ART: The New, The Old and The Ugly

Our Current ARVS

The Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs/ NtRTIs)

Abacavir
Emtricitabine
Lamivudine
Stavudine
Tenofovir
Zidovudine

Fixed-drug combinations
Combivir, Kivexa, Truvada

The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs

Efavirenz
Nevirapine

Triomune, Atripla, Triplavar

The Protease Inhibitors (PIs)

Atazanavir
Darunavir
Lopinavir
Ritonavir

ARVS REGISTSERED IN SOUTH AFRICA

The Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs/ NtRTIs)

Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
Tenofovir
Zidovudine

Fixed-drug combinations
Combivir, Kivexa, Truvada

The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz
Nevirapine
Etravirine
Rilpivirine

Triomune, Atripla, Tripalvar, Complera

The Integrase Inhibitors (ISTIs)

Raltegravir

The Protease Inhibitors (PIs)

Amprenavir
Atazanavir
Darunavir
Indinavir
Lopinavir
Ritonavir
Saquinavir

The HIV Entry Inhibitors

Maraviroc

THE ANTIRETROVIRAL DRUGS

The Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs/ NtRTIs)

Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
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Fixed-drug combinations
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The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs

Efavirenz
Nevirapine
Etravirine
Rilpivirine

Triomune, Atripla, Complera

The Integrase Inhibitors (ISTIs)

Raltegravir
Elvitegravir
Dolutegravir

The QUAD

The Protease Inhibitors (PIs)

Amprenavir
Atazanavir
Darunavir
Indinavir
Lopinavir
Ritonavir
Saquinavir
Tipranavir

The HIV Entry Inhibitors

Maraviroc

Drugs to be covered

- Etravirine
- Rilpivirine
- Raltegravir
- Elvitegravir
- Dolutegravir
- Darunavir/r
- Maraviroc

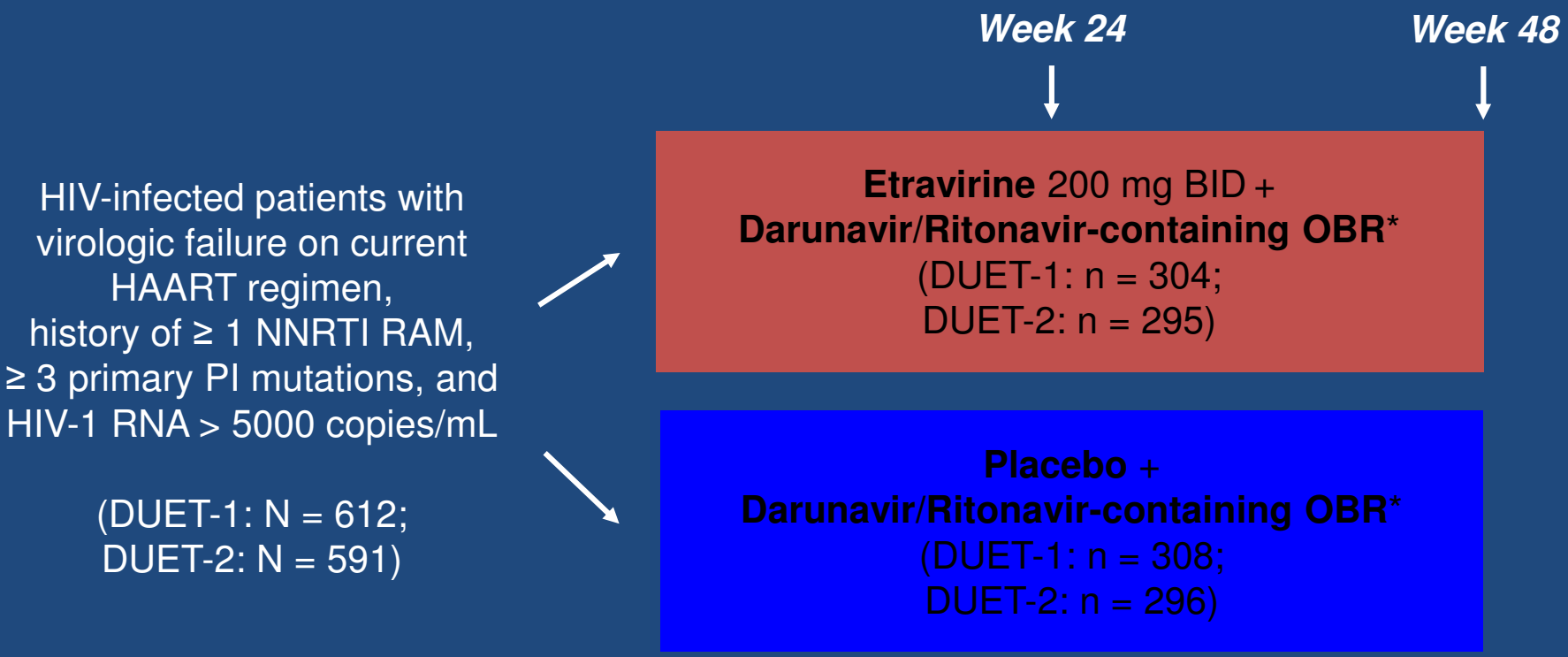
Etravirine

- Etravirine (ETV) is a second generation NNRTI that
- ETV works like other NNRTIs by binding to the catalytic site of the RT enzyme
- Active against HIV with K103N and Y181C
- This potency appears to be related to etravirine's flexibility as a molecule
- Dosage 200mg bd

Etravirine (2)

- Pivotal study DUET 1 and 2
- OBR +darunavir/r +etravirine/placebo
- After 24 weeks, pooled analysis - etravirine study arm achieved an undetectable viral load (58.9% vs 41.1%; $p<0.0001$).
- There was also a significantly greater increase in CD4 cell count from baseline in the etravirine arm (86 vs 67 cells/mm3; $p<0.006$).

Summary of Study Design
DUET 1 and 2



*Investigator-selected OBR included darunavir/ritonavir 600/100 mg twice daily + ≥ 2 NRTIs ± enfuvirtide.

1. Madruga JV, et al. Lancet. 2007;370:29-38.
2. Lazzarin A, et al. Lancet. 2007;370:39-48.

Main Findings

- Significantly more patients achieved HIV-1 RNA < 50 copies/mL with etravirine vs placebo
- HIV-1 RNA reduction from baseline greater in etravirine arms than placebo arms
- Etravirine treatment resulted in greater CD4+ cell count increases from baseline compared with placebo (statistical significance reached in DUET-1 only)

Madruga JV, et al. Lancet. 2007;370:29-38.
Lazzarin A, et al. Lancet. 2007;370:39-48.

- 13 RT mutations at eight positions were found to reduce ETV activity
  - V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S

Etravirine Resistance Score

Weighted mutation score corresponded to response rates as follows :

- 0-2: 74% (highest response)
- 2.5-3.5: 52% (intermediate response)
- ≥ 4: 38% (reduced response)

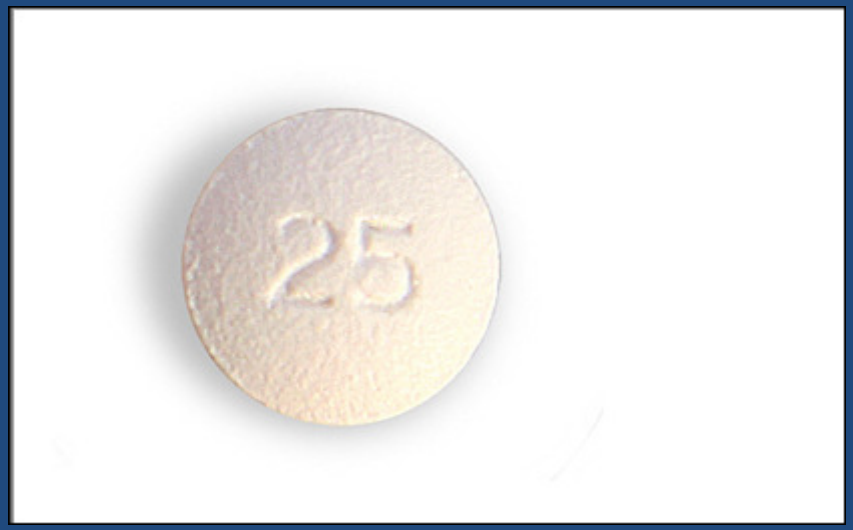
Weighted Mutation Score	1	1.5	2.5	3
Mutation in RT	90I, 179D, 101E, 101H, 98G, 179T, 190A	138A, 106I, 190S, 179F	101P, 100I, 181C, 230L	181I/V

Vingerhoets J, et al. IHDRW 2008; Abstract 24; Picchio G, et al. 15th CROI 2008. Abstract 866.

Etravirine

FDC	**NO**
Single day dosage	**NO**
Low side effect profile	**YES**
High barrier to resistance	**?**
TB friendly	**NO**
Pregnancy friendly	**UNK**

Rilpivirine

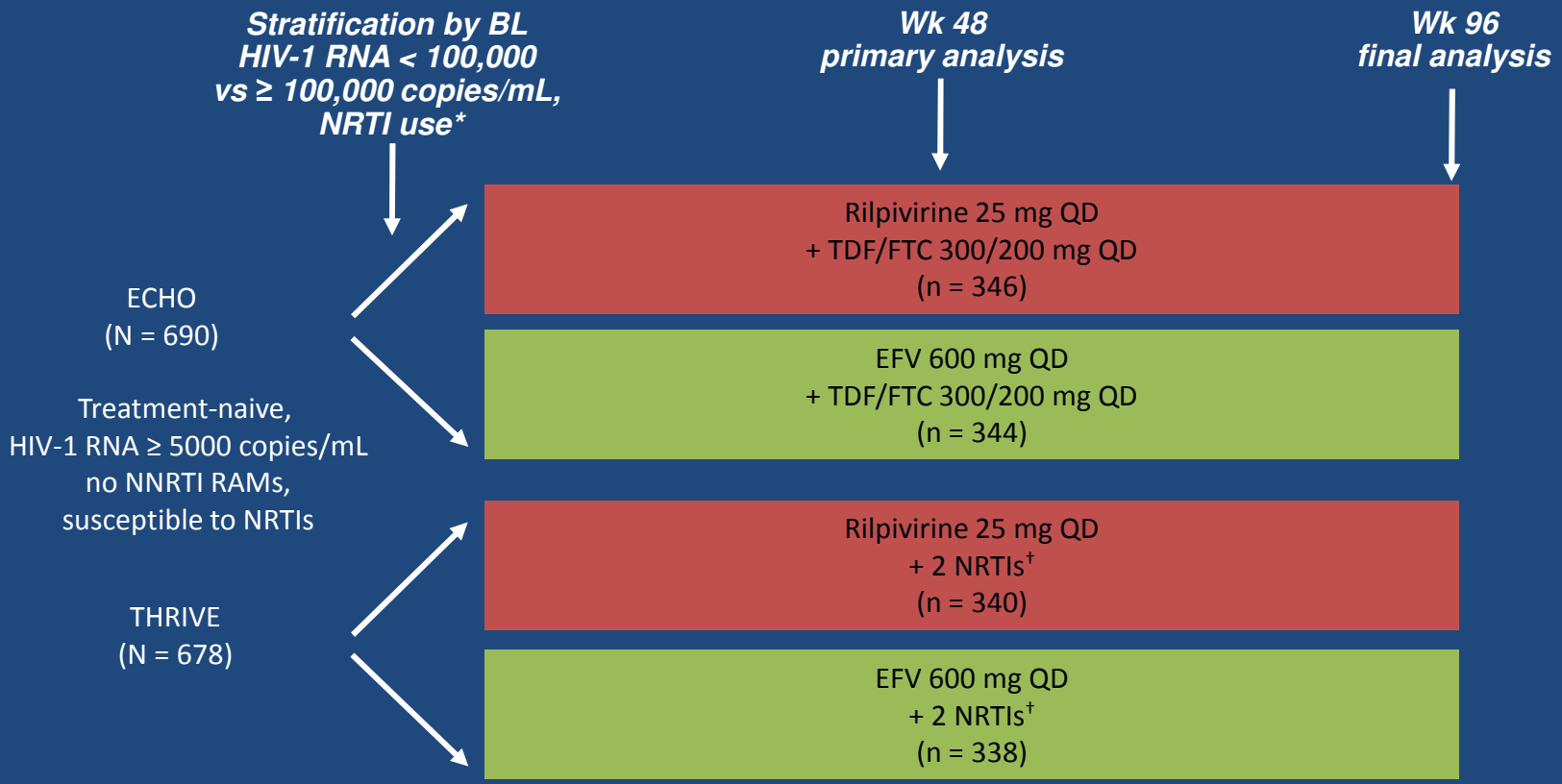


Rilpivirine

- Novel NNRTI
- Single day dosage
- Co-formulated with TDF and FTC as Complera

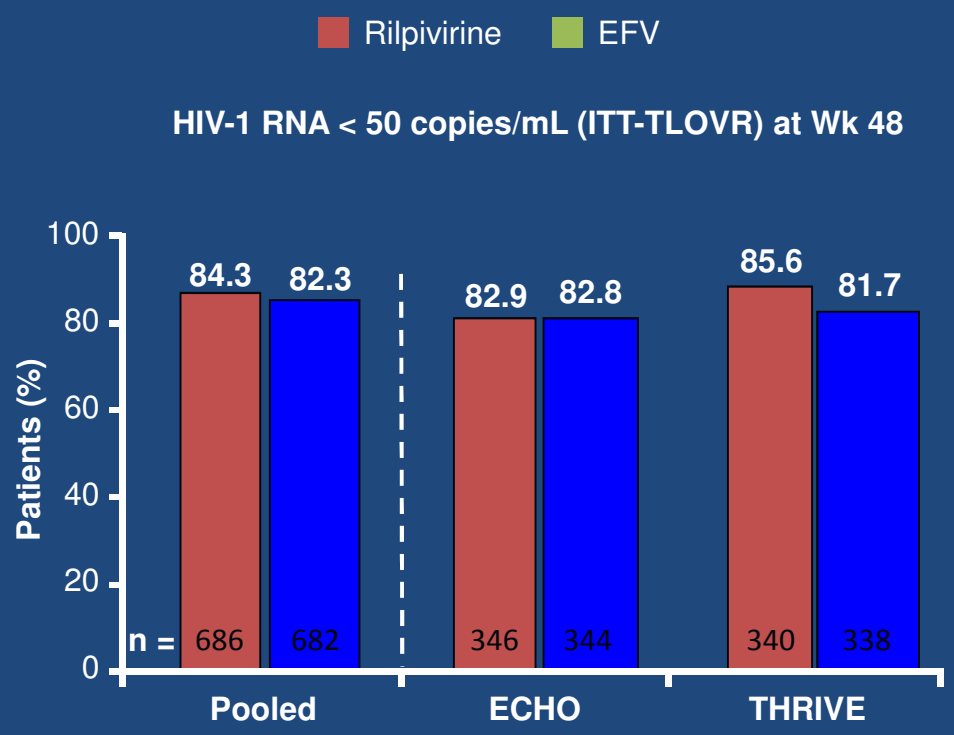
ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients

- Randomized, double-blind phase III trials

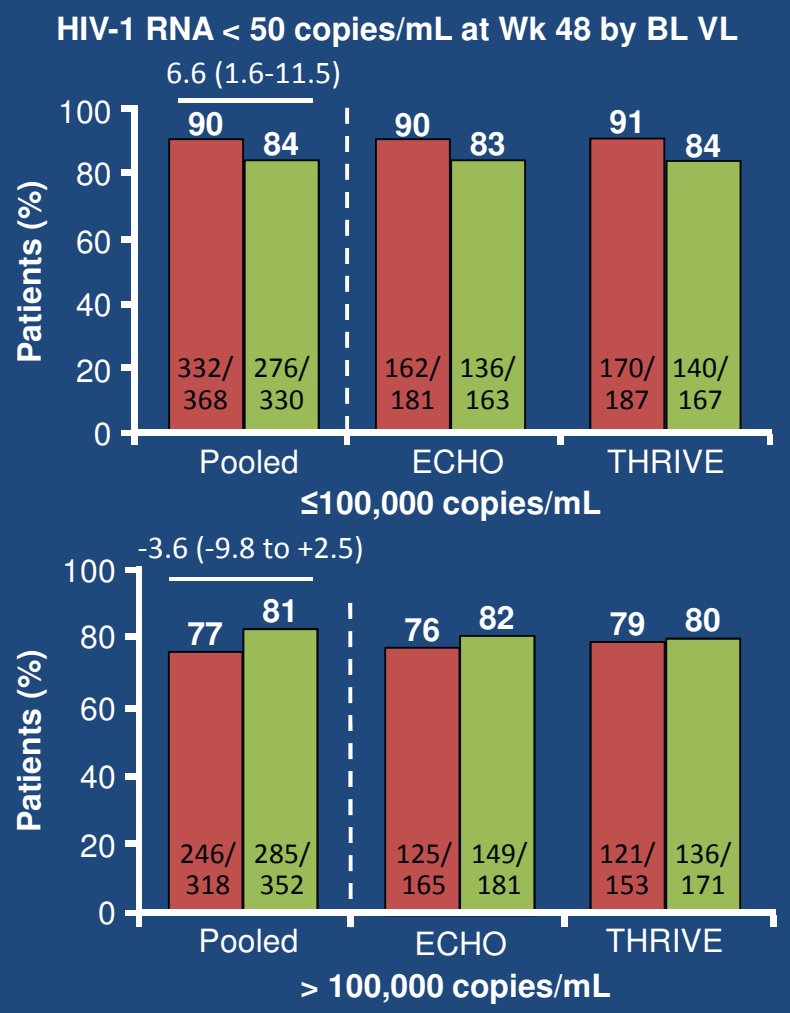


*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients

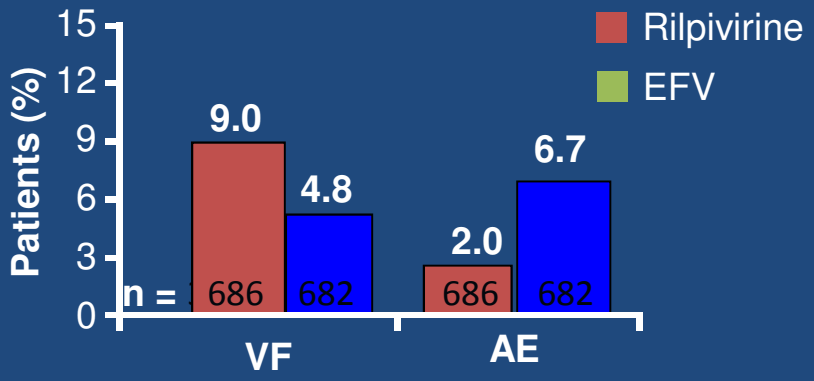


*P < .0001 for noninferiority at -12% margin.



ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events

Treatment Failure in ECHO and THRIVE



Resistance at Virologic Failure

Wk 48 Outcome	Rilpivirine (n = 686)	Efavirenz (n = 682)
VF with resistance data, n	62	28
No NNRTI or NRTI RAMs,%	29	43
≥ 1 Emergent NNRTI RAM,%	63	54
▪ Most frequent NNRTI RAM	E138K	K103N
≥ 1 Emergent NRTI RAMs, %	68	32
▪ Most frequent NRTI RAM	M184I	M184V

Adverse Events and Discontinuation

Wk 48 Outcome, %	Rilpivirine (n = 686)	Efavirenz (n = 682)	*P* Value
DC for AE	3	8	.0005
Most Common AEs of Interest, %			
Any neurologic AE	17	38	< .0001
Any psychiatric AE	15	23	.0002
Any rash	3	14	< .0001

Rilpivirine

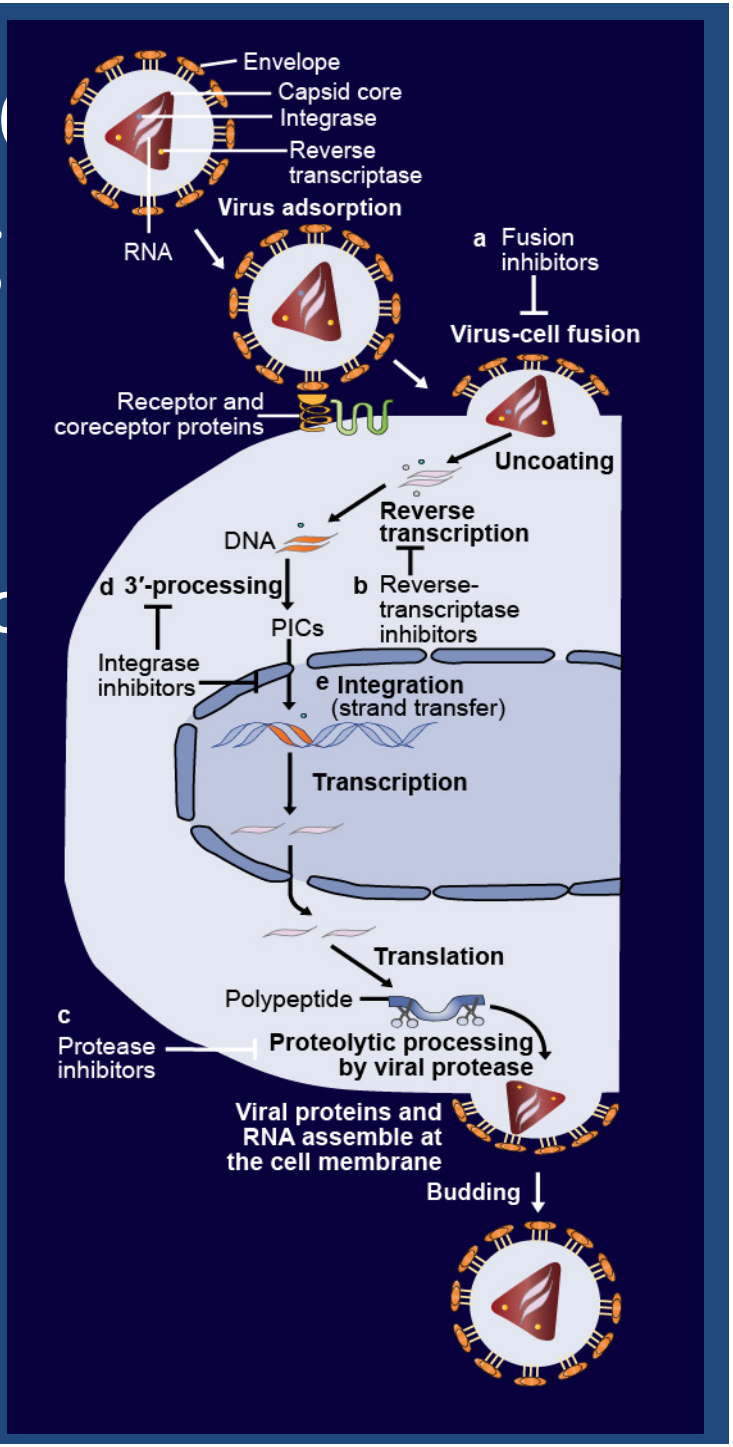
FDC	**YES**
Single day dosage	**YES**
Low side effect profile	**YES**
High barrier to resistance	**NO**
TB friendly	**NO**
Pregnancy friendly	**UNK**

Raltegravir

- Novel mode of action
- Acts on intergrase as an inhibitor
- 400mg bd

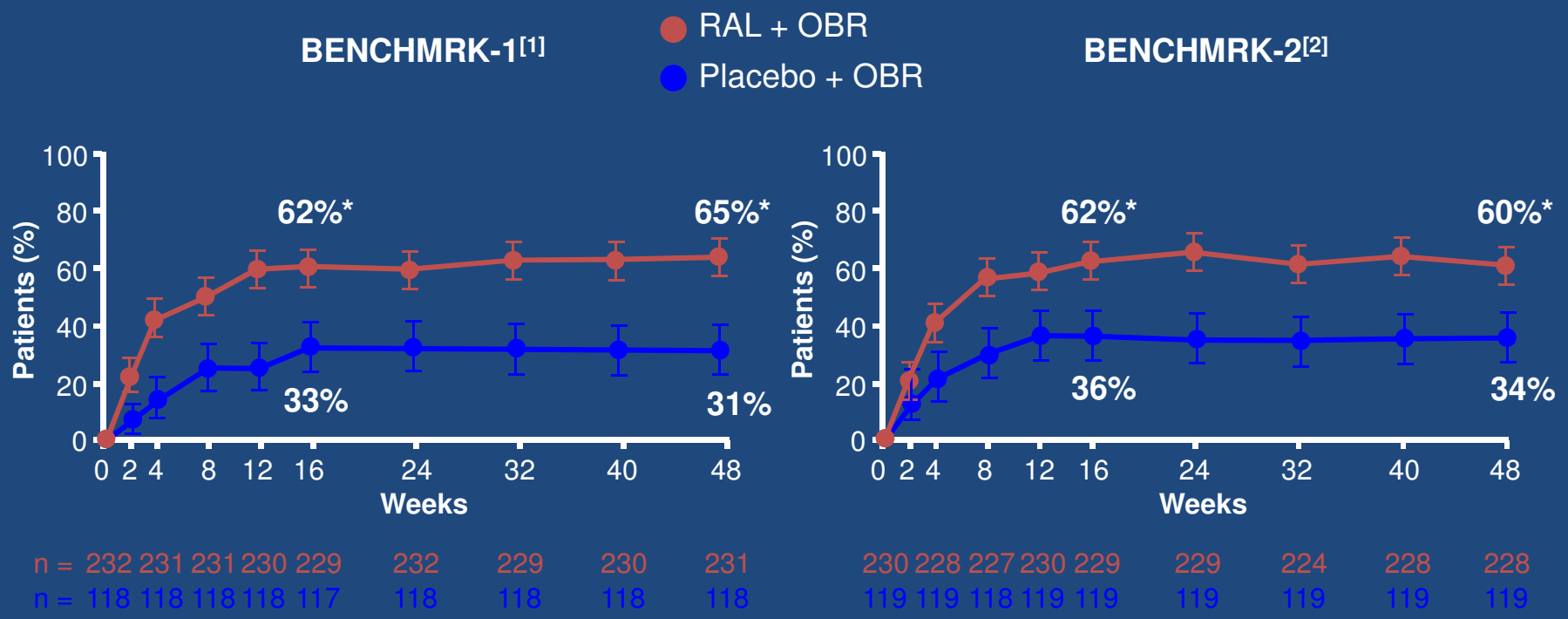
HIV Replication (
and Drug Targ

a. Entry inhibitors
b. Reverse transcriptase inhibito
c. Protease inhibitors
d. 3’-processing inhibitors
e. Strand transfer inhibitors



Pommier Y, et al. Nat Rev Drug Discov. 2005;4:236-248.

BENCHMRK-1 & -2: Patients With HIV-1 RNA < 50 c/mL at Week 48

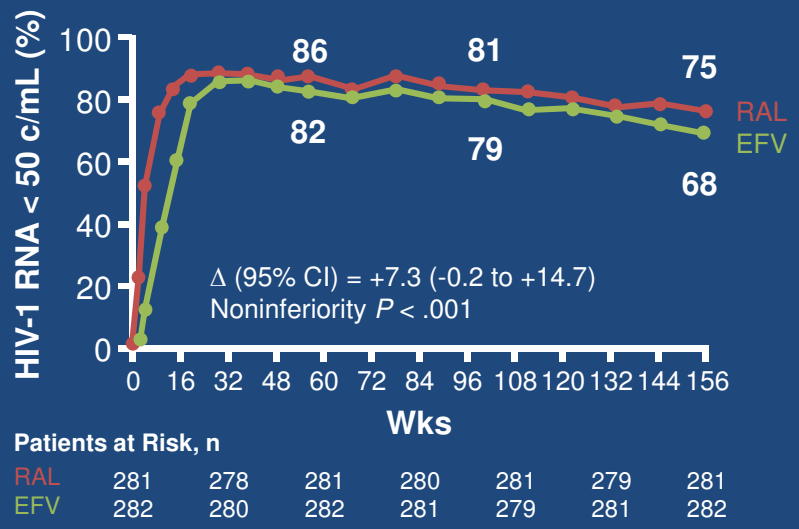


*P < .001 for RAL vs placebo, derived from a logistic regression model adjusted for baseline HIV-1 RNA level ($\log_{10}$), first ENF use in OBR, first DRV use in OBR, active PI in OBR.

1. Cooper DA, et al. CROI 2008. Abstract 788. 2. Steigbigel R, et al. CROI 2008. Abstract 789.

STARTMRK: Efavirenz vs Raltegravir at 156 Wks in Antiretroviral-Naive Patients

- Phase III trial of EFV vs RAL, both with TDF/FTC in tx-naive patients
- At Wk 156, RAL noninferior to EFV (ITT, NC = F analysis)



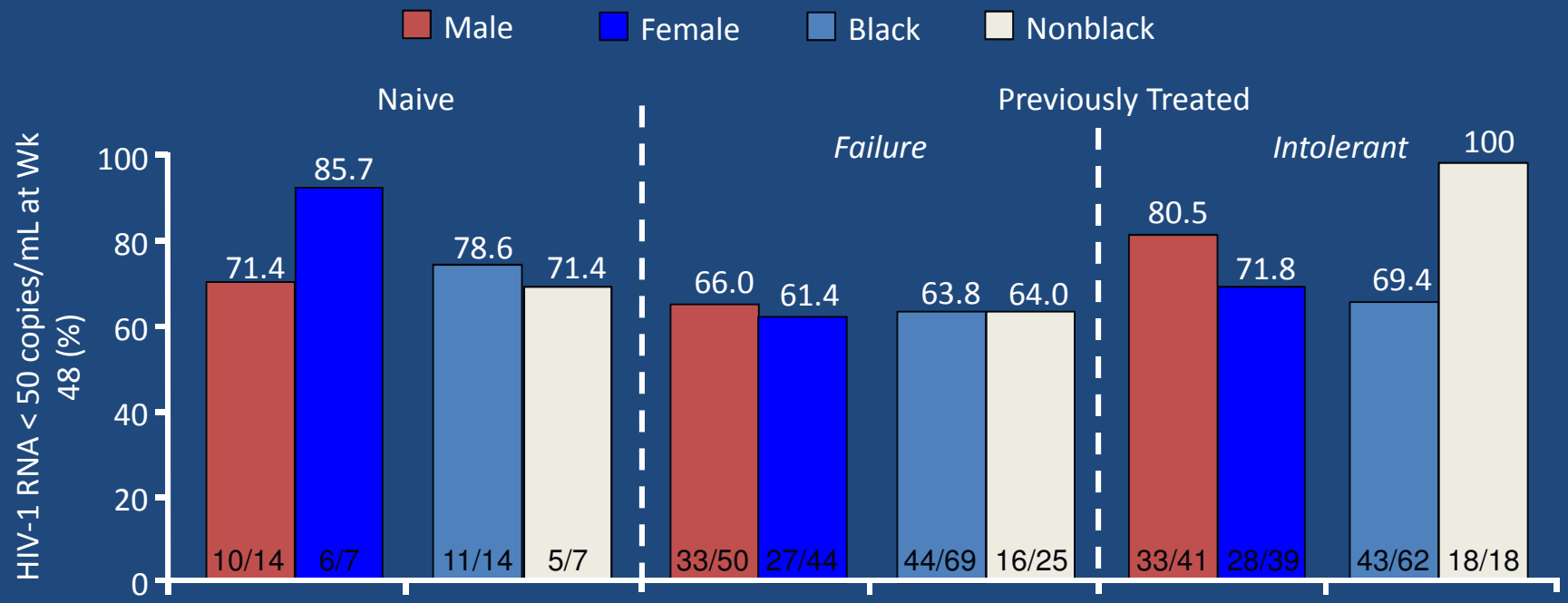
- CD4+ count : +332 (RAL) vs +295 (EFV)

HIV-1 RNA < 50 c/mL by Prespecified BL Characteristic*		
Subgroup, n/N (%)	**RAL**	**EFV**
Male	172/194 (89)	159/188 (85)
Female	40/43 (93)	33/39 (85)
Black	18/23 (78)	17/22 (77)
White	83/94 (88)	82/90 (91)
Latino	50/54 (93)	42/55 (76)
VL ≤ 100K	99/105 (94)	93/111 (84)
VL > 100K	113/132 (86)	99/116 (85)
CD4 ≤ 50	16/23 (70)	24/28 (86)
CD4 > 50 - ≤ 200	80/89 (90)	68/84 (81)
CD4 > 200	116/125 (93)	100/115 (87)
HBV ± HCV	11/12 (92)	11/13 (85)
No coinfection	201/225 (89)	181/214 (85)
Age ≤ median	109/124 (88)	108/131 (82)
Age > median	103/113 (91)	84/96 (88)

*Study not powered for statistical significance for these comparisons.

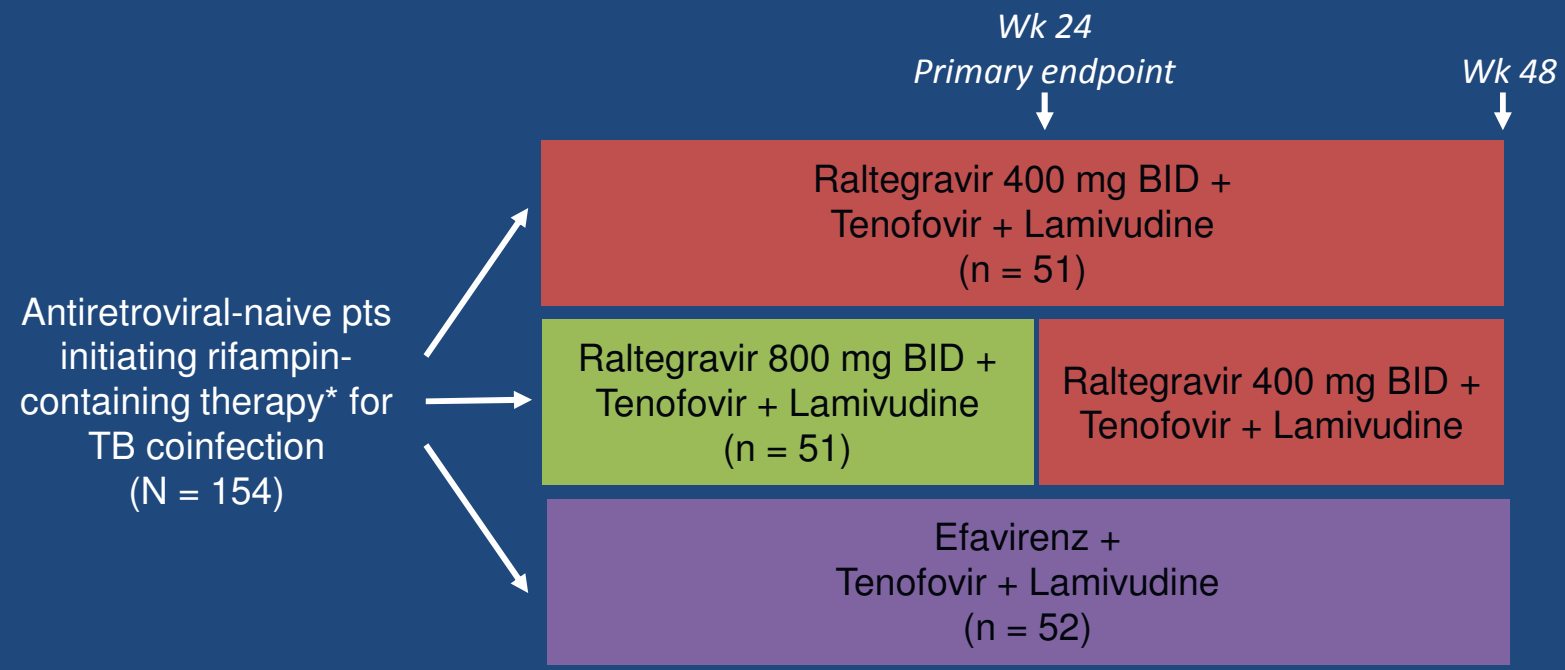
REALMRK: 48-Wk Efficacy of Raltegravir BID in Women, Blacks

- Multicenter, multinational, open-label, single-arm study to determine efficacy of RAL 400 mg BID (+ investigator-selected ARVs) in women, blacks—populations underrepresented in clinical trials
- Enrollment goals: 25% women (actual 47%), 50% black (actual 74%)
- No difference in PK parameters by race or sex; no new RAL safety signals noted
- Retention 84% throughout study; bolstered by strict selection criteria and retention initiatives



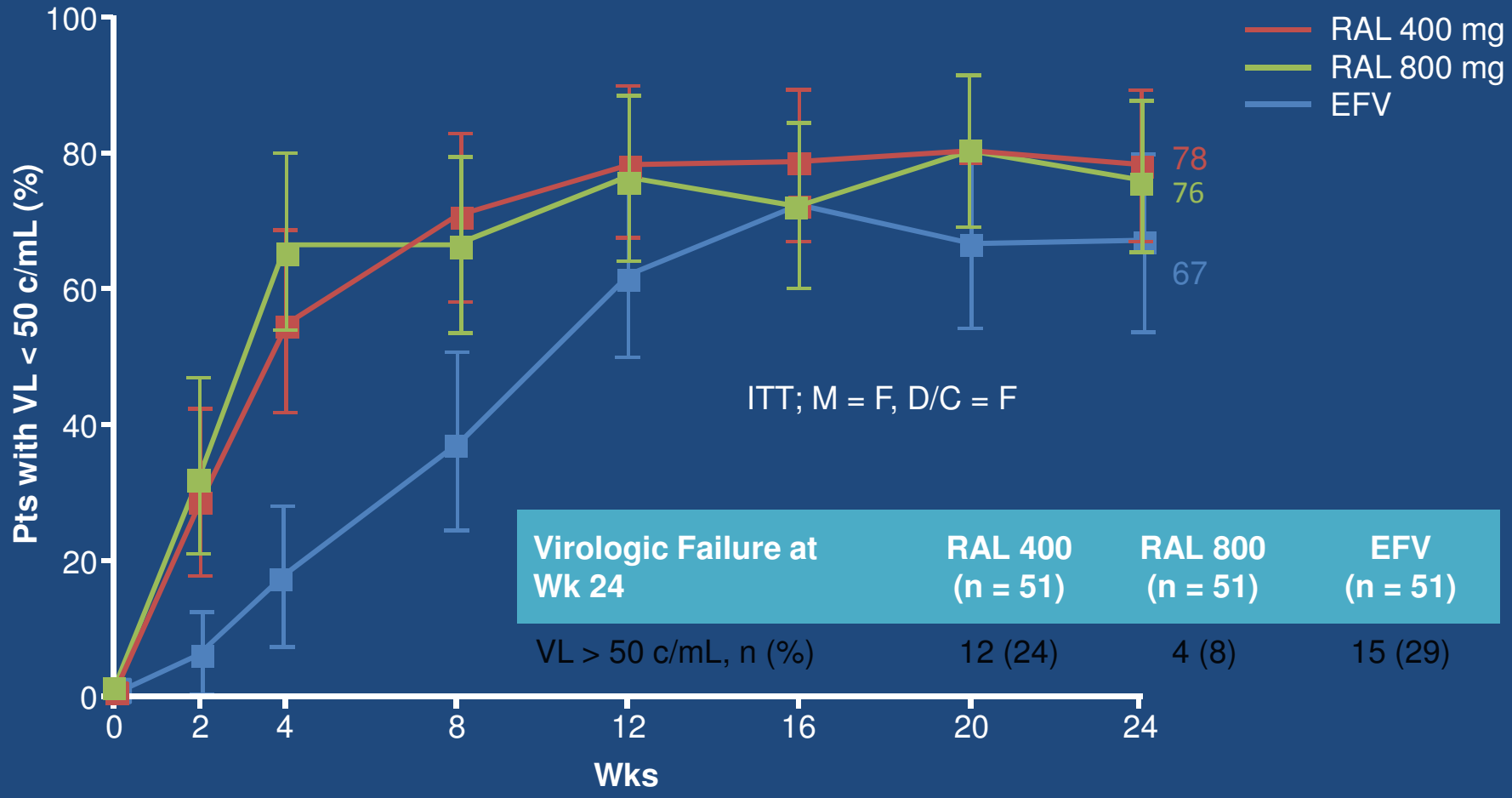
ANRS REFLATE: EFV- vs RAL-Based ART in HIV/TB-Coinfected Pts

- Multicenter, randomized, open-label phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24



*Rifampin-containing therapy initiated before ART and consisted of rifampin, isoniazid, pyrazinamide, and ethambutol for 2 mos, followed by rifampin and isoniazid for 4 mos.

REFLATE: Virologic Suppression at Wk 24 by ART Regimen



Virologic Failure at Wk 24	RAL 400 (n = 51)	RAL 800 (n = 51)	EFV (n = 51)
VL > 50 c/mL, n (%)	12 (24)	4 (8)	15 (29)

Raltegravir

FDC	**NO**
Single day dosage	**NO**
Low side effect profile	**YES**
High barrier to resistance	**NO**
TB friendly	**MAYBE**
Pregnancy friendly	**UNK**

Elvitegravir

- Intergrase inhibitors.
- Requires boosting
  - ritonavir
  - Cobicistat
- Co-formulated with a booster, TDF and FTC
- QUAD-Stribild

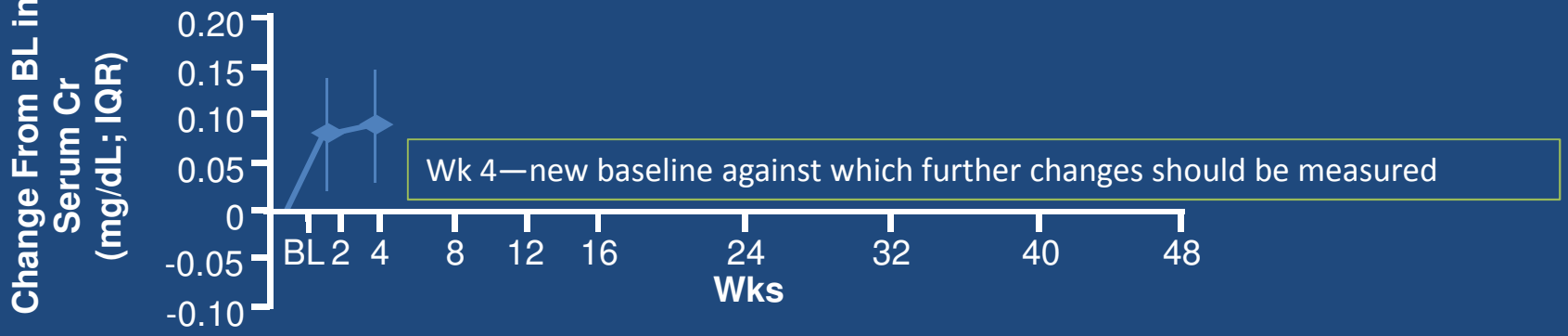
Cobicistat: A New Boosting Agent

- Small molecule with no HIV activity
  - No concern of drug resistance in pts with suboptimal virologic response
- Similar ↑ from BL in fasting TC and TGs compared with RTV when boosting same agent[1]
- Inhibitor of CYP3A4; many drug–drug interactions[2,3]
- Modest, rapid increase in serum Cr due to inhibition of tubular secretion[3]
  - Not associated with any change in actual GFR
  - Other drugs (including ARVs) have similar effect[4,5]
- Availability of cobicistat has allowed for development of new coformulated agents and regimens

1. Gallant JE, et al. J Infect Dis. 2013;208:32-39. 2. DHHS Guidelines February 2013.
3. TDF/FTC/EVG/COBI [package insert]. 4. RPV [package insert]. 5. DTG [package insert].

Renal Monitoring With Cobicistat

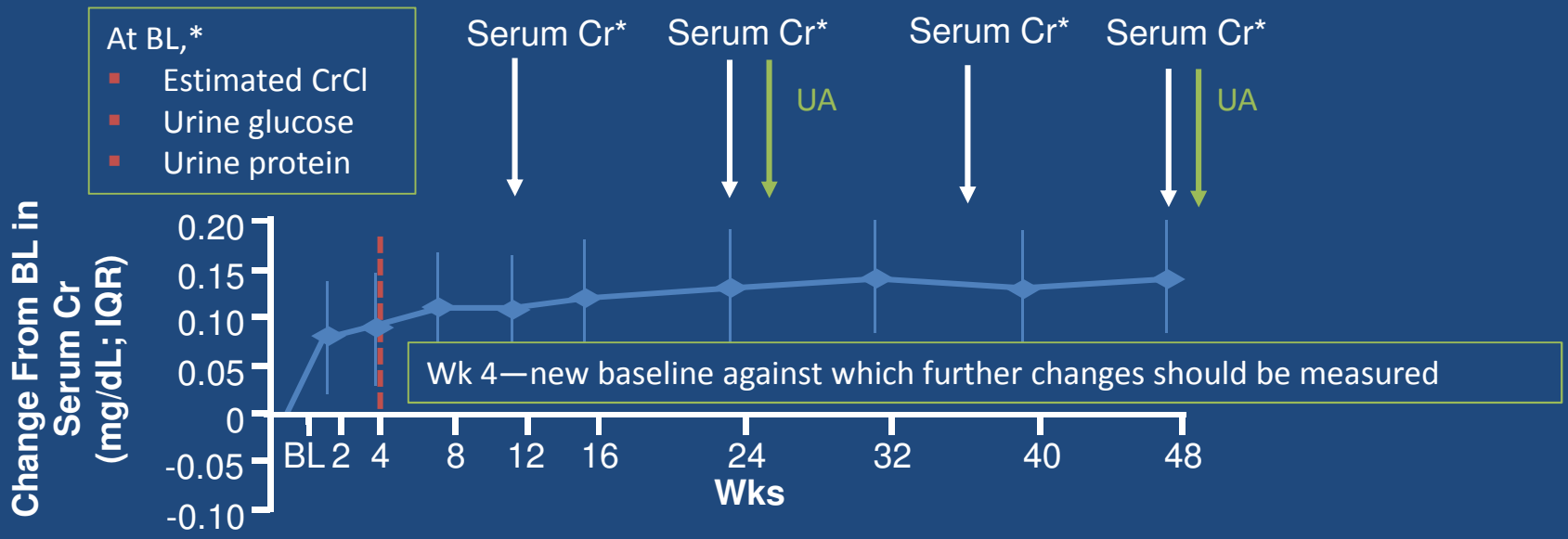
At BL,*
- Estimated CrCl
- Urine glucose
- Urine protein



*Serum phosphorus should be measured in patients at risk for renal impairment

9. TDF/FTC/EVG/COBI [package insert]. 10. DHHS Guidelines February 2013.

Renal Monitoring With Cobicistat



*Serum phosphorus should be measured in patients at risk for renal impairment

- Coformulated drugs containing COBI should not be initiated in pts with estimated CrCl < 70 mL/min
  - Studies ongoing in pts with CrCl < 70
- Interpretation of changes in renal function may be problematic when using coformulations of COBI and TDF
- TDF/FTC/EVG/COBI should not be used with other nephrotoxic drugs

12. TDF/FTC/EVG/COBI [package insert]. 13. DHHS Guidelines February 2013.

Key Drug–Drug Interactions With COBI

- Antacids
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Erectile dysfunction drugs
- Inhaled/injectable corticosteroids
- MVC
- OCPs (norgestimate)
- Rifampin
- Statins

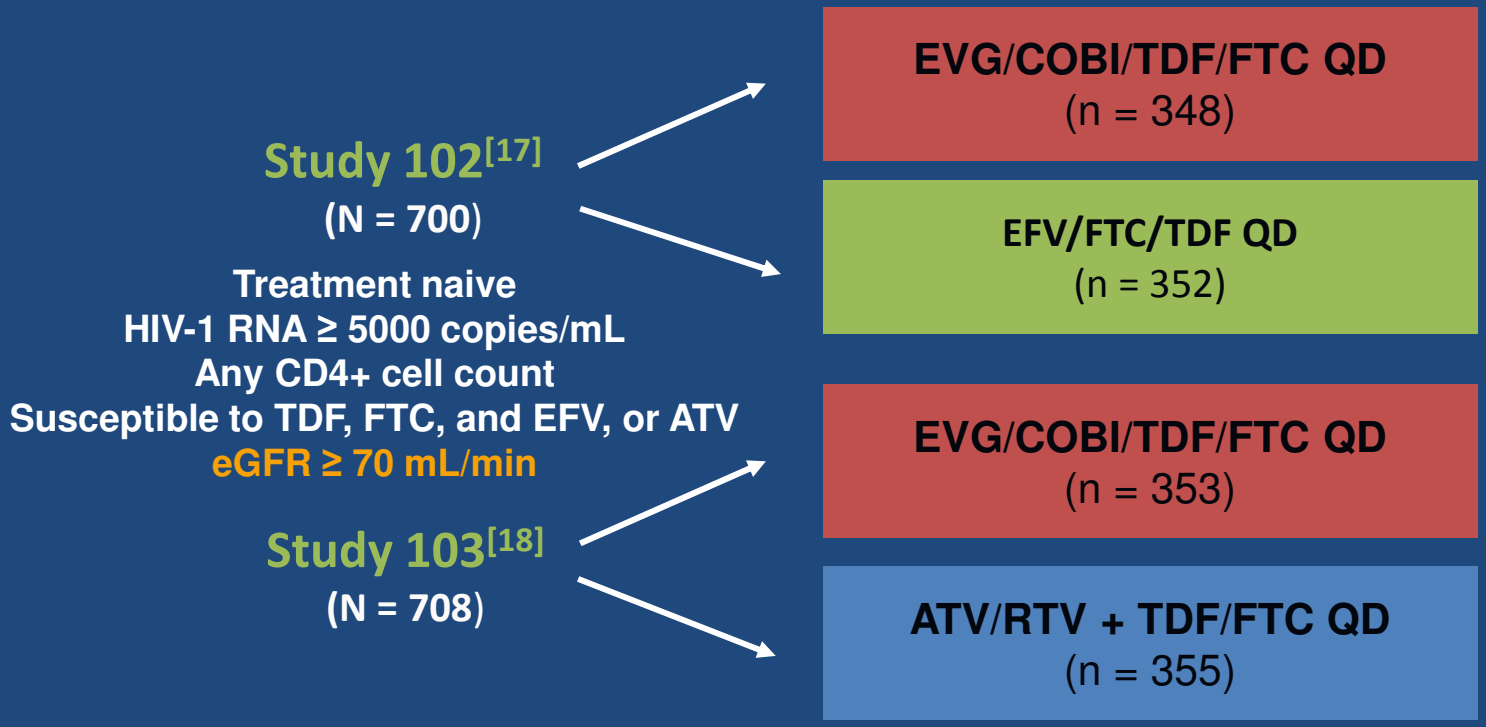
14. DHHS Adult Guidelines. February 2013

Cobicistat—Status in EU and US

- In July 2013, EMEA approved cobicistat as a PK enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of a complete ART regimen in adults
- In US, currently approved only as part of coformulated single-tablet regimen TDF/FTC/EVG/COBI
  - Approval as single agent pending

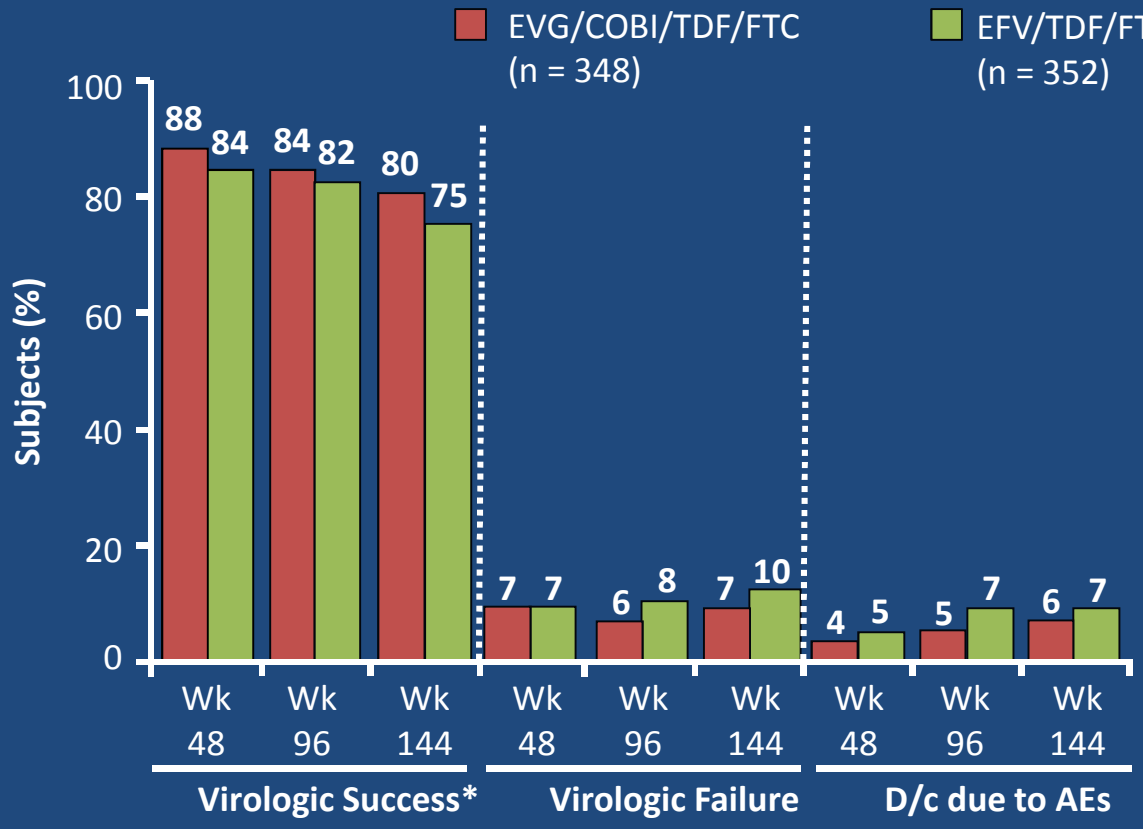
Elvitegravir/Cobicistat vs EFV or ATV/RTV + TDF/FTC in Treatment-Naive Patients

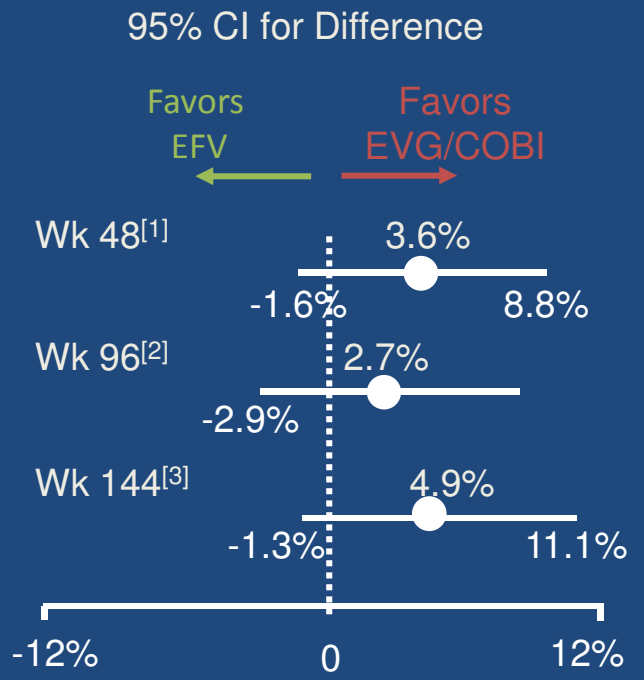
- Randomized, double-blind, active-controlled phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



17. Sax P, et al. Lancet. 2012;379:2439-2448. 18. DeJesus E, et al. Lancet. 2012;379:2429-2438.

EVG/COBI/TDF/FTC Noninferior to EFV/TDF/FTC Through Wk 144

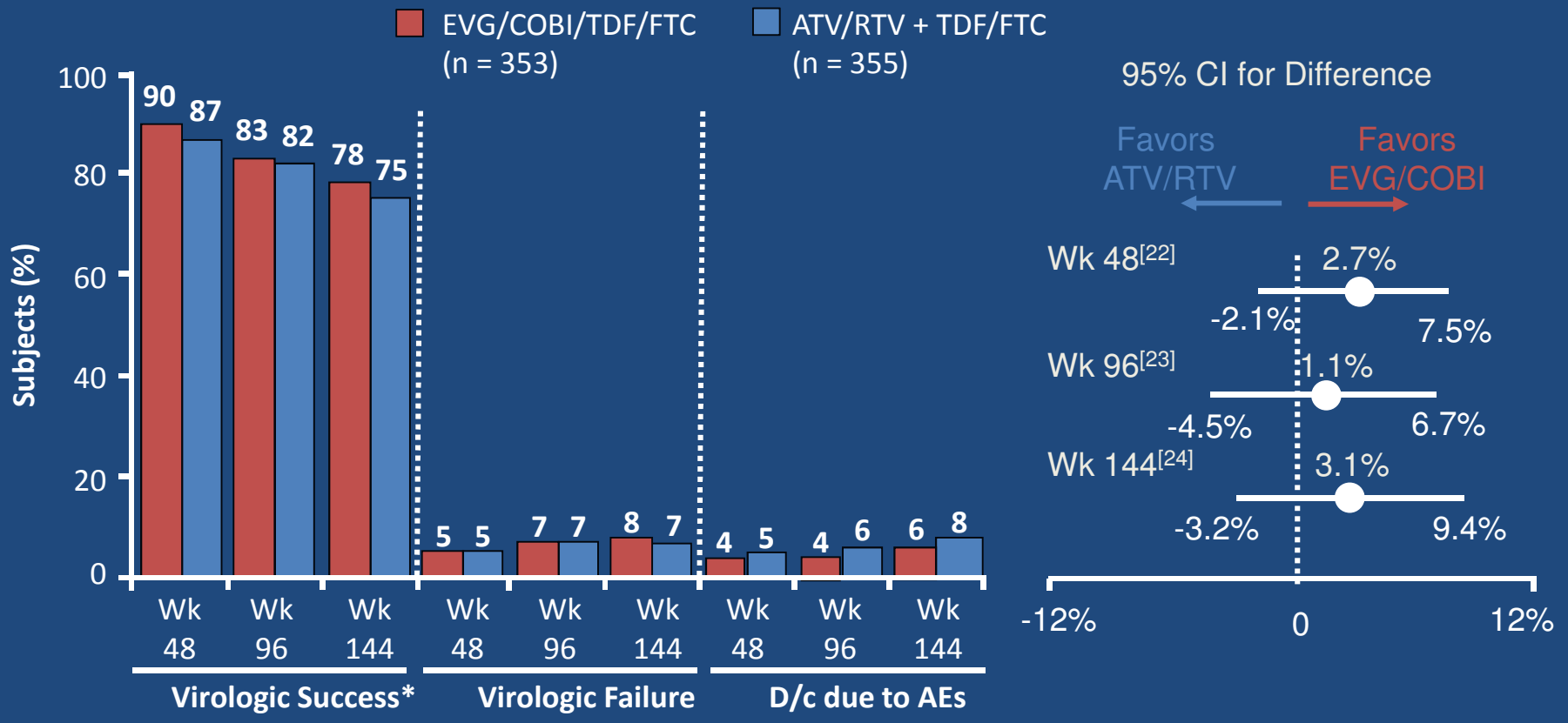




*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.

19. Sax PE, et al. Lancet. 2012;379:2439-2448. 20. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 21. Wohl D, et al. ICAAC 2013. Abstract H-672a.

EVG/COBI/TDF/FTC Noninferior to ATV/RTV + TDF/FTC Through Wk 144



*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.

22. De Jesus E, et al. Lancet. 2012;379:2429-2438. 23. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486. 24. Clumeck N, et al. EACS 2013. Abstract LBPS7/2.

QUAD

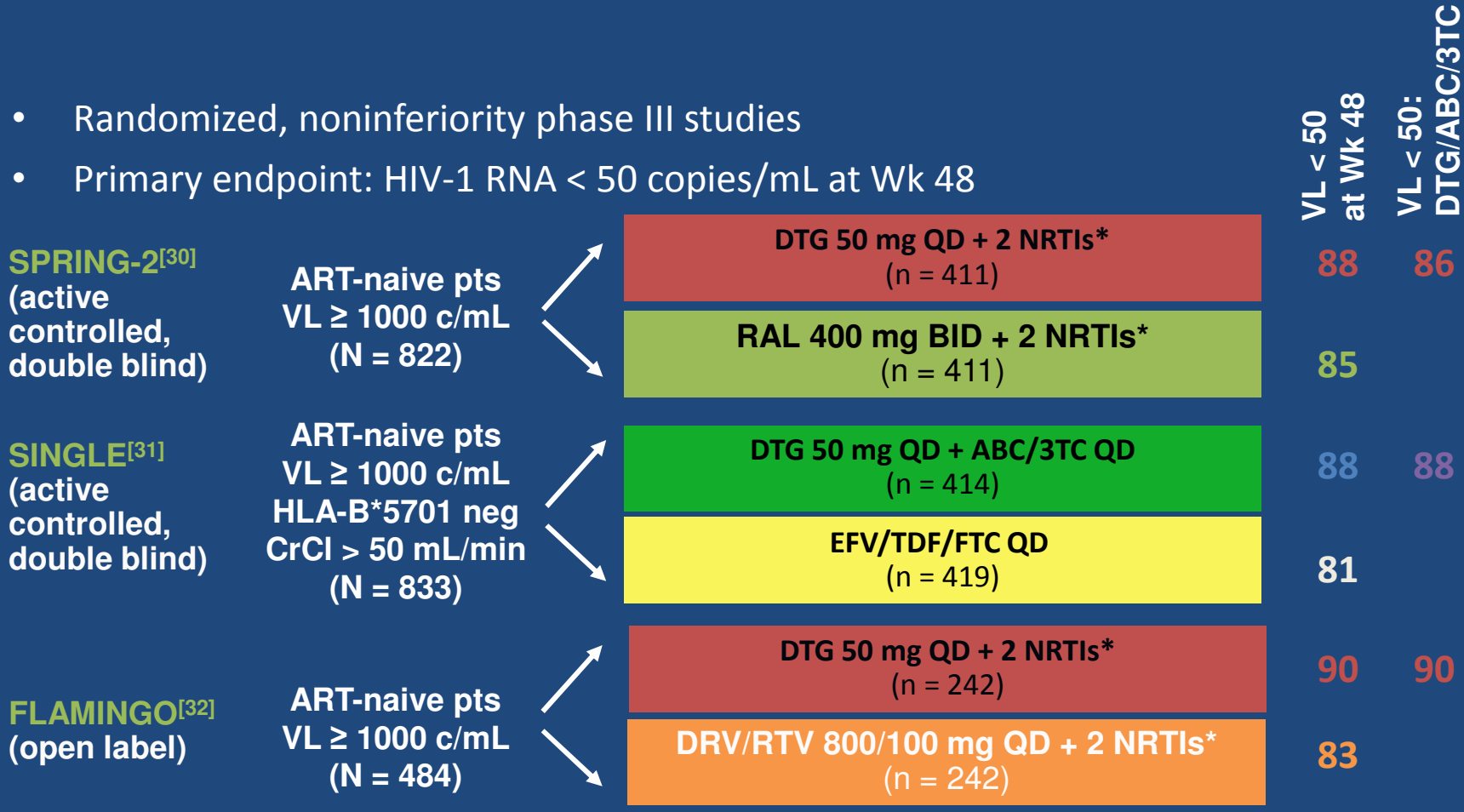
FDC	**YES**
Single day dosage	**YES**
Low side effect profile	**YES**
High barrier to resistance	**YES**
TB friendly	**NO**
Pregnancy friendly	**UNK**

Dolutegravir

- Dolutegravir (DTG) is a newer, potent INSI with low nanomolar activity that is suitable for once-daily, unboosted dosing
- Furthermore, *in vitro*, DTG retains activity against most isolates carrying major integrase resistance mutations to RAL and/or EVG

Dolutegravir Phase III Trials in Treatment-Naive Patients

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



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

N Engl J Med. 2013;369:1807-1818.

Resistance on SPRING 1

- Samples from participants meeting Protocol defined Virological failure criteria were sent for resistance testing.
- No participants on DTG have had emergence of a virus with an INI resistance mutation.
- One participant receiving DTG 10mg developed virus with the mutation M184M/V in reverse transcriptase.

SINGLE

- No treatment-emergent genotypic resistance that resulted in reduced susceptibility to either DLG or the background regimen was seen in the DLG arm in SINGLE.

OF course the ever present TB and pregnancy question

- Increase the dose of DLG- poor evidence
- Category B drug.

DLV/ABC and TDF

- In treatment-naive HIV-infected patients starting initial ART, dolutegravir (DTG) plus abacavir (ABV)/lamivudine (3TC) maintained superiority over efavirenz (EFV)/tenofovir DF (TDF)/emtricitabine (FTC) at Week 96
  - DTG arm associated with higher virologic response rate, primarily due to lower rate of discontinuations related to tolerability
  - DTG arm associated with more favorable safety profile vs control arm, with lower rates of central nervous system (CNS) events, rash, and liver function test elevations
- No major treatment-emergent mutations conferring INSTI or NRTI resistance detected through 96 weeks in DTG-treated patients

Dolutegravir

FDC	**YES**
Single day dosage	**YES**
Low side effect profile	**YES**
High barrier to resistance	**YEs**
TB friendly	**NO**
Pregnancy friendly	**UNK**

Darunavir dosing summary

Darunavir/r dosing is determined by treatment experience and presence or absence of darunavir mutations on genotypic lab analysis.

Treatment-experienced patients

- POWER 1 compared the efficacy and safety of four doses of DRV (TMC114) plus 100 mg RTV with investigator-selected control protease inhibitors (CPIs)
- 63% of the patients were resistant to all commercially available PI.
- Virologic and immunologic outcomes were significantly better in the DRV/r arms compared to the CPI arm. In the 600 mg DRV twice daily arm, mean CD4 gains were as high as 124 cells at 24 weeks and 53 percent attained an HIV RNA level <50 copies/mL;

Treatment-experienced patients

- POWER 3 DRV/r plus optimized background therapy. No comparator arm was used.
- Of 324 patients who were treated for 48 weeks, 45 percent achieved HIV RNA reductions to <50 copies/ml.

Treatment-experienced patients

- Treatment-experienced patients with recent genotypic testing demonstrating the absence of darunavir-associated mutations: darunavir (800 mg) once daily plus ritonavir (100 mg) once daily. The relevant darunavir mutations include: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V.

Treatment-experienced patients

- POWER 1 and POWER 2 were randomized, multinational, phase IIB trials, which compared DRV co-administered with low-dose RTV to other PIs in a population of highly treatment-experienced patients

Treatment-experienced patients

- Darunavir-associated mutations on genotype: darunavir (600 mg; given as one tablet) twice daily plus ritonavir (100 mg) twice daily.
- The relevant darunavir mutations include: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V.

Treatment-naïve patients

- Darunavir (800 mg) once daily plus ritonavir (100 mg) once daily

- ARTEMIS: randomized, open-label, phase 3 non-inferiority trial compared the safety and efficacy of DRV/r (800/100 mg once daily) with LPV/r in 689 treatment-naive patients

Treatment-naïve patients

- At week 48, DRV/r was found to be non-inferior to LPV/r; viral suppression was achieved in 84 versus 78 percent, respectively.
- At 96 weeks, significantly more patients in the DRV/r arm achieved viral suppression than in the LPV/r arm (79 versus 71 percent)
- Both treatments were well tolerated.

Darunavir

FDC	**NO**
Single day dosage	**MAYBE**
Low side effect profile	**YES**
High barrier to resistance	**YES**
TB friendly	**NO**
Pregnancy friendly	**UNK**

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

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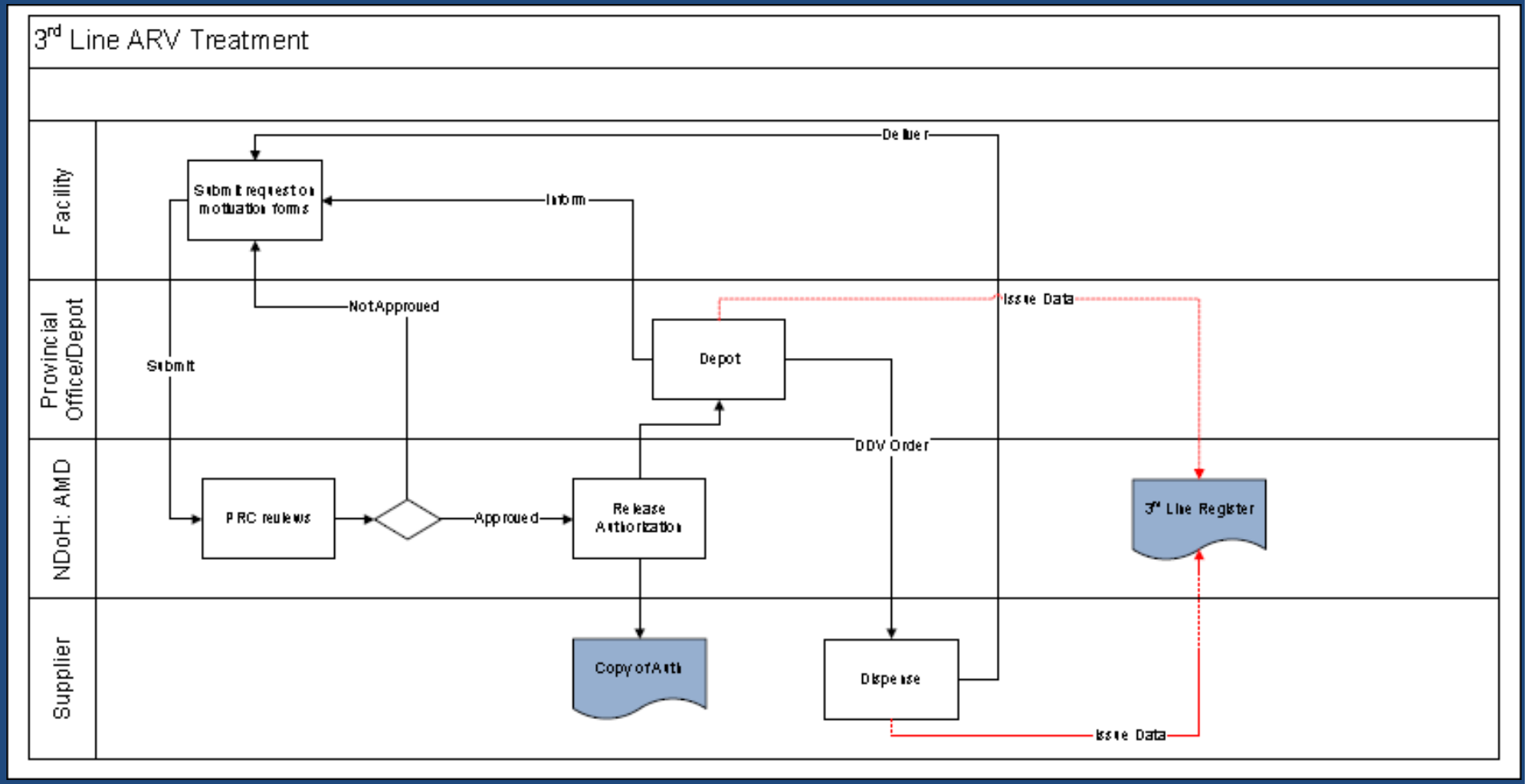
HAST Managers and Heads of Pharmaceutical Services

Re: Third line antiretroviral medicines (darunavir, raltegravir and etravirine)

On a pilot basis, the National Department of Health has managed the authorisation and procurement of third line ARV medicines. Going forward, provinces are to take full responsibility for the procurement of 3rd Line ARV agents as per the normal provincial DDV procurement process. Provinces must ensure that the necessary funding required for 3rd Line therapy (ARV's and laboratory tests) are included in their provincial business plans for 2014/15.


3rd Line ARV Treatment
Facility
Provincial Office/Depot
NDoH: AMD
Supplier
Deliver
Submit request on motivation forms
Inform
Not Approved
Submit
Depot
Issue Data
DDV Order
PRC reviews
Approved
Release Authorization
3rd Line Register
Copy of Auth
Dispense
Issue Data

Third line Peer Revivew committee

- Third line drugs now on tender
- Centrally procured
  - Receive motivation
  - Screen
  - Add to database
  - Send to Virtual Committee
  - Committee recommendation to motivator and CPU
  - Update database

Third line committee

- 130 patients on the database.
- 115 have already been reviewed.
- (5 motivations no GT results)
- Number of motivations declined 12
- Number of patients on third line treatment 98