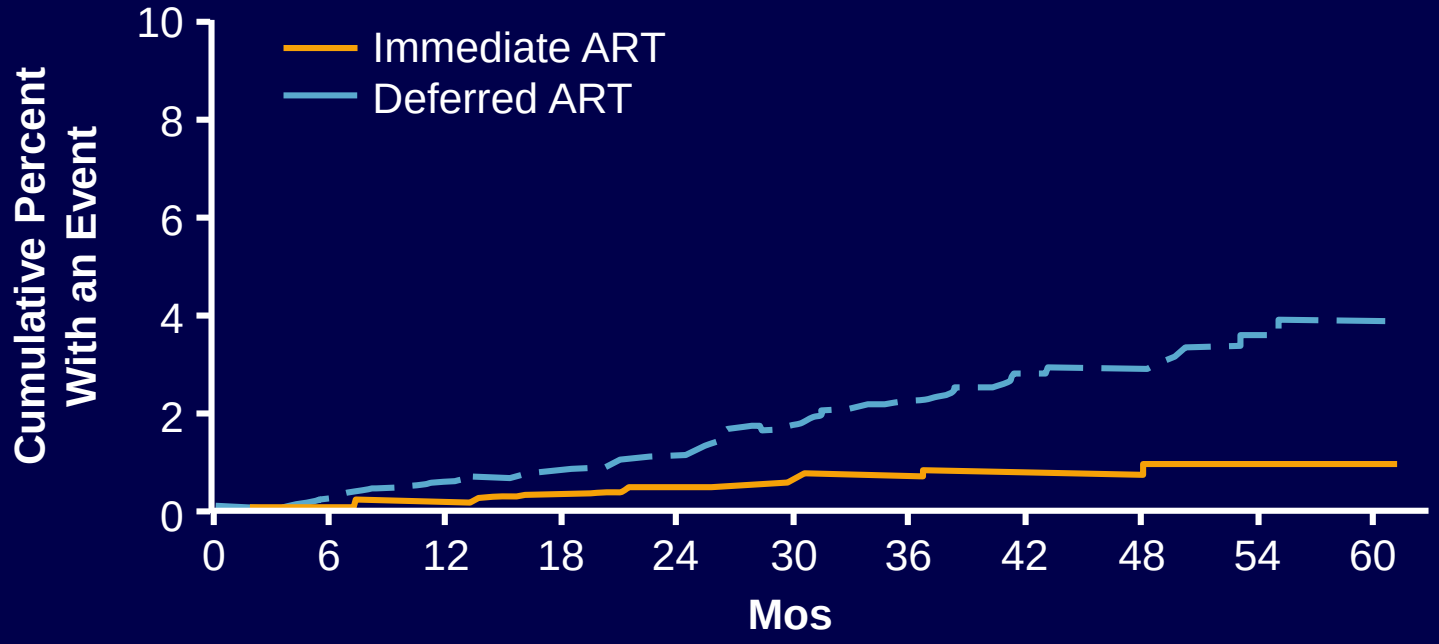
START: Immediate vs. Deferred Initiation of ART





START: Serious AIDS Events

- 72% reduced risk of serious AIDS events with immediate ART



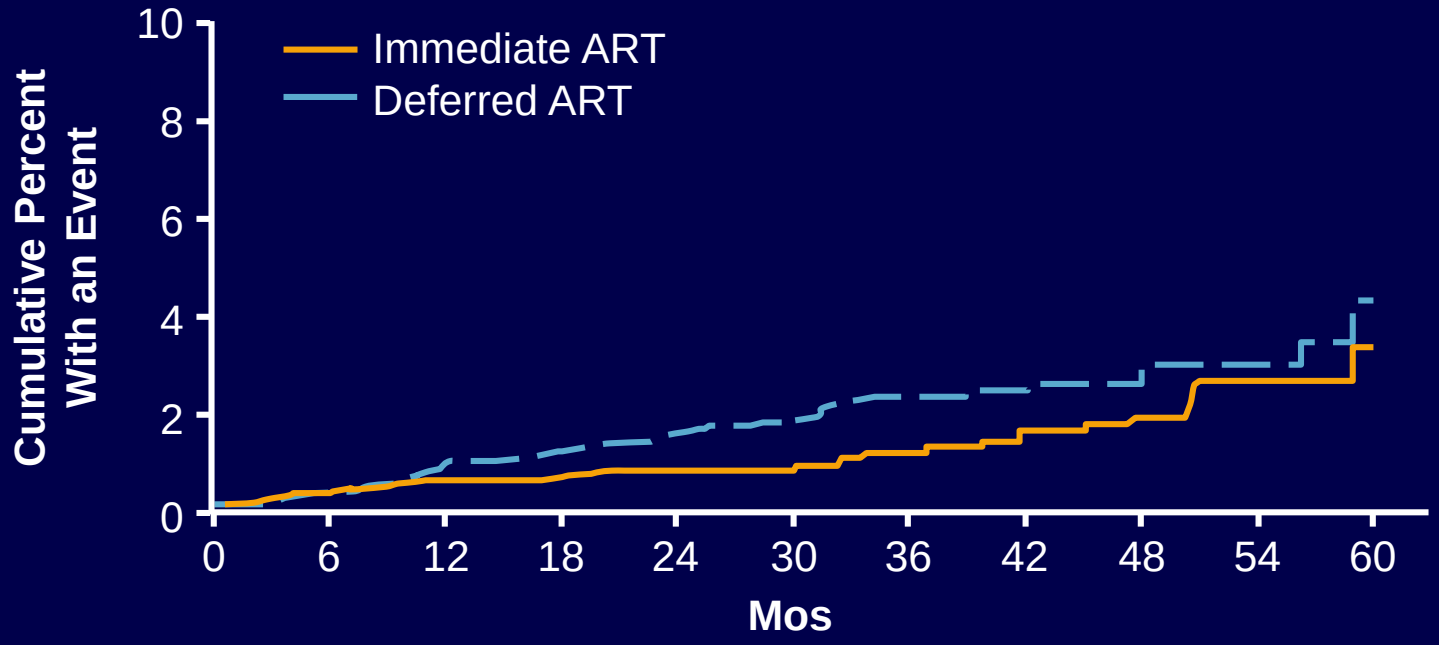
Serious AIDS Events	Immediate ART	Deferred ART
No. with event (%)	14	50
Rate/100 PY	0.20	0.72
HR (immediate/deferred)	0.28 (95% CI: 0.15-0.50; *P* < .001)	

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Slide credit: clinicaloptions.com

START: Serious Non-AIDS Events

- 39% reduced risk of serious non-AIDS events with immediate ART



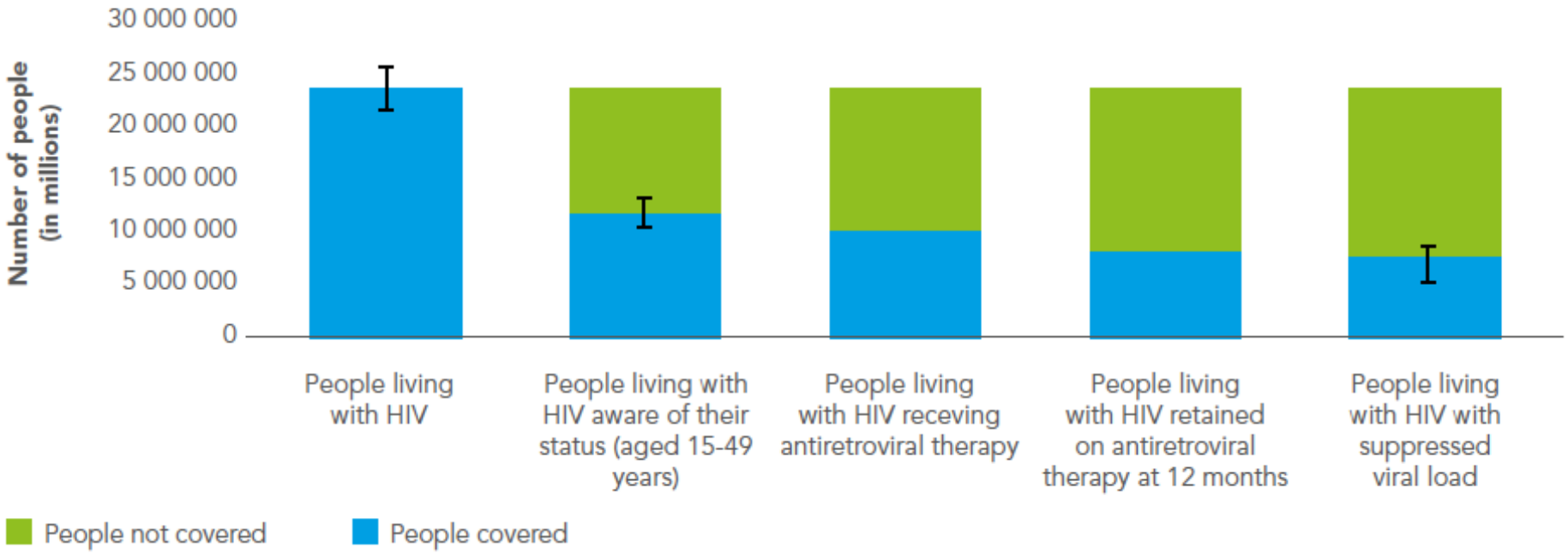
Serious Non-AIDS Events	Immediate ART	Deferred ART
No. with event (%)	29	47
Rate/100 PY	0.42	0.67
HR (immediate/deferred)	0.61 (95% CI: 0.38-0.97; *P* = .04)	

INSIGHT START Study Group. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Slide credit: clinicaloptions.com

The Treatment Cascade

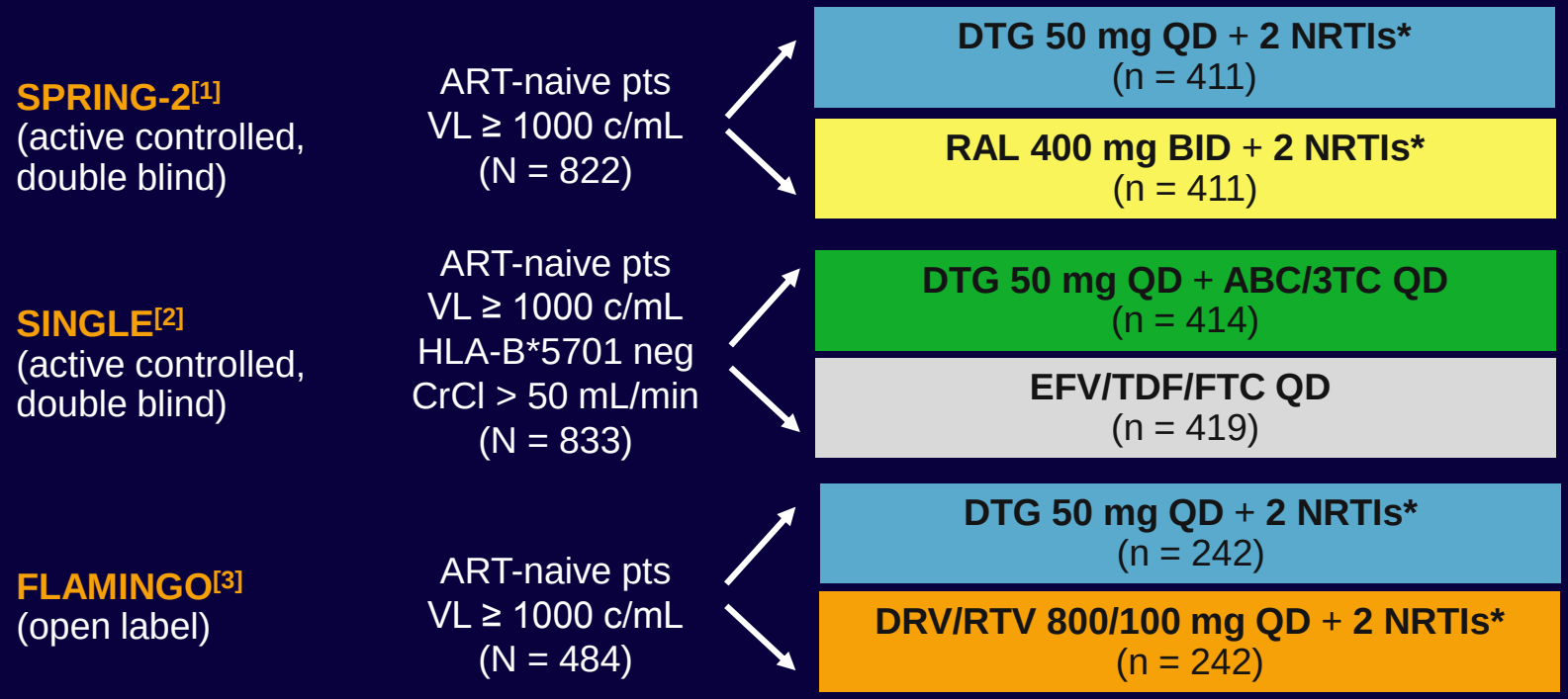
Fig. 13. **HIV treatment cascade for people aged 15 years and over in sub-Saharan Africa, 2014**



What's New with "Newer" Antiretroviral Drugs

Dolutegravir Phase III Trials in Treatment-Naive Pts

- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48

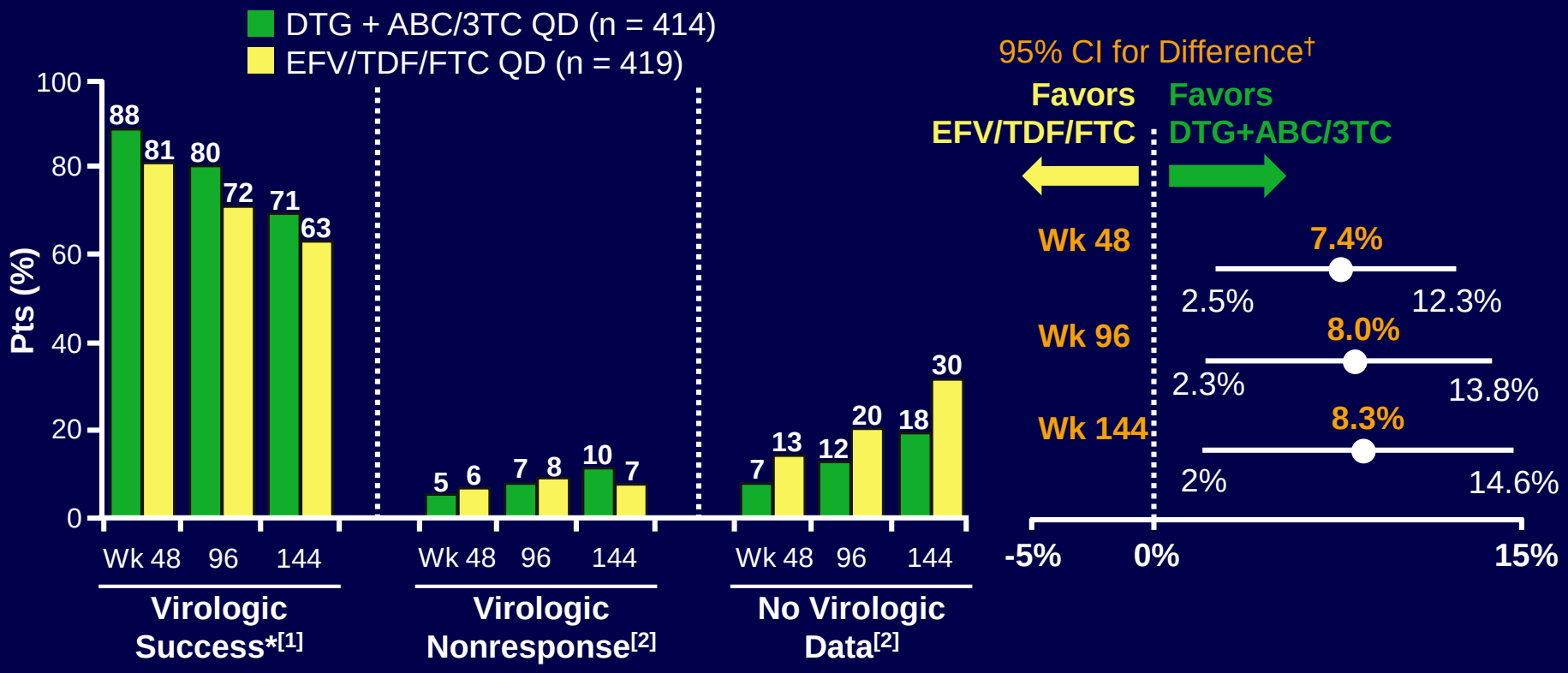


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Pappa K, et al. ICAAC 2014. Abstract H-647a.
3. Molina JM, et al. Glasgow HIV 2014. Abstract O153.

SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC in Tx-Naive Pts Through Wk 144

- Emergent resistance in those with VF: 0/39 (DTG) vs 7/33 (EFV)

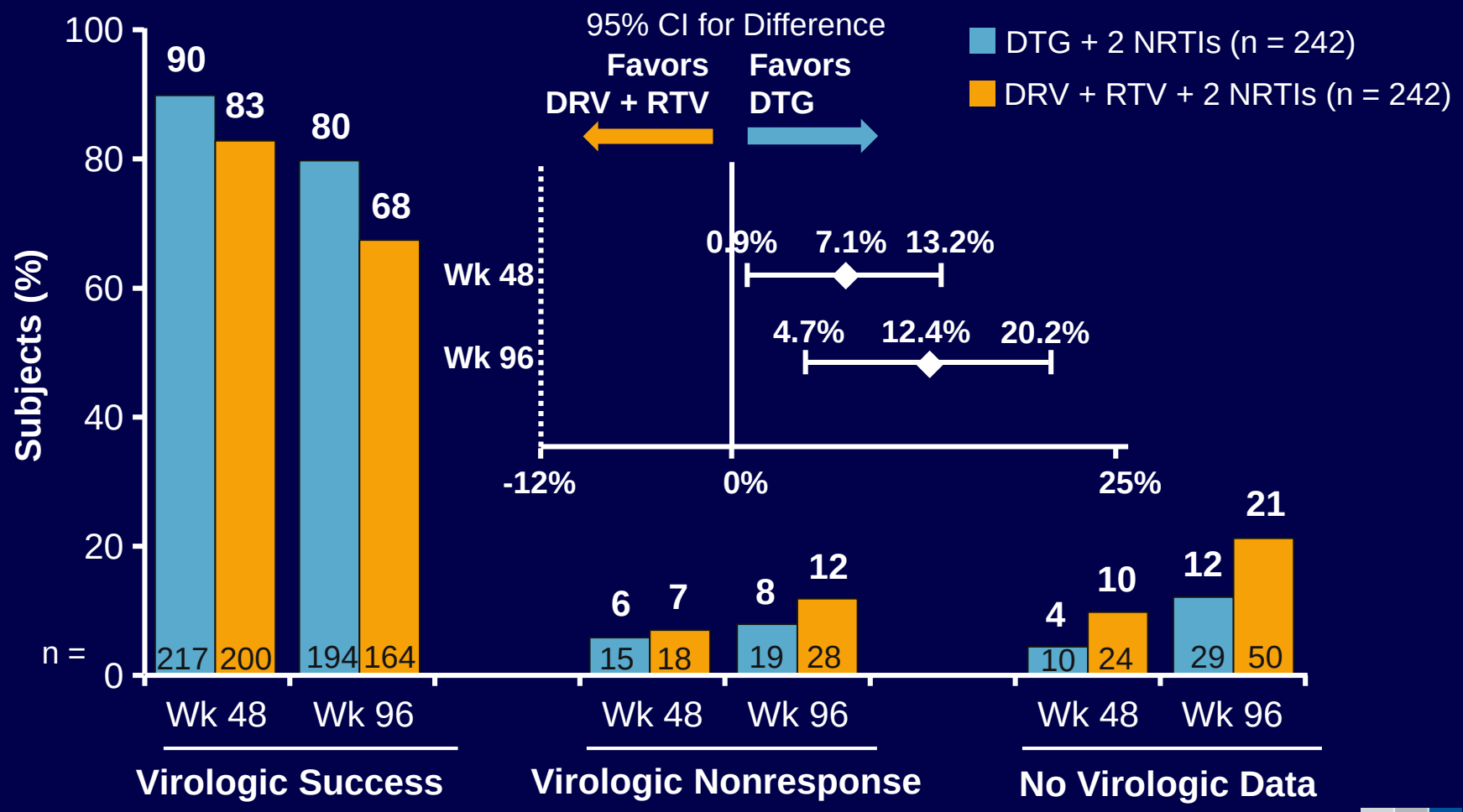


*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.
†-10% noninferiority margin.

1. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70:515-519.
2. Pappa K, et al. ICAAC 2014. Abstract H-647a.

Slide credit: clinicaloptions.com

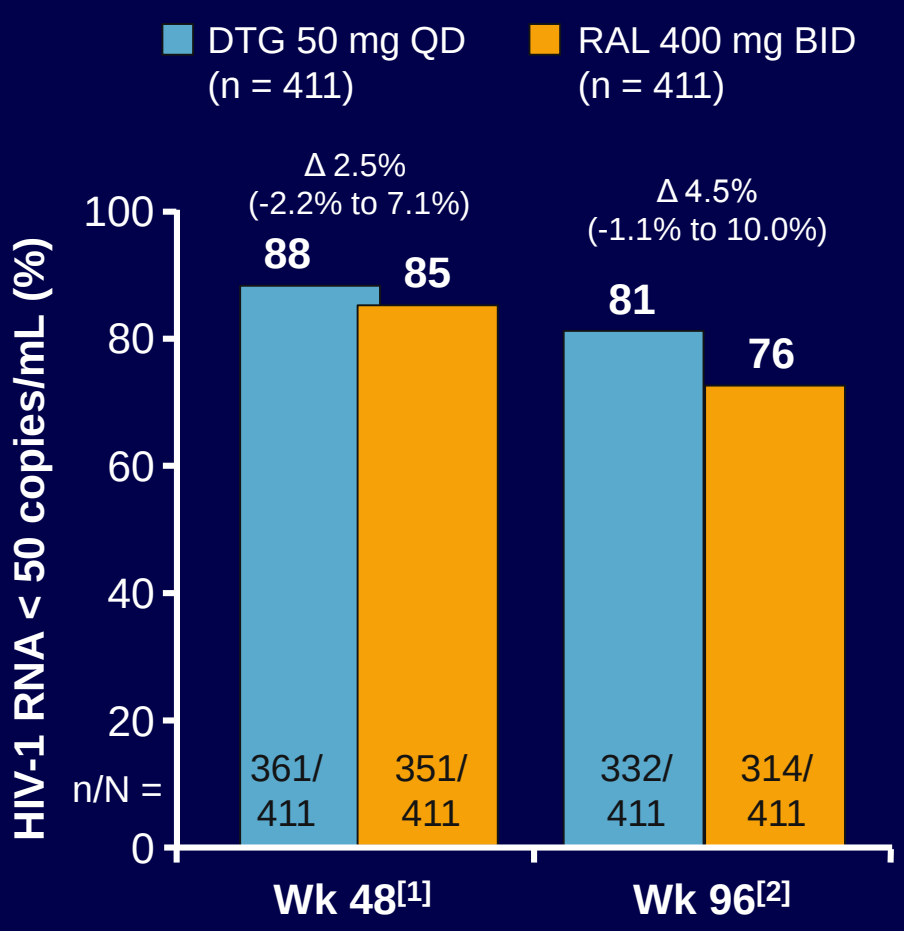
FLAMINGO: DTG Superior to DRV + RTV in ART-Naive Pts Through Wk 96



Molina J-M, et al. Lancet HIV 2015;2:e127–36.

Slide credit: clinicaloptions.com

SPRING-2: DTG + 2 NRTIs Noninferior to RAL + 2 NRTIs Through Wk 96



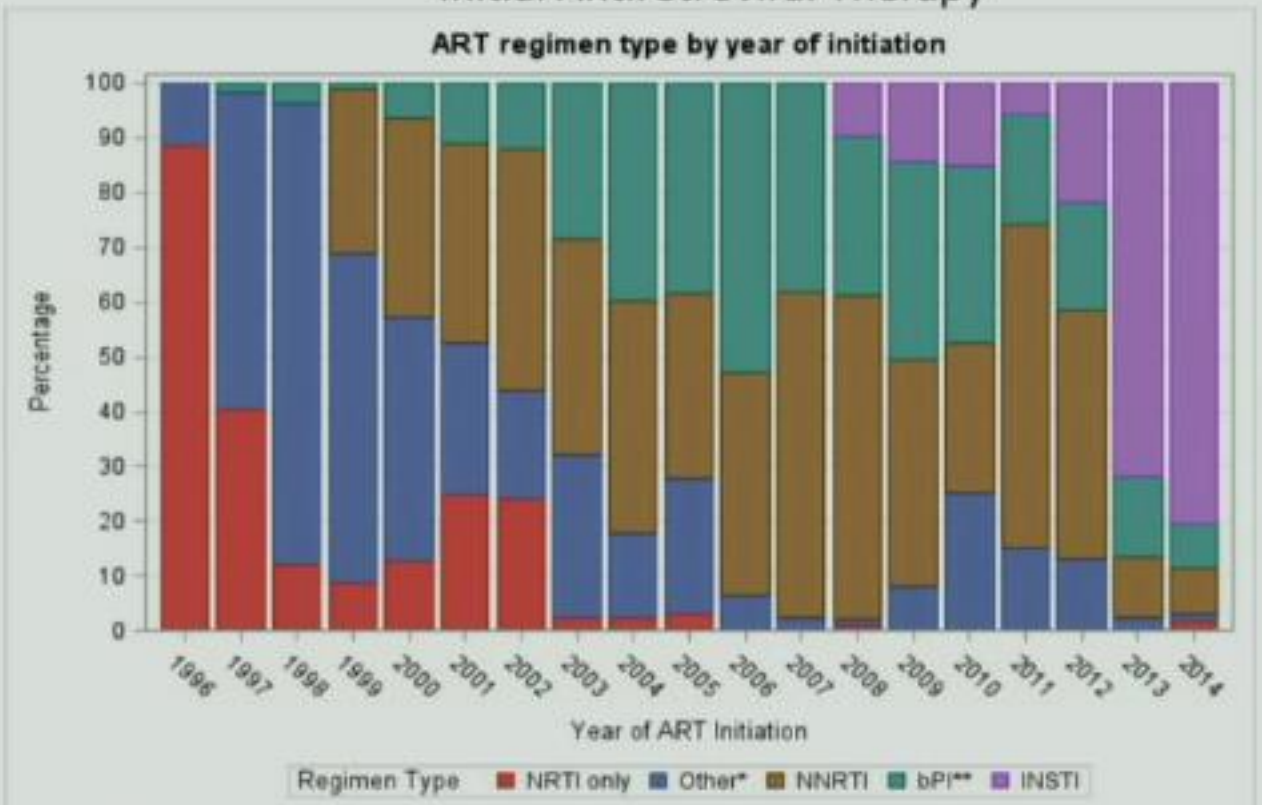
Outcomes at Wk 96[2]	DTG + NRTIs	RAL + NRTIs
D/c for AEs or death, %	2	2
Virologic nonresponse, %	5	10
Mean CD4+ cell count increase, cells/mm^3	276	264

1. Raffi F, et al. Lancet. 2013;381:735-743.
2. Raffi F, et al. Lancet Infect Dis. 2013;13:927-935.

Initial ART with Integrase Inhibitor Based Regimens

UCHCC: UNC CFAR
HIV Clinical Cohort

Shift To Integrase Inhibitor-based Therapy



1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

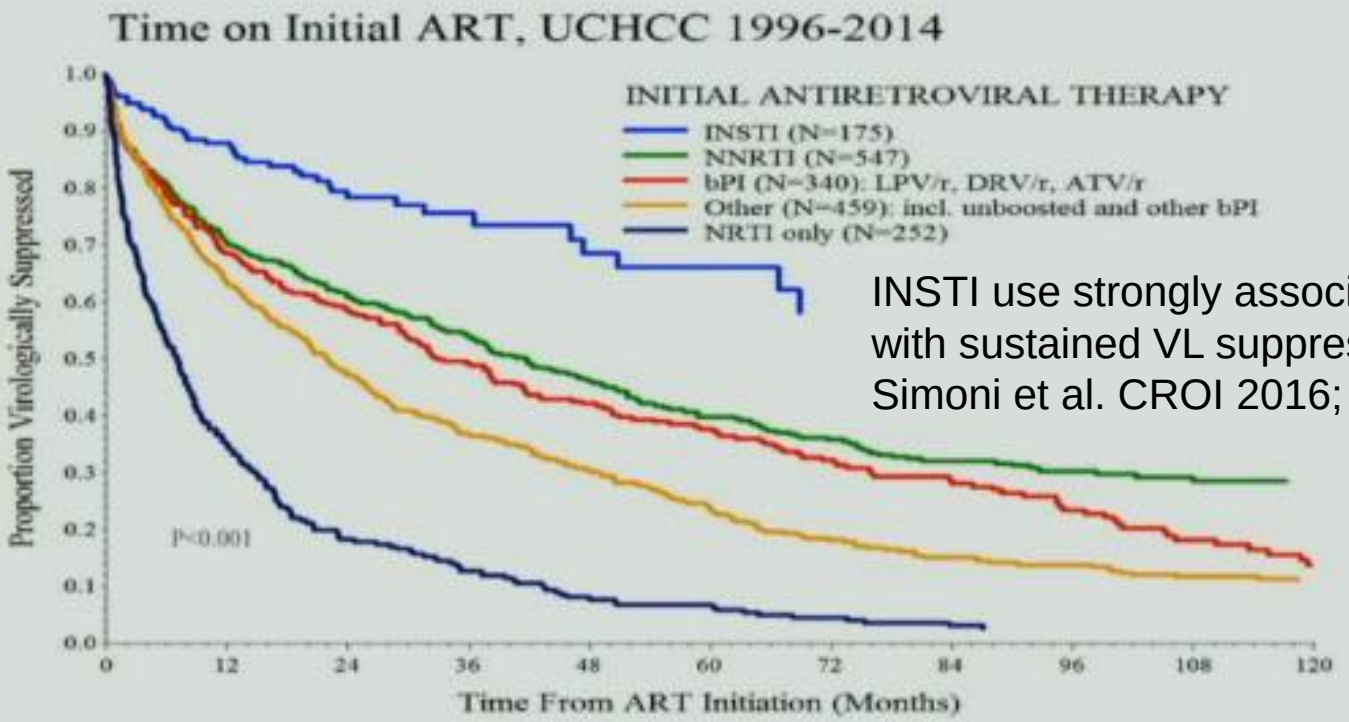
Courtesy of Thibaut Davy and Sonia Napravnik

Eron J, CROI 2016

Time on First-Line Regimens Longer with Integrase Inhibitors

UCHCC: UNC CFAR HIV Clinical Cohort

Persistence of Initial ART



INSTI use strongly associated with sustained VL suppression
Simoni et al. CROI 2016; Abstr. 1034

- 1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015
- Persistence defined as no switch in anchor agent class

Eron J, CROI 2016

PADDLE: Dolutegravir + Lamivudine in Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial
- BL RNA: median 24,128 copies/mL; IQR 11,686 to 36,794 copies/mL

Treatment-naive pts with HIV-1 RNA 5000-100,000 copies/mL; CD4+ ≥ 200 cells/mm^3; HBsAg negative (N = 20)

→ **DTG 50 mg QD + 3TC 300 mg QD** (N = 20*)

- 20 of 20 pts met primary endpoint of HIV-1 RNA < 50 copies/mL at Wk 24 (ITT-e, FDA snapshot analysis)
  - Including 4 pts with BL HIV-1 RNA > 100,000 copies/mL
  - All pts virologically suppressed by Wk 8

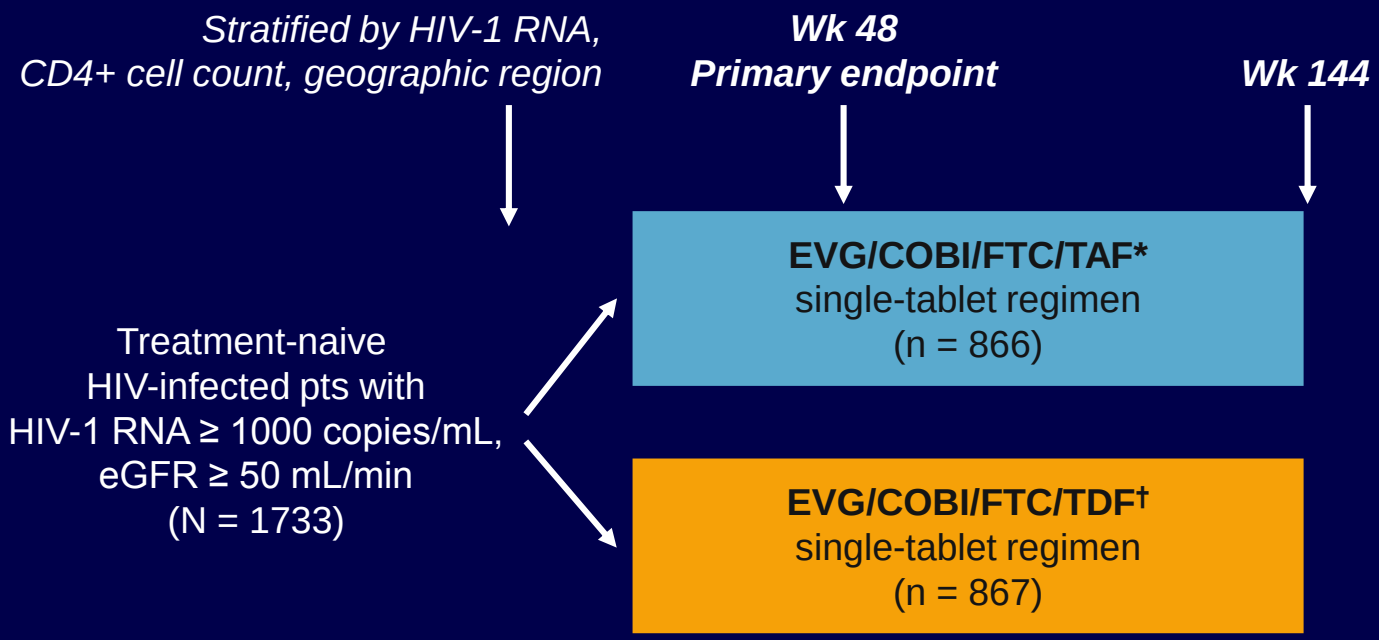
*Pts enrolled in 2 cohorts of 10 pts. Second cohort enrolled following confirmation of first cohort success at Wk 8.

Figueroa MI, et al. EACS 2015. Abstract 1066.

Slide credit: clinicaloptions.com

Studies 104/111: Tenofovir Alafenamide Fumarate vs TDF in Treatment-Naive Pts

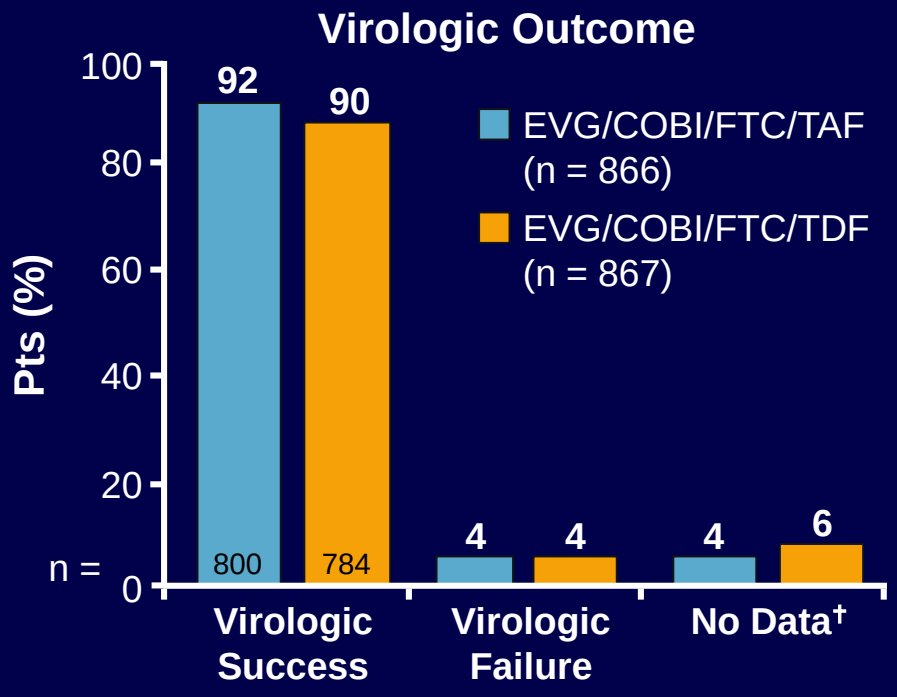
- Parallel, randomized, double-blind, active-controlled phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48, as defined by FDA Snapshot algorithm

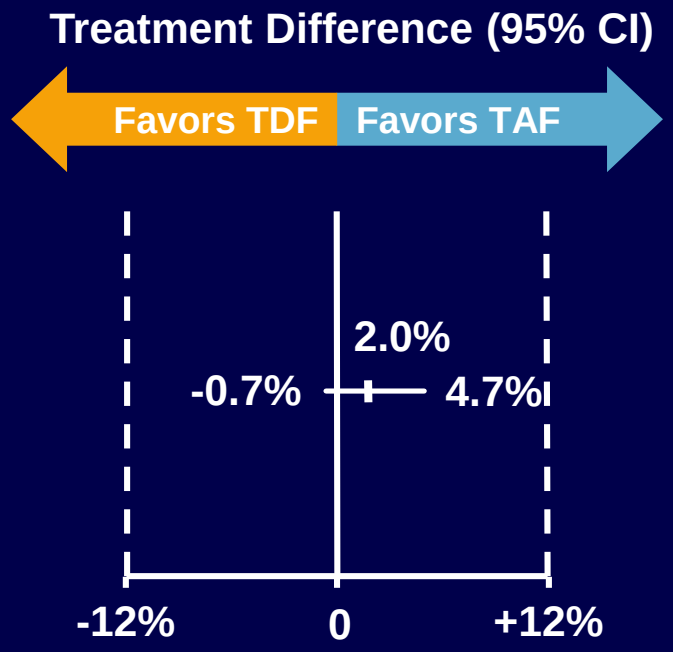


*150/150/200/10 mg once daily.
†150/150/200/300 mg once daily.

Sax PE, et al. Lancet. 2015;385:2606-2615.

Studies 104/111: TAF Noninferior to TDF at Week 48





†Discontinued for AE, death, or missing data.

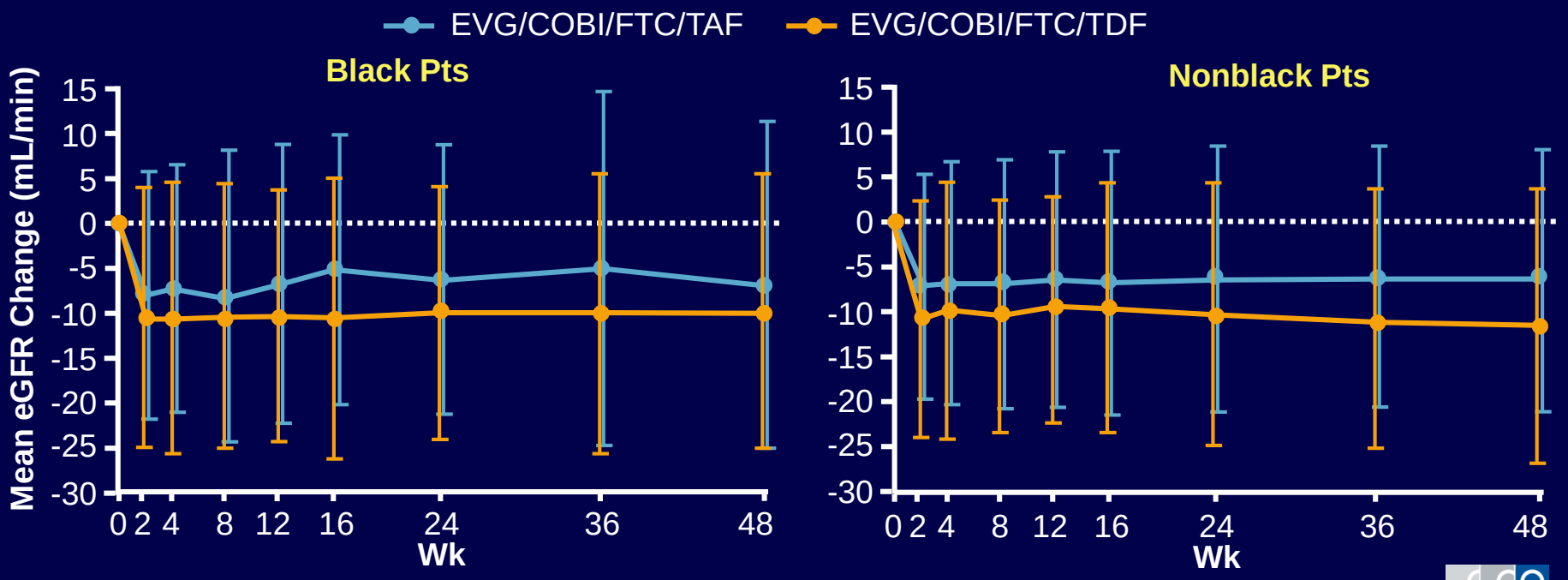
- EVG/COBI/FTC/TAF was noninferior to EVG/COBI/FTC/TDF at Wk 48 in each study: 93% vs 92% (Study 104); 92% vs 89% (Study 111)
  - Race not significant predictor of virologic efficacy in multivariate analysis
- Declines in eGFR and in hip and spine BMD significantly less in TAF arm

1. Sax PE, et al. Lancet. 2015;385:2606-2615.
2. Wohl D, et al. ID Week 2015. Abstract 1073.

Slide credit: clinicaloptions.com

Studies 104/111: Renal and Bone Outcomes With TAF vs TDF

- In black pts, decrease in median eGFR significantly smaller with TAF vs TDF
- Less spine and hip BMD loss with TAF vs TDF both in black and nonblack pts



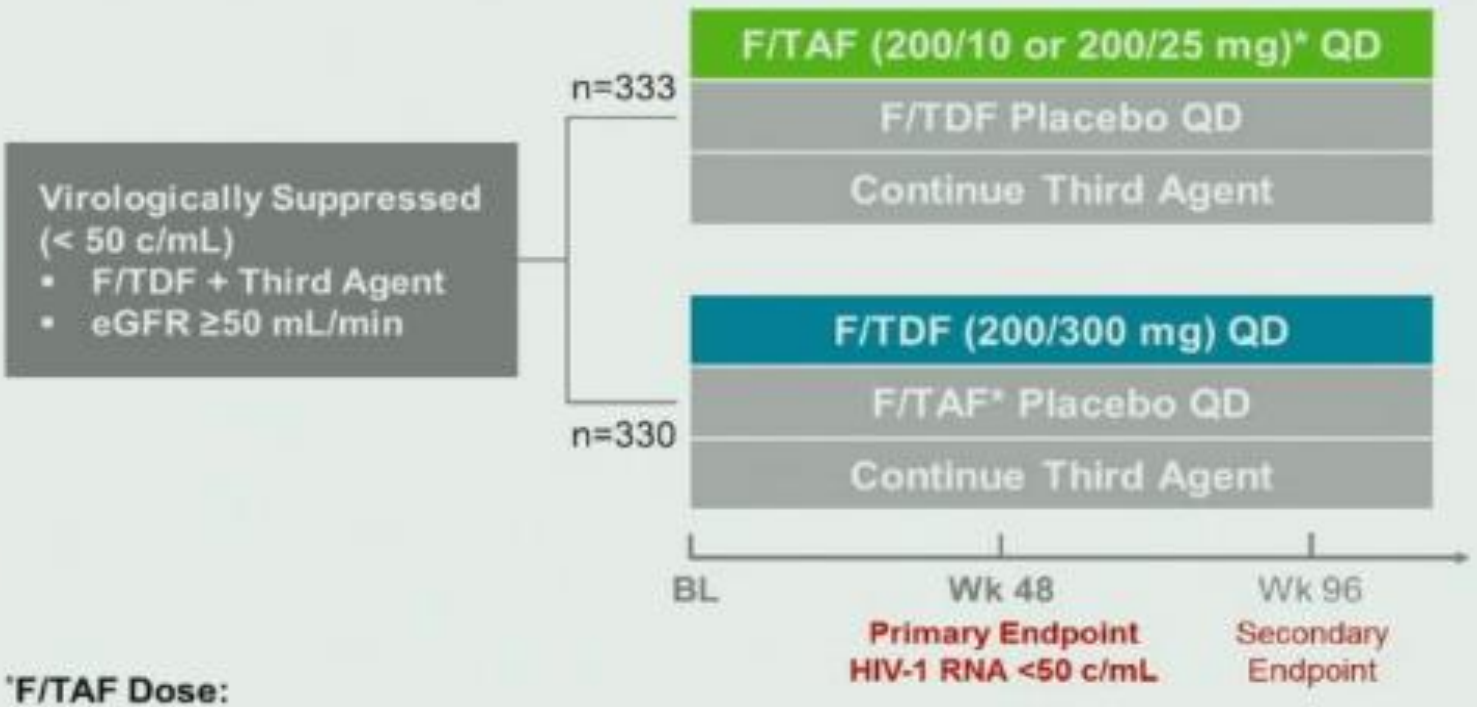
Wohl D, et al. ID Week 2015. Abstract 1073.

Slide credit: clinicaloptions.com

Switching TDF to TAF in Virologically Suppressed Adults

Switch from F/TDF to F/TAF

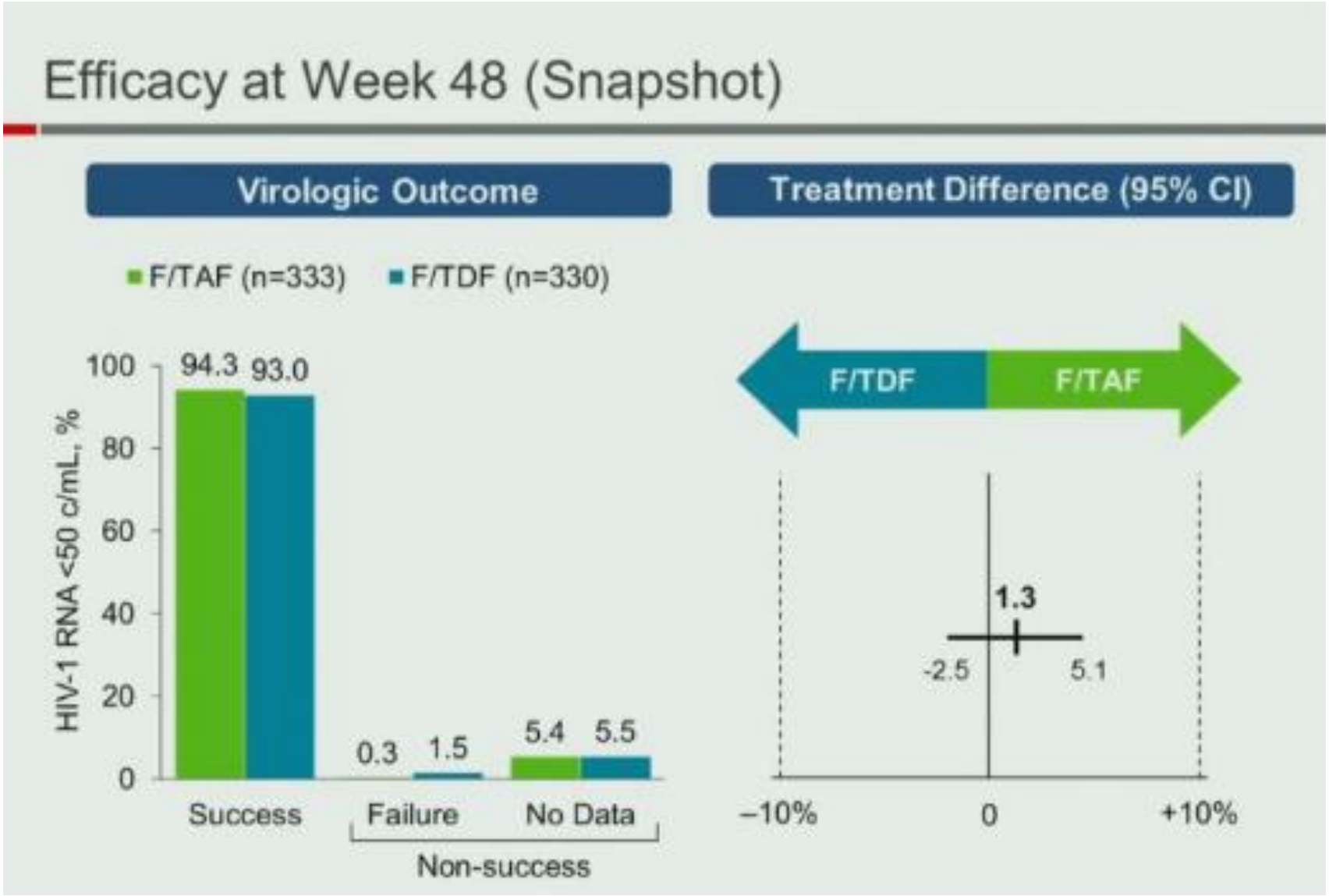
- Randomized, double-blind, double-dummy, active-controlled study



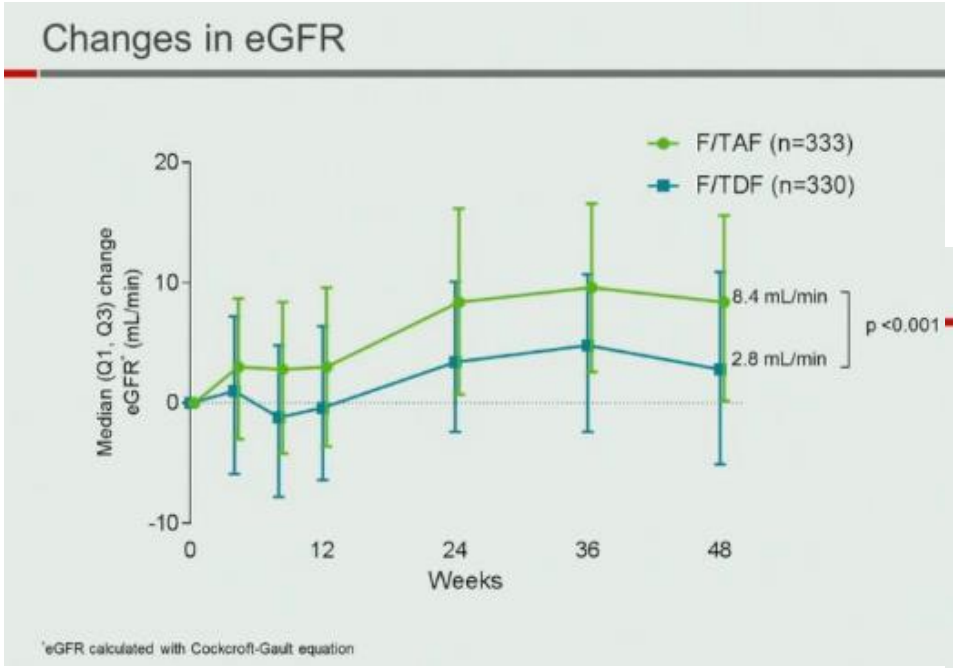
*F/TAF Dose:
- 200/10 mg with boosted PIs
- 200/25 mg with unboosted third agents

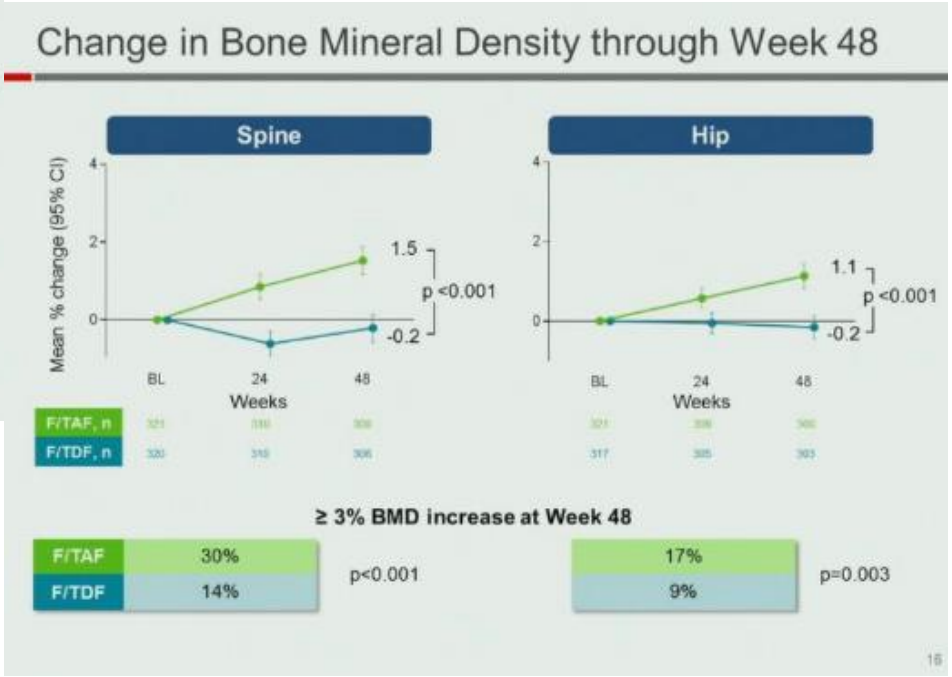
Gallant JE, CROI 2016; Abstr. 29

Switching TDF to TAF in Virologically Suppressed Adults



Switching TDF to TAF Improves eGFR and Bone Mineral Density





Gallant JE, CROI 2016; Abstr. 29

DHHS, IAS-USA, EACS Guidelines: Recommended Regimens for First-line ART

Class	DHHS[1]	IAS-USA[2]	EACS[3]
INSTI	▪ **DTG/ABC/3TC** ▪ DTG + TDF/FTC ▪ **EVG/COBI/TDF/FTC** ▪ **EVG/COBI/TAF/FTC** ▪ RAL + TDF/FTC	▪ **DTG + ABC/3TC** ▪ DTG + TDF/FTC ▪ **EVG/COBI/TDF/FTC** ▪ RAL + TDF/FTC	▪ **DTG/ABC/3TC** ▪ DTG + TDF/FTC ▪ **EVG/COBI/TDF/FTC** ▪ RAL + TDF/FTC
Boosted PI	▪ DRV + RTV + TDF/FTC	▪ DRV + RTV + TDF/FTC ▪ ATV + RTV + TDF/FTC ▪ ATV + RTV + ABC/3TC	▪ DRV + RTV + TDF/FTC
NNRTI		▪ **EFV/TDF/FTC** ▪ EFV + ABC/3TC ▪ **RPV/TDF/FTC**	▪ **RPV/TDF/FTC**

- Recommendations may differ based on baseline viral load, CD4+ count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status
- Publication of these guidelines preceded the availability of DTG/ABC/3TC as a single-tablet regimen

1. DHHS Guidelines. November 2015.
2. Günthard HF, et al. JAMA. 2014;312:410-425. 3. EACS Guidelines. October 2015.

Slide credit: clinicaloptions.com

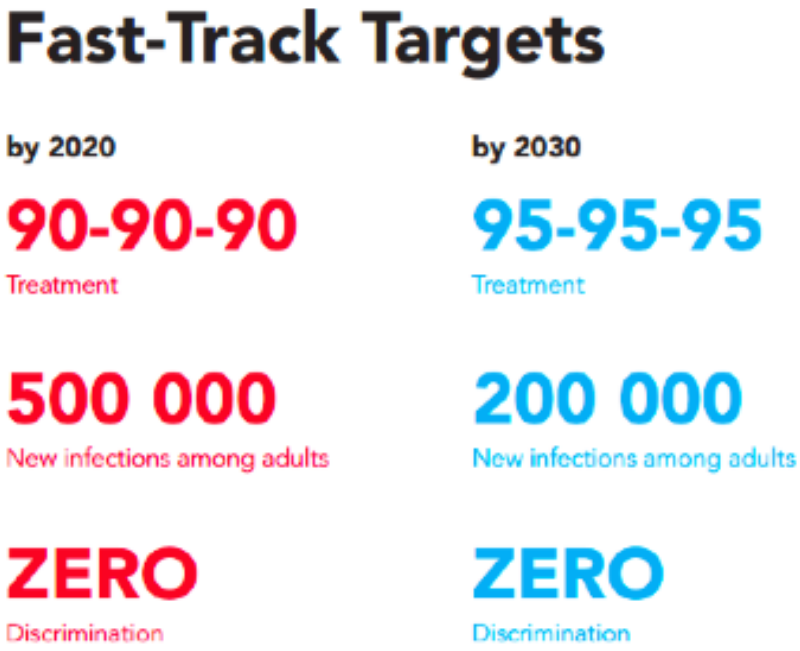
Summary Recommendations

- Randomized trial data support ART initiation in all patients regardless of CD4 cell count
  - Prioritize those at highest risk as resources are developed to treat all
- Choices for initial therapy have evolved
  - Urgent need to expand access to integrase inhibitor-based therapy in low- and middle-income settings

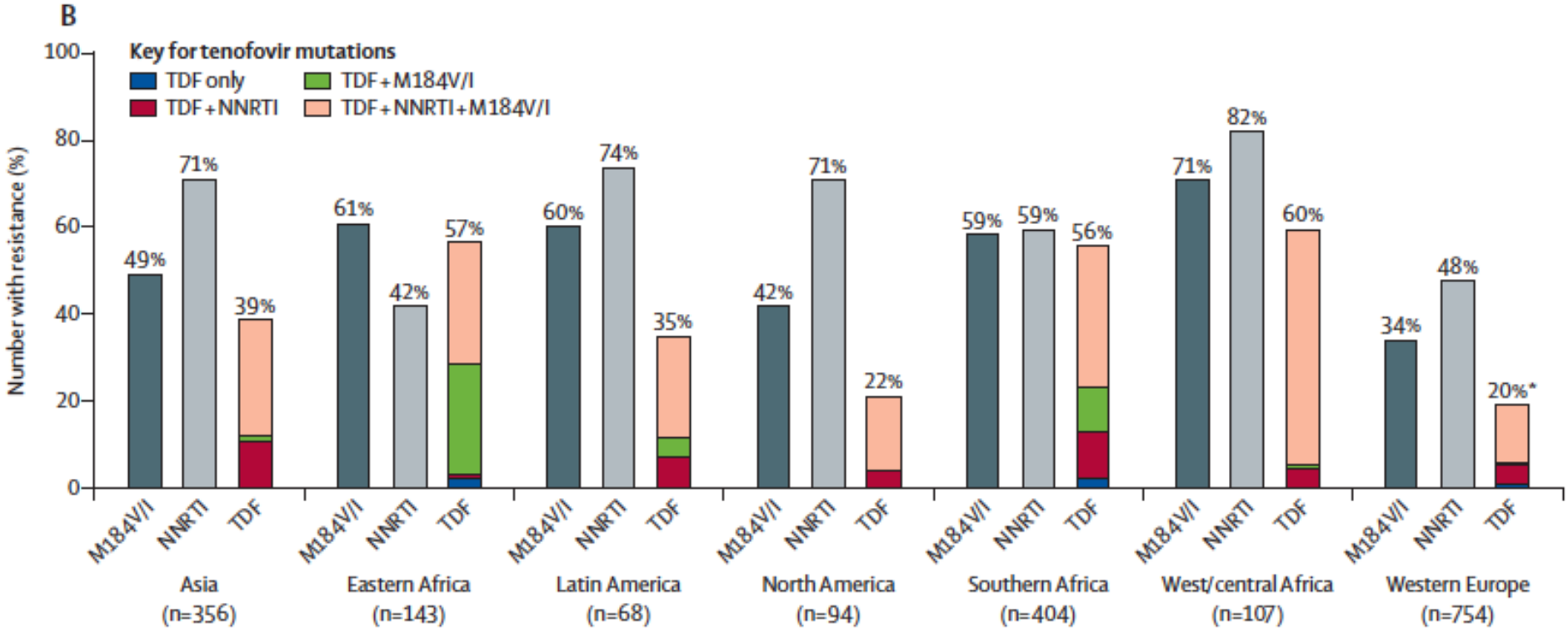
What's New with Novel Investigational Drugs

Do We Really Need New ARVs?

- Bigger goals
- Real challenges
  - Treatment gap
  - Treatment for up to 8 decades
    - Renal, cardiovascular, liver and bone toxicity
    - Therapy options for infants, children, pregnant women
    - Adherence, life chaos, treatment fatigue, aging
    - Drug interactions (TB)
  - HIV resistance will emerge to existing ARVs
    - Especially in regions with limited VL and DR testing



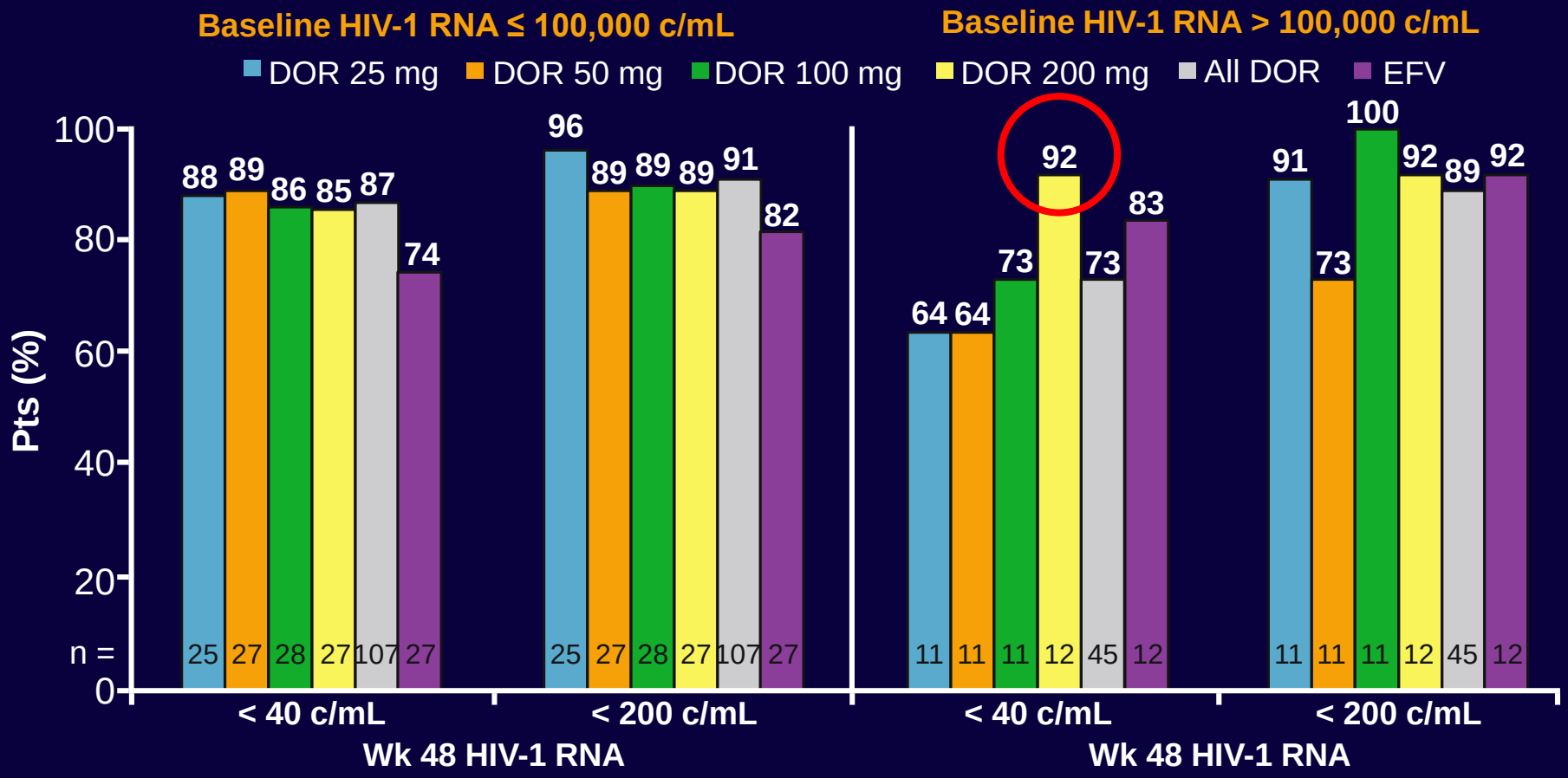
Global Epidemiology of Drug Resistance After Failure of WHO First Line Regimens



TenoRes Study Group, Lancet Inf Dis 2016

Novel NNRTI: Doravirine + TDF/FTC: Week 48 Virologic Response by Baseline HIV-1 RNA

- Part 1: ad hoc analysis, Wk 48 (observed failure)



Gatell JM, et al. Glasgow HIV 2014. Abstract O434. Gatell JM, et al. J Int AIDS Soc 2014; 17(4 Suppl 3):19532

Doravirine vs. Efavirenz in ART-Naïve Patients

- Doravirine 100 mg/d + TDF/FTC vs. EFV + TDF/FTC (N=108 per arm)
  - Stratified by HIV RNA > or ≤ 100,000 copies/ml
  - CD4 > 100 cells/mm^3
  - Evenly matched by treatment arm

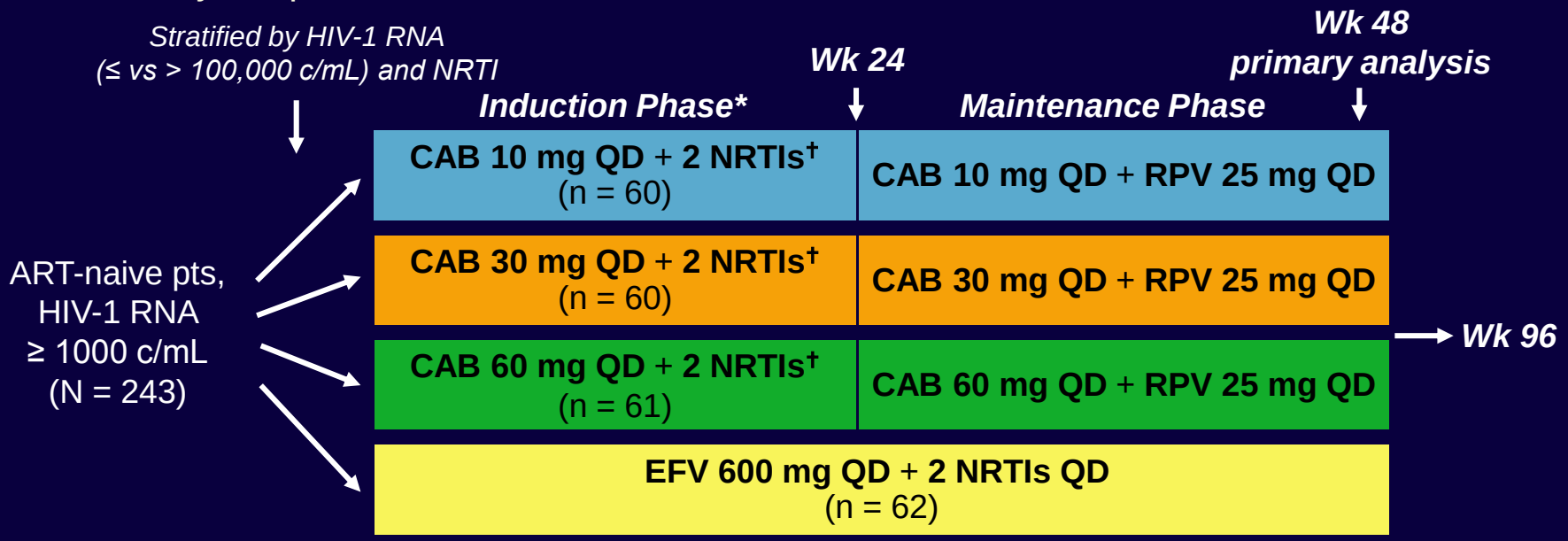
Conclusions:
Drug related CNS AEs lower with DVR than EFV
DVR-emergent resistance mutations not detected at VF
Efficacy modestly reduced in pts with high VL at baseline

Week 48 Results	VL ≤ 100,000		VL > 100,000	
	DVR	EFV	DVR	EFV
HIV-RNA < 40 c/ml	86.6%	87.1%	74.3%	83.8%

Gatell JM, et al. CROI 2016, Abstr. 470

LATTE: Cabotegravir (GSK1265744) + RPV as Maintenance ART: Wk 96 Results

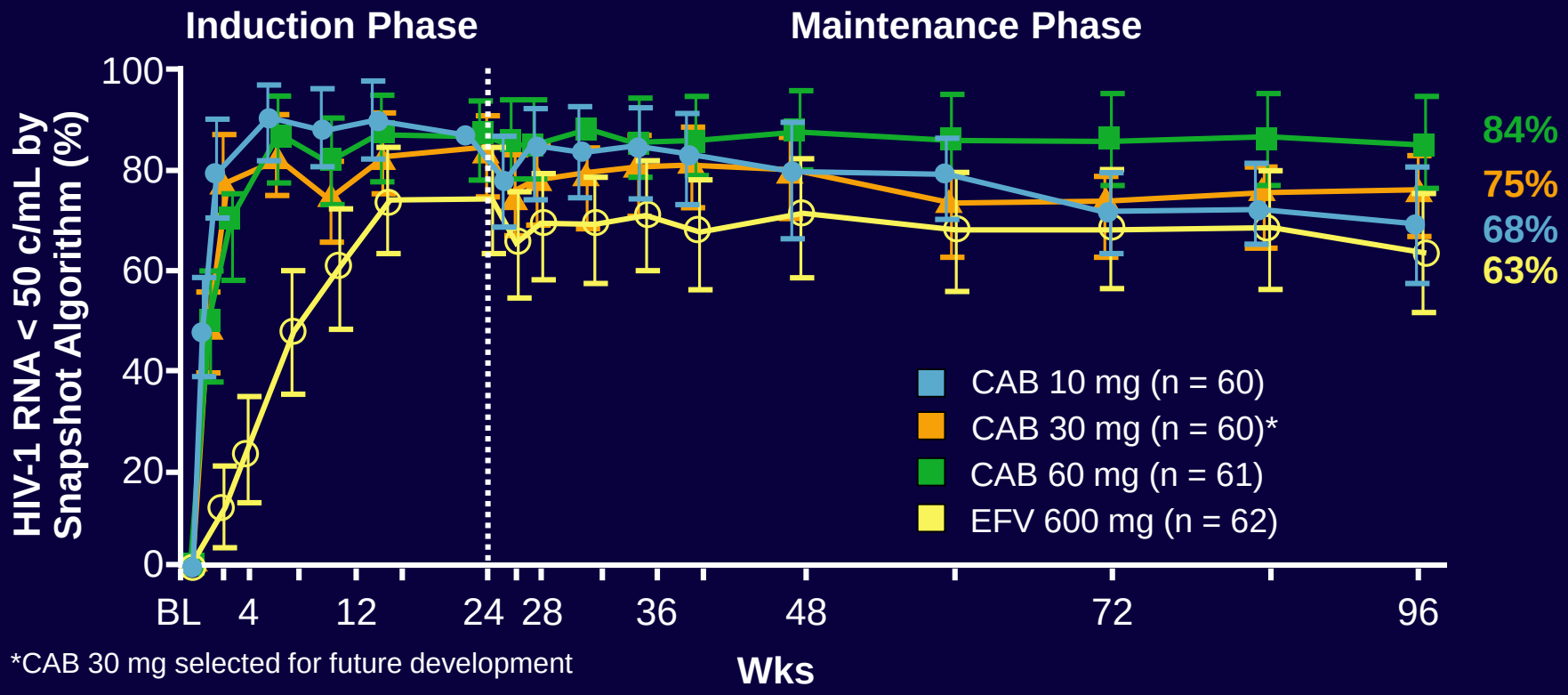
- Cabotegravir, DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

Margolis D, et al. CROI 2015. Abstract 554LB.

LATTE: Virologic Success Through Maintenance Wk 96

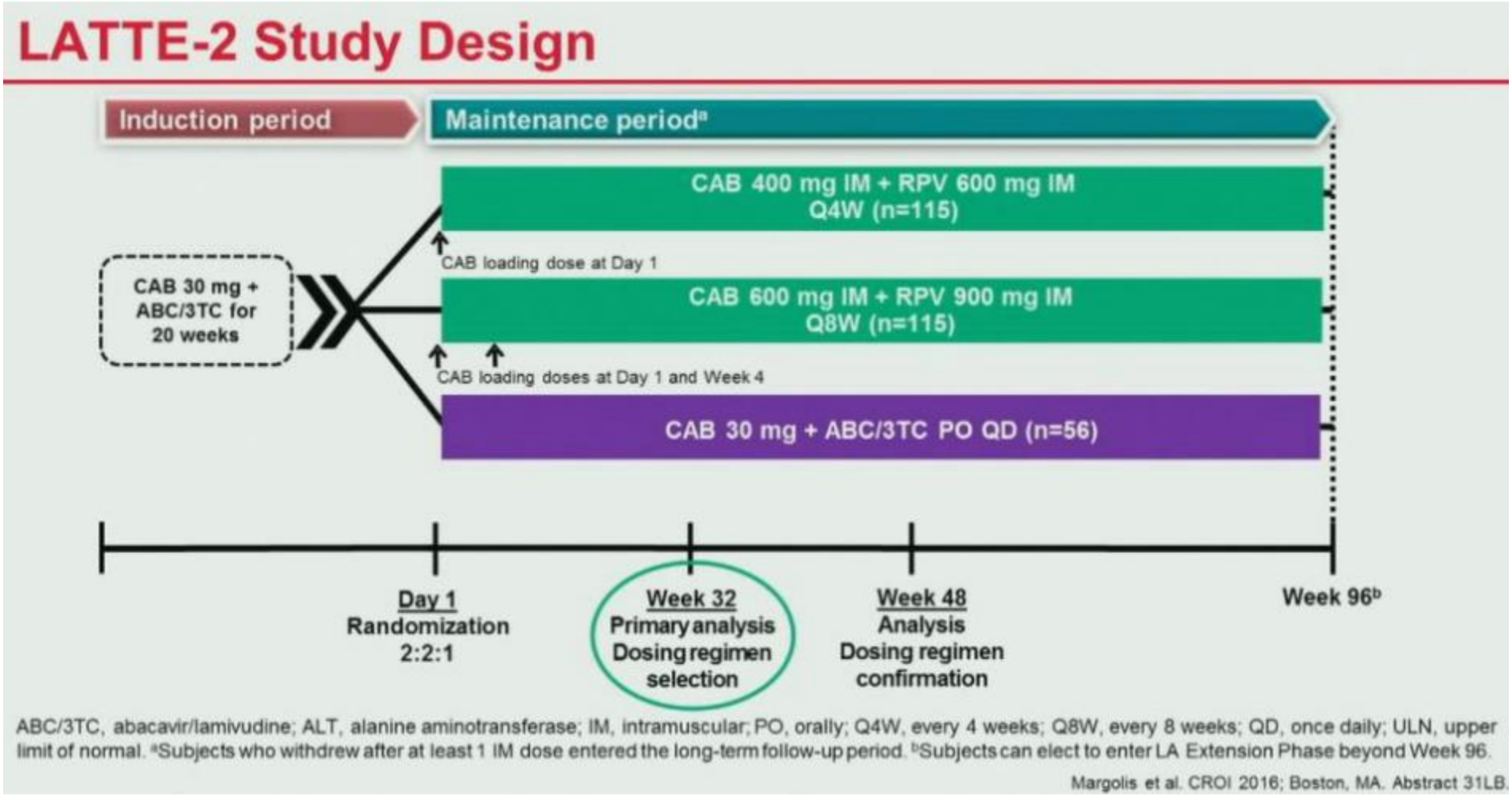


*CAB 30 mg selected for future development

- 6 pts in CAB arms with PDVF at Wk 96; 4 additional pts since Wk 48
  - 3 pts in CAB 10-mg arm with treatment-emergent NNRTI resistance; 1 of these with both NNRTI + INSTI RAMs but decreased ARV exposure in PK analysis

Margolis D, et al. CROI 2015. Abstract 554LB. Reproduced with permission.

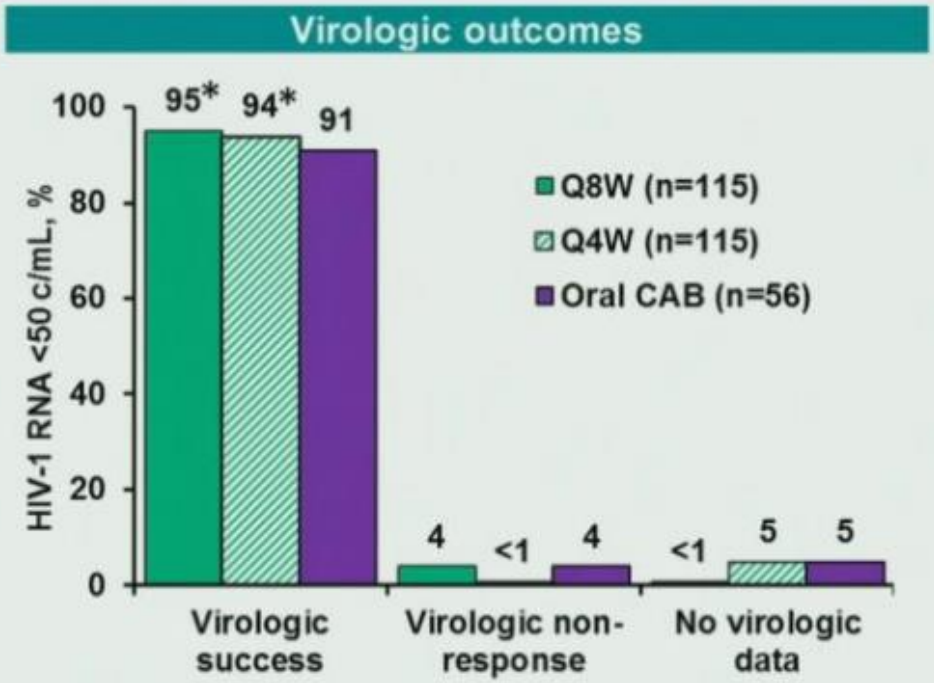
Long-Acting Cabotegravir + Rilpivirine

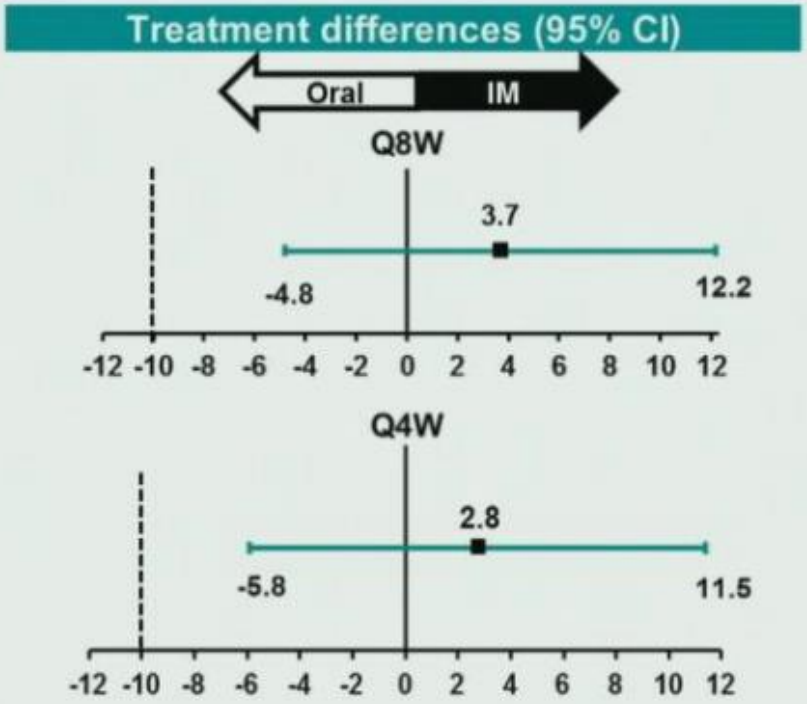


Margolis D, et al. CROI 2016, Abstr. 31LB

LATTE-2: Week 32 Results

LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)





Both Q8W and Q4W comparable to oral CAB at Week 32

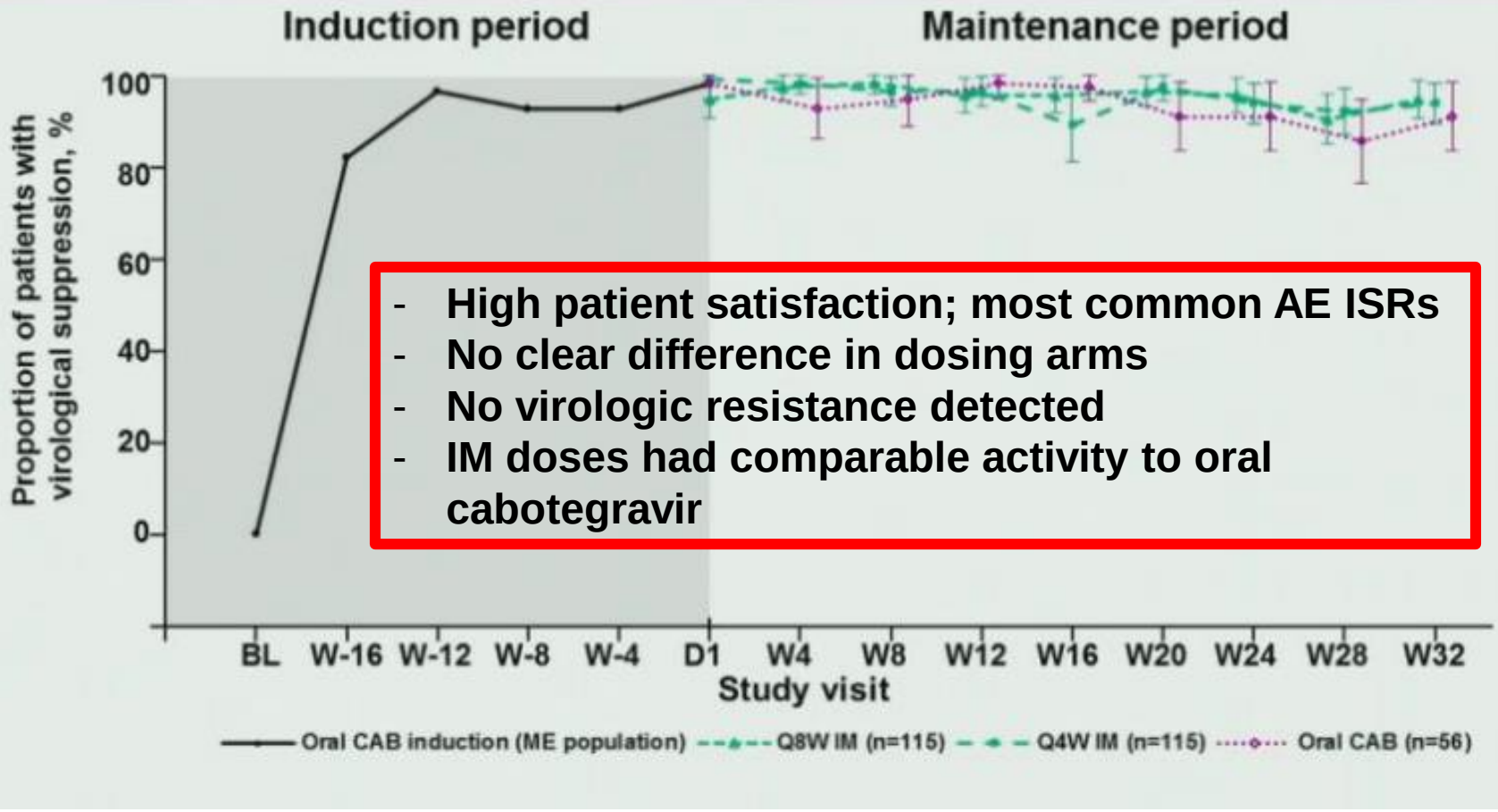
*Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

Margolis D, et al. CROI 2016, Abstr. 31LB

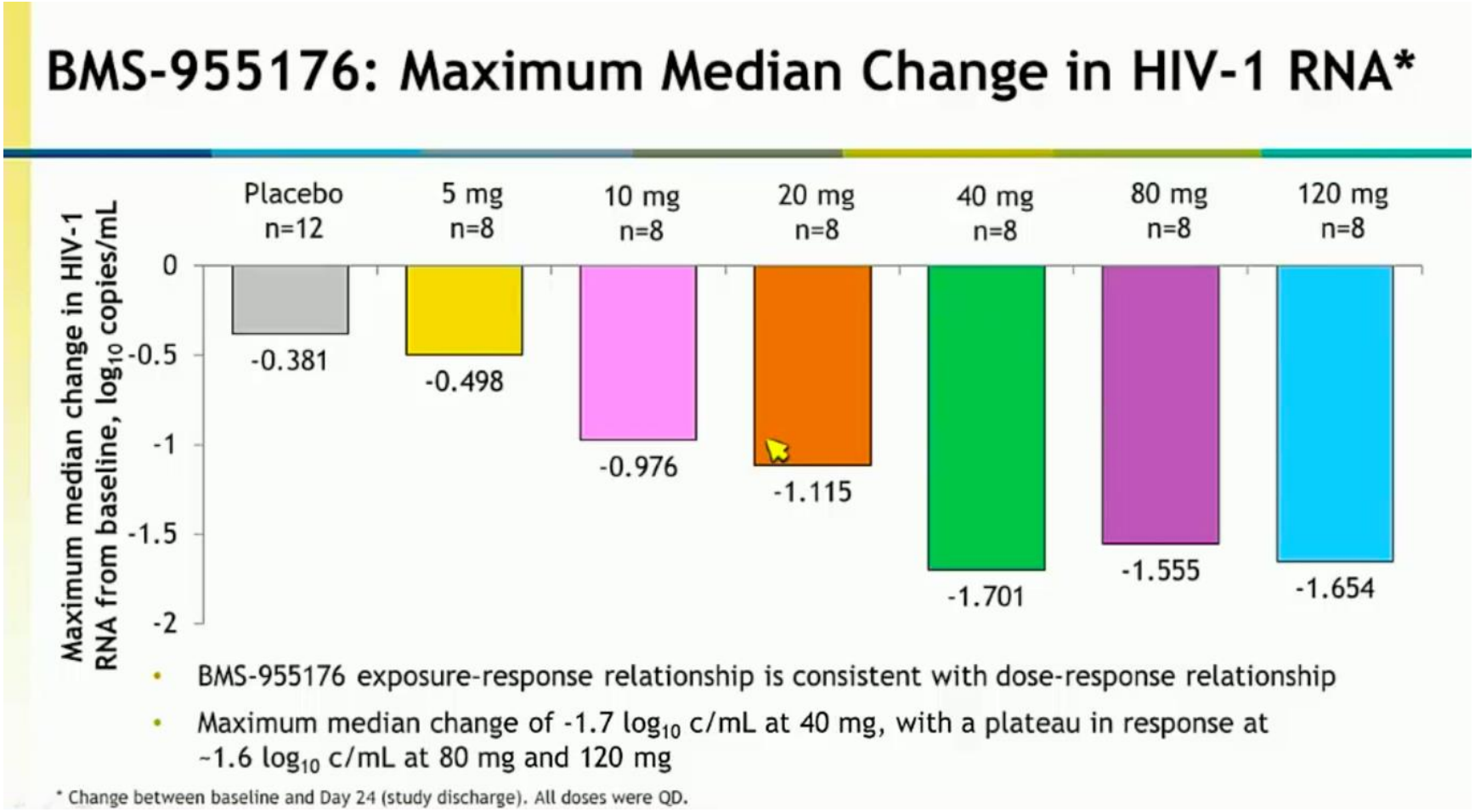
Long-Acting Cabotegravir + Rilpivirine

LATTE-2 Week 32 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



- High patient satisfaction; most common AE ISRs
- No clear difference in dosing arms
- No virologic resistance detected
- IM doses had comparable activity to oral cabotegravir

BMS-955176: Novel 2nd Generation Maturation Inhibitor



Hwang C, et al. CROI 2015, Abstr. 114LB

Summary

- What's new in the guidelines
  - Treat everyone regardless of CD4 count
- What's new with "newer" drugs and regimens
  - Improved activity, tolerability; use of INSTI-based regimens in first line
- What's new with investigational drugs and regimens
  - Exciting new classes of drugs; novel approaches
- Where do we go from here?
  - Long-acting antiretroviral drugs

Questions?