Inibitori dell'integrasi: presente e futuro

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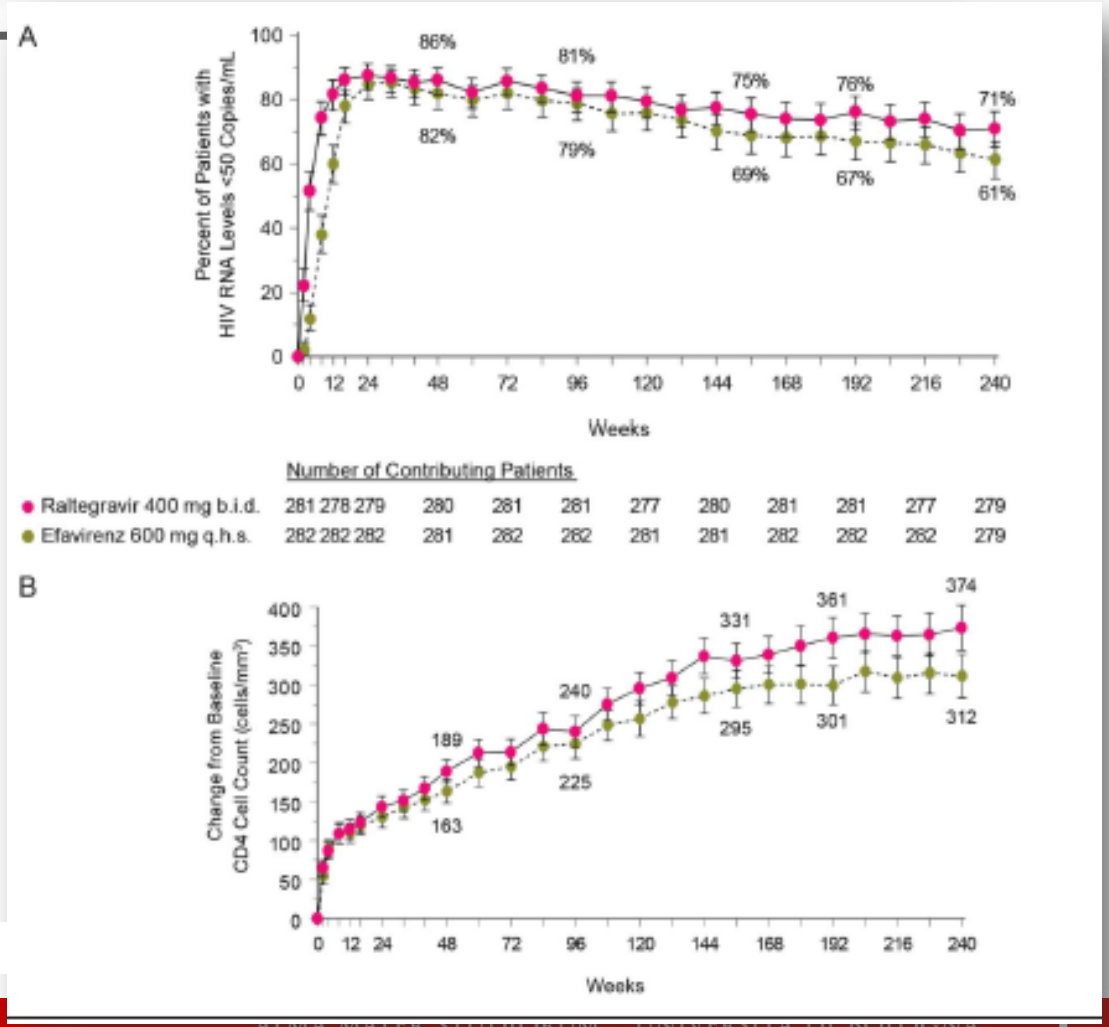
The present…

Raltegravir

Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1–Infected Patients: Final 5-Year Results From STARTMRK

- Randomized, double-blind, placebo-controlled phase III trial
- 563 naive patients
- TDF/FTC + RTG or EFV
- 5-year follow-up

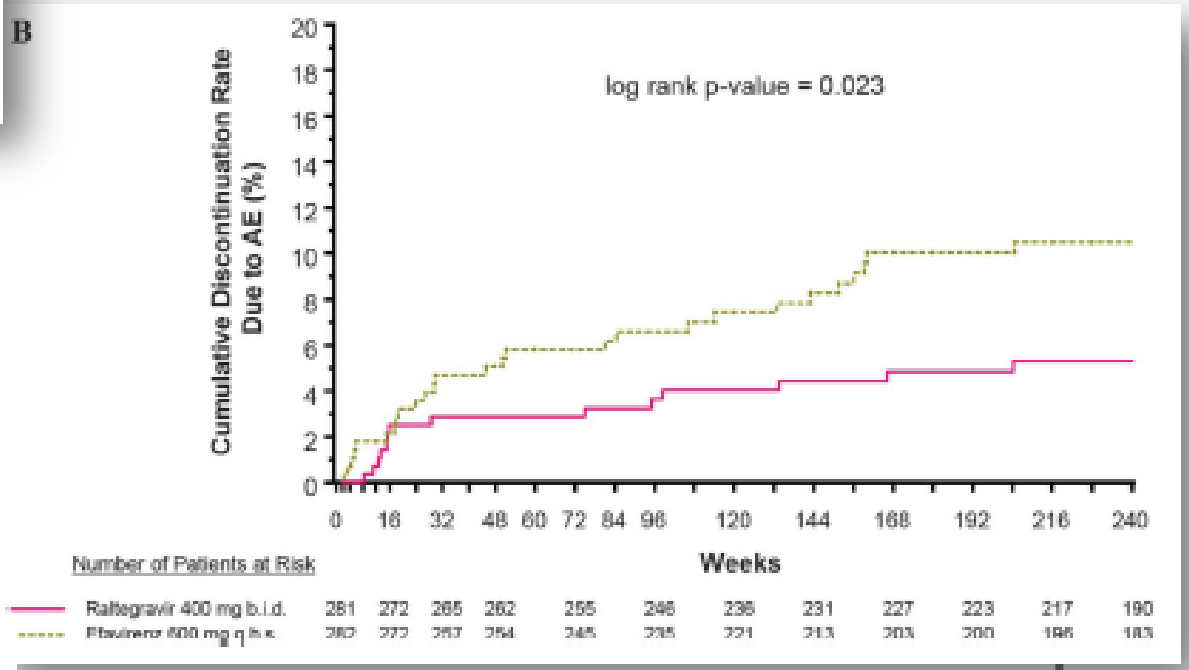


(Rockstroh JK et al., J AIDS 2013)

TABLE 3. Number (%) of Patients With Specific Drug-Related Clinical Adverse Experiences Reported in ≥5% of Either Treatment Group

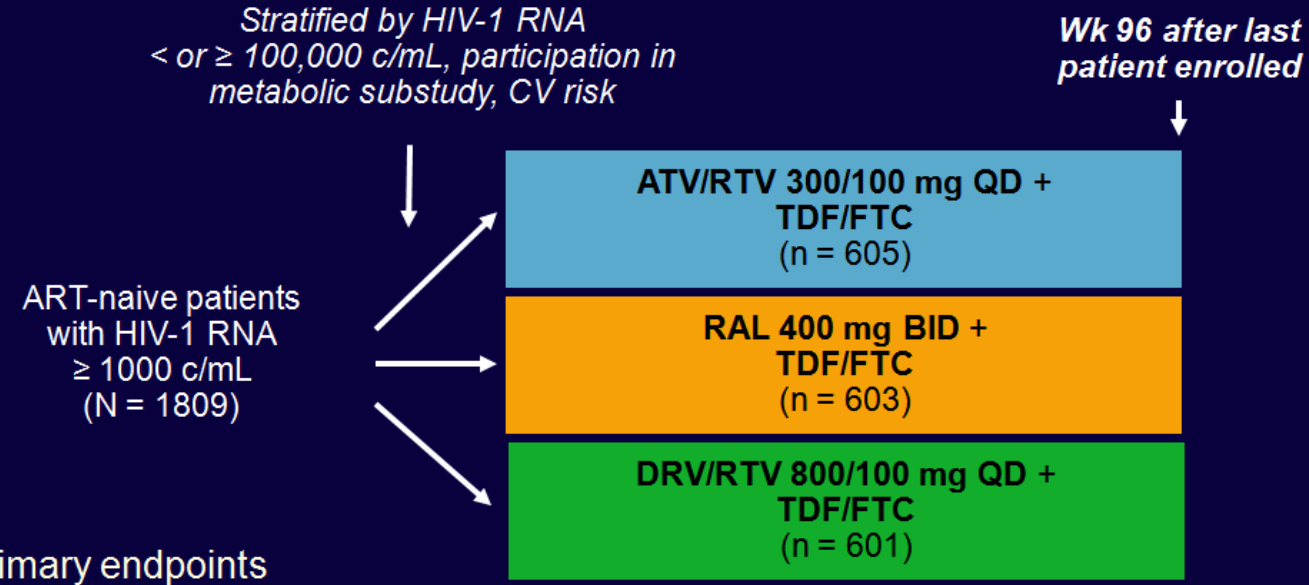
	Raltegravir Group (N = 281) n (%)	Efavirenz Group (N = 282) n (%)
Gastrointestinal disorders	61 (21.7)	83 (29.4)
Diarrhea	15 (5.3)	28 (9.9)
Flatulence	10 (3.6)	14 (5.0)
Nausea	25 (8.9)	31 (11.0)
General disorders	28 (10.0)	47 (16.7)
Fatigue	12 (4.3)	25 (8.9)
Nervous system disorders	52 (18.5)	140 (49.6)
Dizziness	22 (7.8)	99 (35.1)
Headache	26 (9.3)	40 (14.2)
Somnolence	3 (1.1)	21 (7.4)
Psychiatric disorders	52 (18.5)	87 (30.9)
Abnormal dreams	19 (6.8)	37 (13.1)
Insomnia	21 (7.5)	23 (8.2)
Nightmare	8 (2.8)	15 (5.3)
Skin and subcutaneous tissue disorders	17 (6.0)	63 (22.3)
Rash	3 (1.1)	23 (8.2)

- Virological and immunological outcomes significantly better with RTG at week 240
- RAL associated with
  - Fewer CNS adverse events (39.1% vs 64.2%; *P* < .001)
  - Fewer drug-related clinical adverse events (52.0% vs 80.1%; *P* < .001)
  - Fewer discontinuations due to adverse events (5% vs 9%)



(Rockstroh JK et al., J AIDS 2013)

ACTG 5257: Open-Label ATV/RTV vs RAL vs DRV/RTV in First-line ART

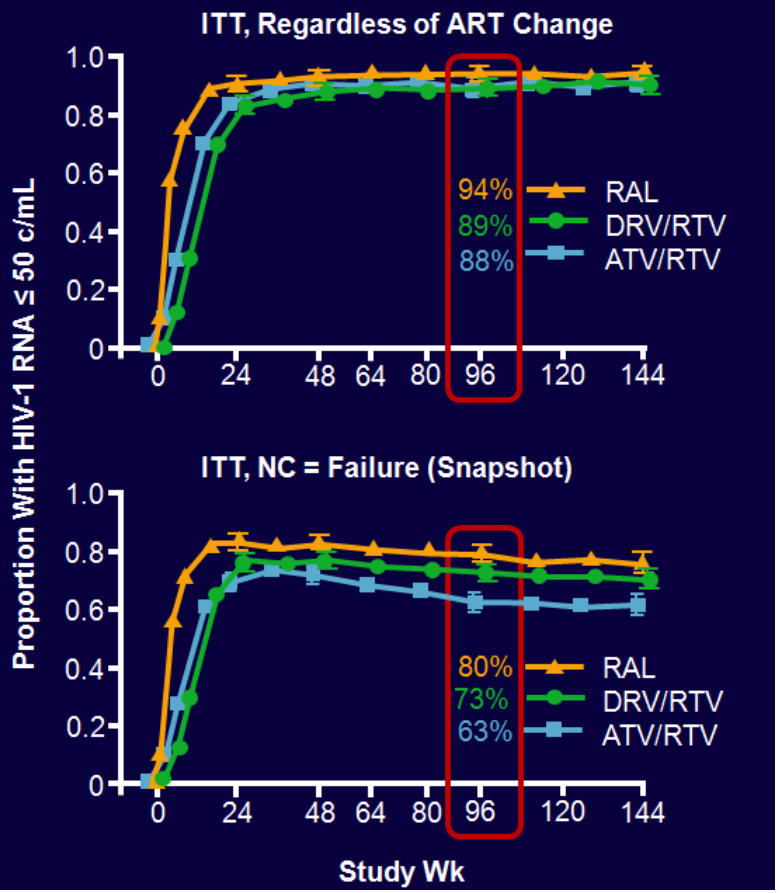


- Primary endpoints
  - **Virologic failure:** time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
  - **Tolerability failure:** time to discontinuation of randomized component for toxicity
- Composite endpoint: the earlier occurrence of either VF or TF in a given participant
- Switch of regimens allowed for tolerability

Landovitz R, et al. CROI 2014. Abstract 85.

ACTG 5257: Virologic Efficacy

- In ITT analysis with ART changes allowed (per protocol), regimens similar in virologic efficacy at Wk 96 and through Wk 144
- In ITT analysis when change = failure (Snapshot), RAL superior to both boosted PIs at Wk 96 and DRV/RTV superior to ATV/RTV at Wks 96 and 144
- Similar mean change in CD4+ count across arms
  - ATV/RTV (+284); RAL (+288) DRV/RTV (+256) cells/mm^3



Landovitz R, et al. CROI 2014. Abstract 85.
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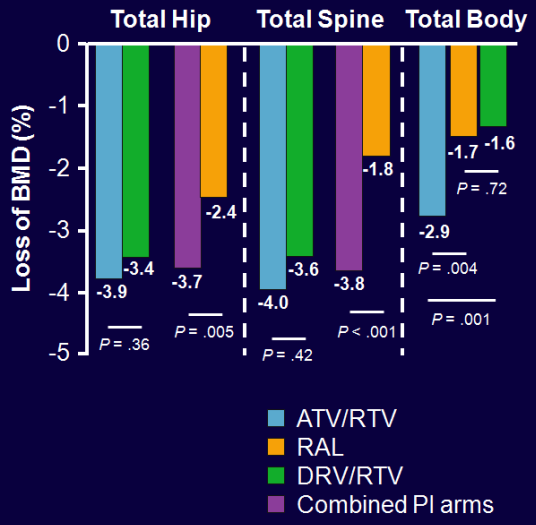
ACTG 5257: Resistance and Lipids

- VF with drug resistance occurred more often in pts initially assigned to RAL[1]
  - 3% of those randomized to RAL had ≥ 1 resistance mutation and 1.8% had INSTI mutations
  - 1.5% randomized to ATV/RTV and < 1% randomized to DRV/RTV developed resistance
  - No major PI mutations observed
- PI-containing regimens associated with significantly greater increases in TC, LDL-C, TGs vs RAL at Wk 96[2]
  - Lipids remained stable or decreased in RAL arm
  - Lipids changes in boosted PI arms similar

1. Landovitz R, et al. CROI 2014. Abstract 85. 2. Ofotokun I, et al. CROI 201

ACTG 5257: Loss of BMD With First-line Boosted PI vs RAL

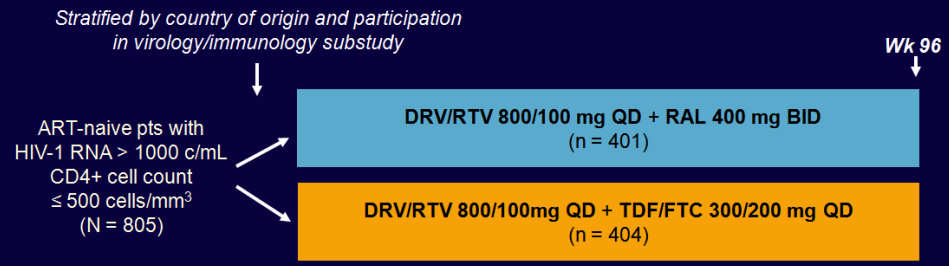
- All arms associated with significant loss of BMD through Wk 96 ($P < .001$)
- Total body BMD loss significantly greater with ATV/RTV than either DRV/RTV or RAL
- At hip and spine, similar loss of BMD in the PI arms
  - Significantly greater loss in the combined PI arms than in the RAL arm



Brown T, et al. CROI 2014. Abstract 779LB. Reproduced with permission.

NEAT-001/ANRS 143: DRV/RTV + RAL vs DRV/RTV + TDF/FTC in Naive Pts

- Randomized, open-label phase III study

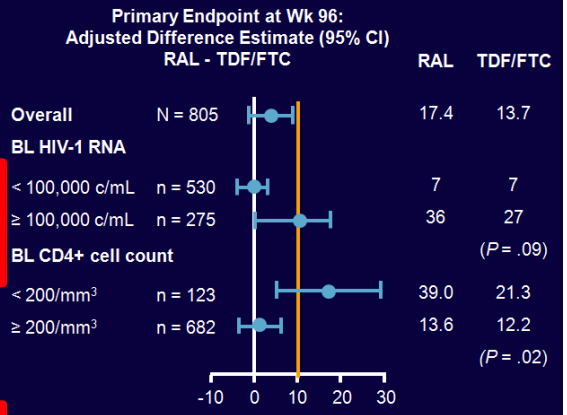


- Primary endpoint
  - Virologic: change of treatment before Wk 32 because of insufficient response or HIV-1 RNA ≥ 50 c/mL at Wk 32 or beyond
  - Clinical: death, any new AIDS-defining event, any new non-AIDS event

Raffi F, et al. CROI 2014. Abstract 84LB.

NEAT: RAL + DRV/RTV Noninferior to TDF/FTC + DRV/RTV at 96 Weeks

- Overall, regimens noninferior by % reaching composite primary endpoint of 6 virologic and clinical endpoints at Wk 96
  - RAL: 17.4%; TDF/FTC: 13.7%
  - Inferior response in pts with BL CD4 < 200 and a trend toward more primary endpoints in pts with BL VL ≥ 100K.
- Similar numbers of pts with PDVF (RAL: n = 66; TDF/FTC: n = 52)
- No pts with resistance in TDF/FTC arm vs 5 with integrase mutations and 1 with K65R in RAL arm



- Significantly greater mean increases in fasting lipids in RAL arm

Raffi F, et al. CROI 2014. Abstract 84LB. Reproduced with permission.

Pharmacokinetic Study of Dual Therapy With Raltegravir 400 mg Twice Daily and Darunavir/Ritonavir 800/100 mg Once Daily in HIV-1–Infected Patients

- Pilot, open-lable, fixed-sequence, prospective, single-arm PK study
- Switch to RTG + DRV/rtv (800/100 mg daily)
- 15 patients

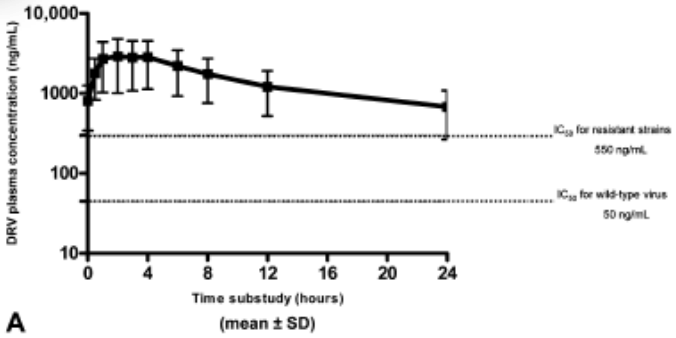


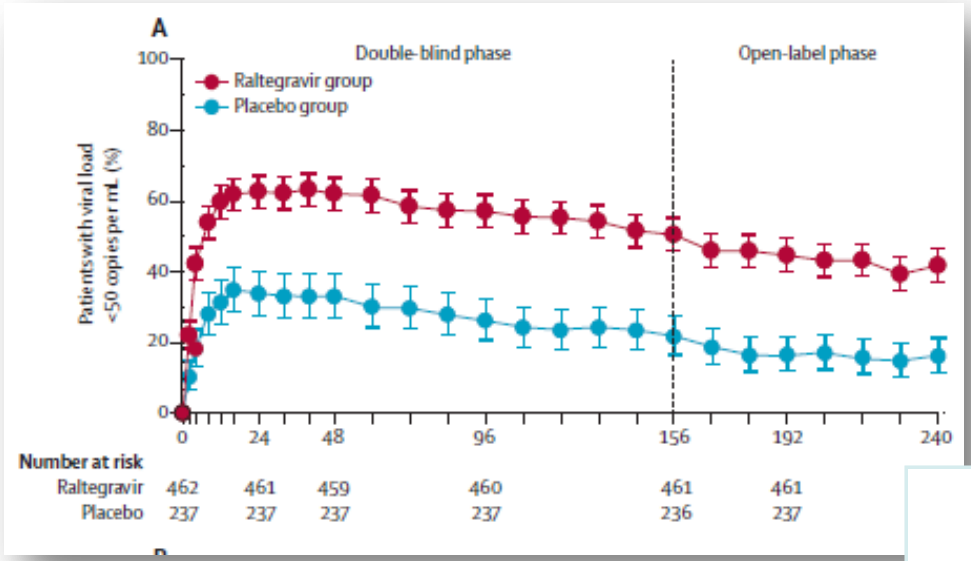
TABLE 2. Pharmacokinetic parameters

Parameters	Darunavir	Raltegravir	Ritonavir
C_{trough}, ng/mL	1330 (1110–1760)	40 (30–80)	90 (70–140)
C_{max}, ng/mL	7630 (6740–9000)	970 (840–2270)	490 (410–630)
AUC, $ng \cdot hm^{-1} \cdot L^{-1}$	68,730 (58,970–86,480)	3050 (2530–5180)	5470 (4500–7420)
$t_{1/2}$, h	10.91 (9.20–13.99)	2.68 (1.97–4.40)	9.48 (8.15–11.63)

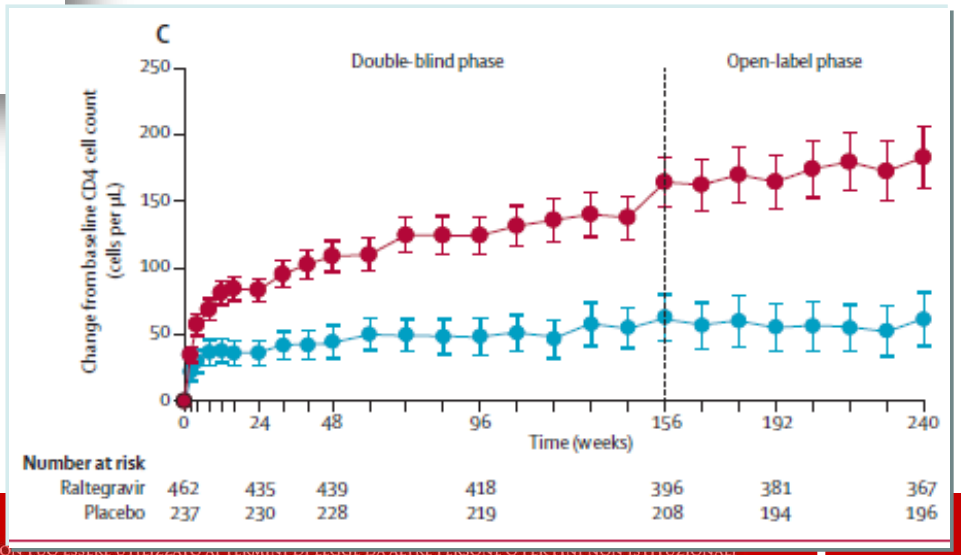
All values are represented as geometric mean.

(Martinez-Rebollar M et al., Ther Drug Monit 2013)

Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials



- BENCHMRK-1 and BENCHMRK-2 studies
- Randomized, double-blind, placebo-controlled phase III trials
- 699 patients naive to INSTIs and resistant to NRTIs, NNRTIs and PIs
- OBT + RTG or placebo
- 5-year follow-up



(Eron JJ et al., Lancet Infect Dis 2013)

TRIO Study (ANRS 139): RAL + ETR + DRV/RTV in Treatment-Experienced Pts

- Multicenter phase II study of DRV/RTV + ETR + RAL (N = 103); addition of NRTIs, ENF at discretion of physician
  - Inclusion criteria: susceptibility to DRV and ETR based on ≤ 3 DRV and ≤ 3 ETR RAMs, respectively
  - 59% of pts had < 1 active agent in OBR, as assessed by GSS
- 86% of pts reached HIV-1 RNA < 50 c/mL at Wk 48 (95% CI: 79% to 93%)[1]
- Of 100 pts entering extension trial through Wk 96, 88% achieved HIV-1 RNA < 50 c/mL (95% CI: 82% to 94%)[2]
- Median CD4+ cell count change: +150 cells/mm^3
- 4 tx-related grade 3/4 AEs reported before Wk 48: recurrent epidermal necrolysis (n = 1) (study d/c); nephrolithiasis (n = 1); lipodystrophia (n = 1); muscle spasm (n = 1)
- No further events between Wks 48 and 96

1. Yazdanpanah Y, et al Clin Infect Dis. 2009;49:1441-1449.
2. Fagard C, et al. Acquir Immune Defic Syndr. 2012;59:489-493.

Switching Virologically Suppressed Patients to RAL

- SWITCHMRK-1 and -2[1]
  - Switching to RAL inferior to remaining on LPV/RTV-based regimen in pts with HIV-1 RNA < 50 c/mL for > 3 mos, particularly among those with previous VF
  - TC, non–HDL-C, and TG improved in switch pts
- SPIRAL[2]
  - Switching from to RAL noninferior to remaining on boosted PI-based regimens through Wk 48 in pts with HIV-1 RNA < 50 c/mL for ≥ 6 mos
    - Switching to RAL significantly improved lipids and TC:HDL-C ratio
- EASIER/ANRS 138[3]
  - Switch from ENF to RAL regimens maintained virologic suppression through Wk 48 in patients with multidrug resistance and HIV-1 RNA < 400 c/mL for ≥ 3 mos

1. Eron J, et al. Lancet. 2010;375:396-407. 2. Martinez E, et al. AIDS. 2010;24:1697-1707.
3. Gallien S, et al. J Antimicrob Chemother. 2011;66:2099-2106.

Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks*

(Open-label, pilot study; 37 patients; 48-week follow-up)

Table 2 Changes in bone mineral density and bone turnover markers

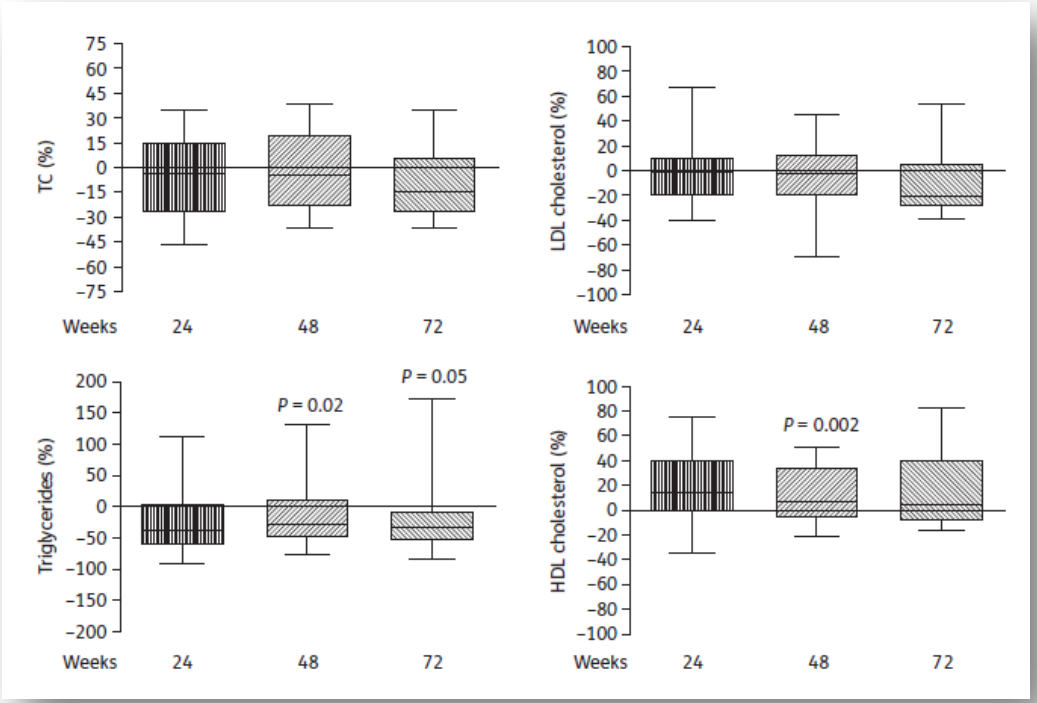
Parameter	Baseline Mean (SD)	Week 24 Mean % change (95% CI)	*P*	Week 48 Mean % change (95% CI)	*P*	*F*-value (ANOVA)	*P*
Bone mineral density (g/cm^2)							
Spine	1.06 (0.12)	1.5 (0.5, 2.5)	0.0038	3.0 (1.9, 4.0)	<0.0001	19.41	<0.001
Left hip							
Total hip	0.94 (0.09)	1.4 (0.8, 2.0)	0.0001	2.5 (1.6, 3.3)	<0.0001	19.57	<0.001
Femoral neck	0.90 (0.08)	1.5 (0.3, 2.7)	0.0027	2.1 (0.9, 3.2)	0.0011	6.28	0.003
		Mean absolute change (95% CI)		Mean absolute change (95% CI)			
T-score							
Spine	−1.38 (1.01)	0.143 (0.054, 0.231)	0.0023	0.151 (0.061, 0.241)	0.0017	6.94	0.001
Left total hip	−1.32 (1.38)	0.097 (0.052, 0.143)	0.0001	0.106 (0.049, 0.163)	0.0006	8.65	<0.001
Fracture risk over 10 years (%)							
Major osteoporotic fracture	4.25 (1.53)	−0.06 (−0.34, 0.23)	ns	−0.04 (−0.29, 0.22)	ns	0.14	ns
Hip fracture	0.90 (0.73)	−0.12 (−0.24, 0.00)	ns	−0.12 (−0.25, 0.00)	0.045	3.24	0.043
Bone turnover markers							
Urinary N-telopeptide (nmol/mmol creatinine)	41.8 (26.5)	−10.3 (−16.5, −4.1)	0.0017	−12.9 (−18.8, −6.9)	0.0001	..	..
Osteocalcin (μg/L)	32.3 (12.4)	−7.2 [−9.6, −4.7]	<0.0001	−9.6 [−11.6, −7.5]	<0.0001	..	..
Bone alkaline phosphatase (U/L)	16.5 (5.9)	−4.4 [−4.7, −3.0]	<0.0001	−3.6 [−11.6, −2.5]	<0.0001	..	..

ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; ns, not significant ($P > 0.2$); SD, standard deviation.

(Bloch M et al., HIV Med 2014)

Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study

- Prospective, cohort study
- 25 virologically suppressed patients on NRTIs and PIs
- Switch to RTG + ETV
- 48-week follow-up
- **Efficacy: 84% (ITT) and 93% (PP)**



(Monteiro P et al., J Antimicrob Chemother 2014)

No Effect of Raltegravir Intensification on Viral Replication Markers in the Blood of HIV-1–Infected Patients Receiving Antiretroviral Therapy

(Randomized, placebo-controlled study; 50 patients)

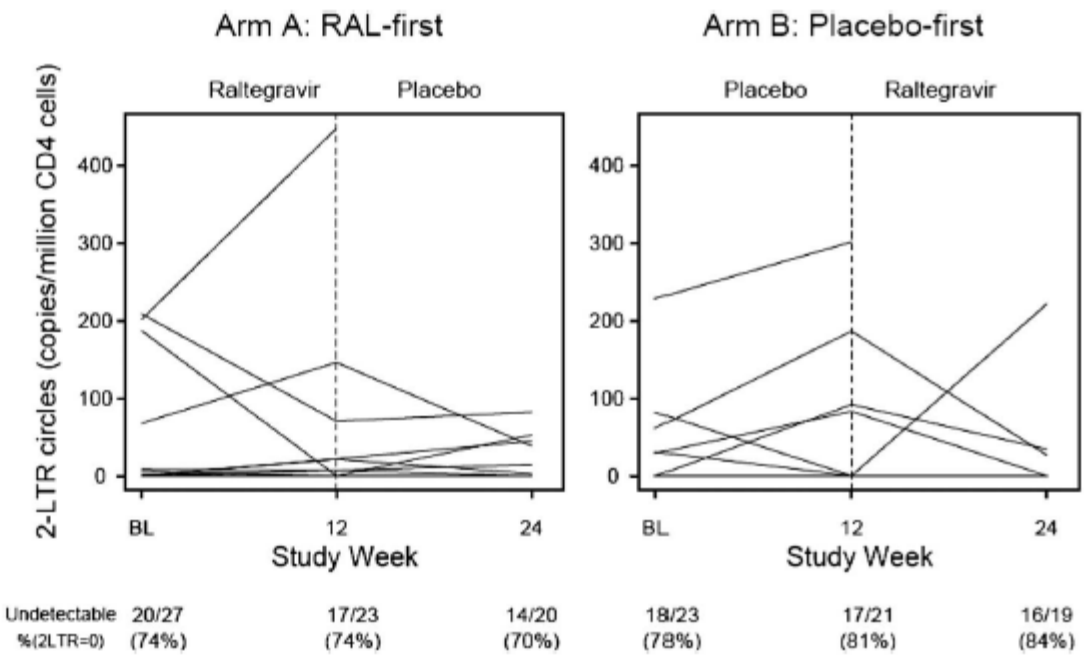
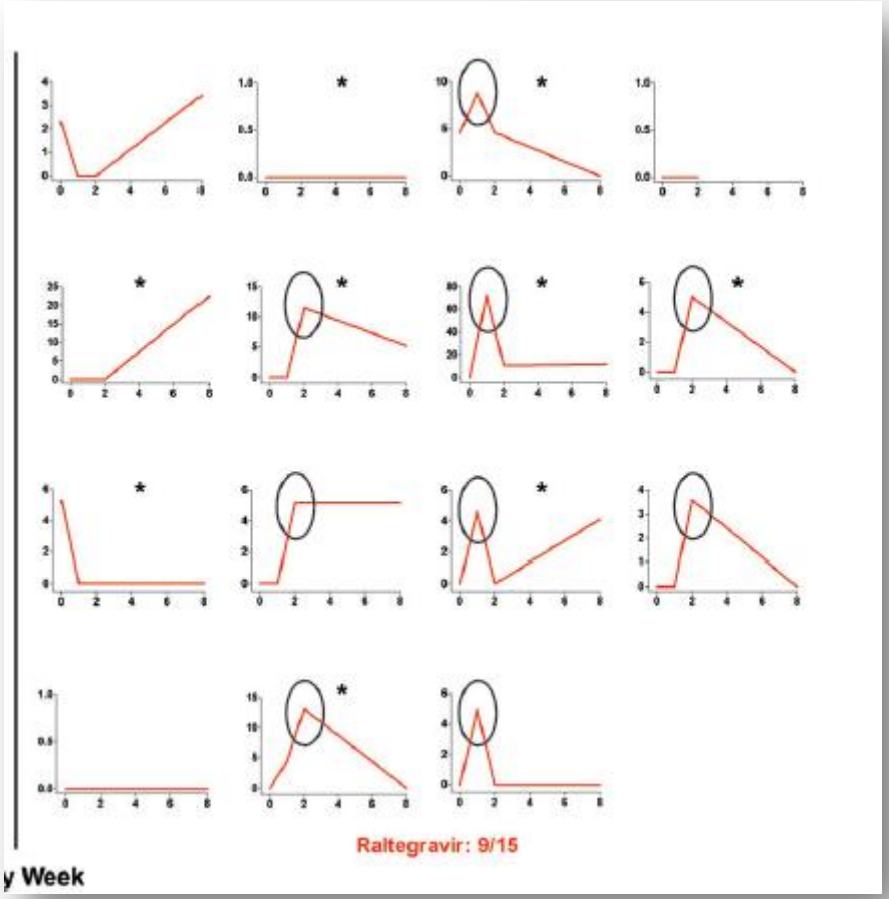


FIGURE 1. 2-LTR circles during raltegravir intensification. 2-LTR circles were measured at baseline, week 12, and week 24 in patients who received RAL first or placebo first; 12 weeks after initial treatment assignment, the 2 groups crossed over to the other treatment (Methods). BL, baseline; RAL, raltegravir.

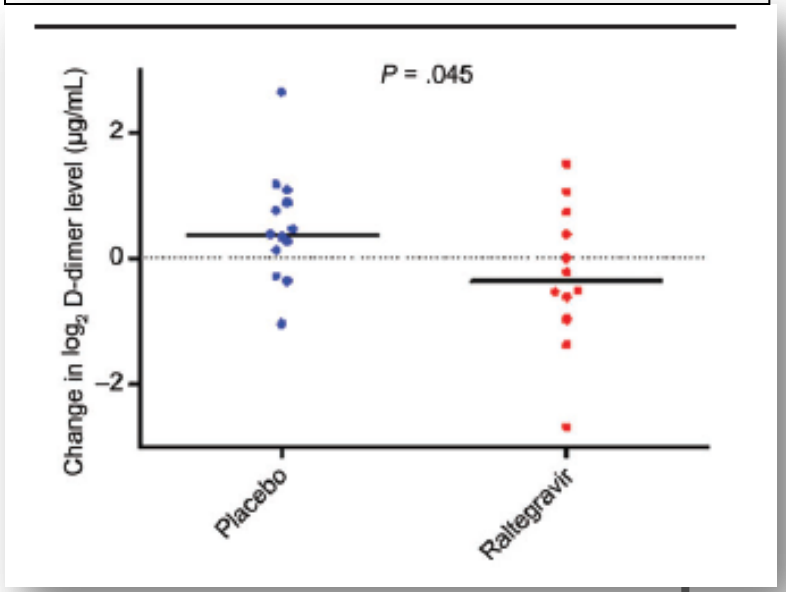
(Gandhi RT et al., J AIDS 2012)

Increase in 2–Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial



(Hatano H et al., J Infect Dis 2013)

- Randomized, double-blind, placebo-Controlled study
- 31 patients with ART-suppressed HIV RNA
- HAART + RTG or placebo



Raltegravir summary: advantages and disadvantages

Advantages

- Preferred INSTI owing to longest track record of safety and efficacy (approved in 2007)
- Great antiviral efficacy
- Noninferior or superior to EFV or PIs in initial therapy
- Fewer CNS adverse effects and metabolic alterations than EFV and PIs
- Few drug–drug interactions
- Integral part of many regimens in treatment-experienced pts
- Good option for dual NRTI-sparing regimens
- Conflicting data on efficacy in switch and intensification strategies

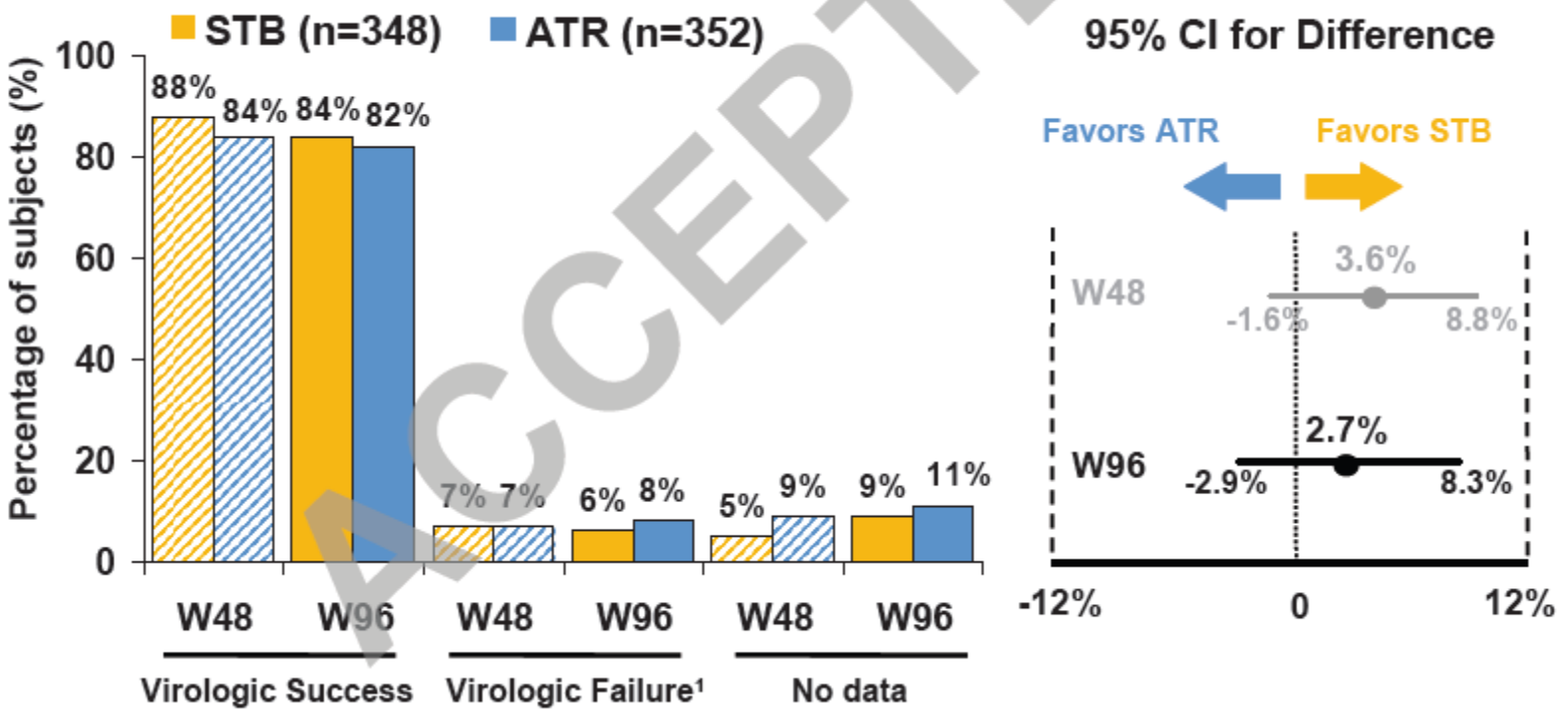
Disadvantages

- Twice-daily dosing
- No FDC available or planned
- Lower efficacy in naïve patients with poor immunological status
- Inferior to DTG in treatment-experienced patients
- Risk of resistance at VF, especially in treatment-experienced pts
- When VF failure occurs with resistance, 2-class resistance is common

Elvitegravir

A randomized, double-blind comparison of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir DF versus efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results

GS-236-0102 Study



(Zolopa A et al., J AIDS 2013)

A Randomized, Double-Blind Comparison of Single-Tablet Regimen Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir DF Versus Single-Tablet Regimen Efavirenz/ Emtricitabine/Tenofovir DF for Initial Treatment of HIV-1 Infection: Analysis of Week 144 Results

METHODS

A full description of the methods has been published.[1] A brief description is provided below.

Study Design and Patients

This study was conducted in North America and was approved by Institutional Review Boards at all sites. Participants were HIV-1–infected treatment-naive adults aged ≥18 years with HIV-1 RNA of ≥5000 copies per milliliter. An estimated glomerular filtration rate of ≥70 mL/min and susceptibility of the virus to EFV, FTC, and TDF by genotype were required. Eligible patients were randomized (1:1) to receive either EVG/COBI/FTC/TDF (150/150/200/300 mg) or EFV/FTC/

sample (Monogram Biosciences, South San Francisco, CA). Study drug could be continued at the investigator's discretion, if no resistance was detected. Adherence was assessed by pill count at every visit except week 2 visit.

Statistical Analysis

The primary end point was the proportion in the intention-to-treat population with HIV-1 RNA of <50 copies per milliliter at week 48 with a prespecified noninferiority margin of 12% per FDA-defined snapshot analysis.[1] The difference, weighted by baseline HIV-1 RNA stratum, for response rate and its 95% confidence interval (CI) were calculated based on stratum-adjusted Mantel–Haenszel proportions. The snap-

(Wohl DA et al., J AIDS 2014)

A Randomized, Double-blind Comparison of Single-Tablet Regimen Elvitegravir/Cobicistat/ Emtricitabine/ Tenofovir DF vs Ritonavir-Boosted Atazanavir Plus Emtricitabine/ Tenofovir DF for Initial Treatment of HIV-1 Infection: Analysis of Week 144 Results

Thailand and was approved by institutional review boards at all sites. Participants were HIV-1–infected, treatment-naive adults ≥18 years with HIV-1 RNA ≥5000 copies per milliliter. An estimated glomerular filtration rate ≥70 mL/min and susceptibility of the virus to atazanavir (ATV), FTC, and TDF by screening genotype were required. Eligible patients were randomized (1:1) to receive EVG/COBI/FTC/TDF (150/150/200/300 mg) or ATV (300 mg) plus RTV (100 mg) plus FTC/TDF (200/300 mg), once daily orally with food with matching placebo.

After week 48, study visits occurred every 12 weeks until week 144. The resistance analysis population consisted of patients taking study drugs who had confirmed virologic failure of <1 $\log_{10}$ reduction from baseline and ≥50 copies per milliliter of HIV-1 RNA by week 8 and confirmed at the next visit, or at any visit, a virologic

to-treat population with HIV-1 RNA <50 copies per milliliter at week 48 with a prespecified noninferiority margin of 12% as per Food and Drug Administration–defined snapshot analysis.[3] The difference, weighted by baseline HIV-1 RNA stratum, for response rate and its 95% confidence interval (CI) were calculated based on the stratum-adjusted Mantel–Haenszel proportions. The snapshot analysis was also conducted on subgroups. Other end points were HIV-1 RNA <50 copies per milliliter at week 144 when treating missing as failure and change in CD4 cell count from baseline. Proximal renal tubulopathy (PRT) events were identified through investigator-reported adverse event (AE) and/or renal laboratory parameters (increases serum creatinine, hypophosphatemia, proteinuria, or normoglycemic glycosuria). In a subset of patients, dual energy x-ray absorptiometry scans of the spine and hip were

(Clumeck N et al., J AIDS 2014)

Cobicistat Renal Safety

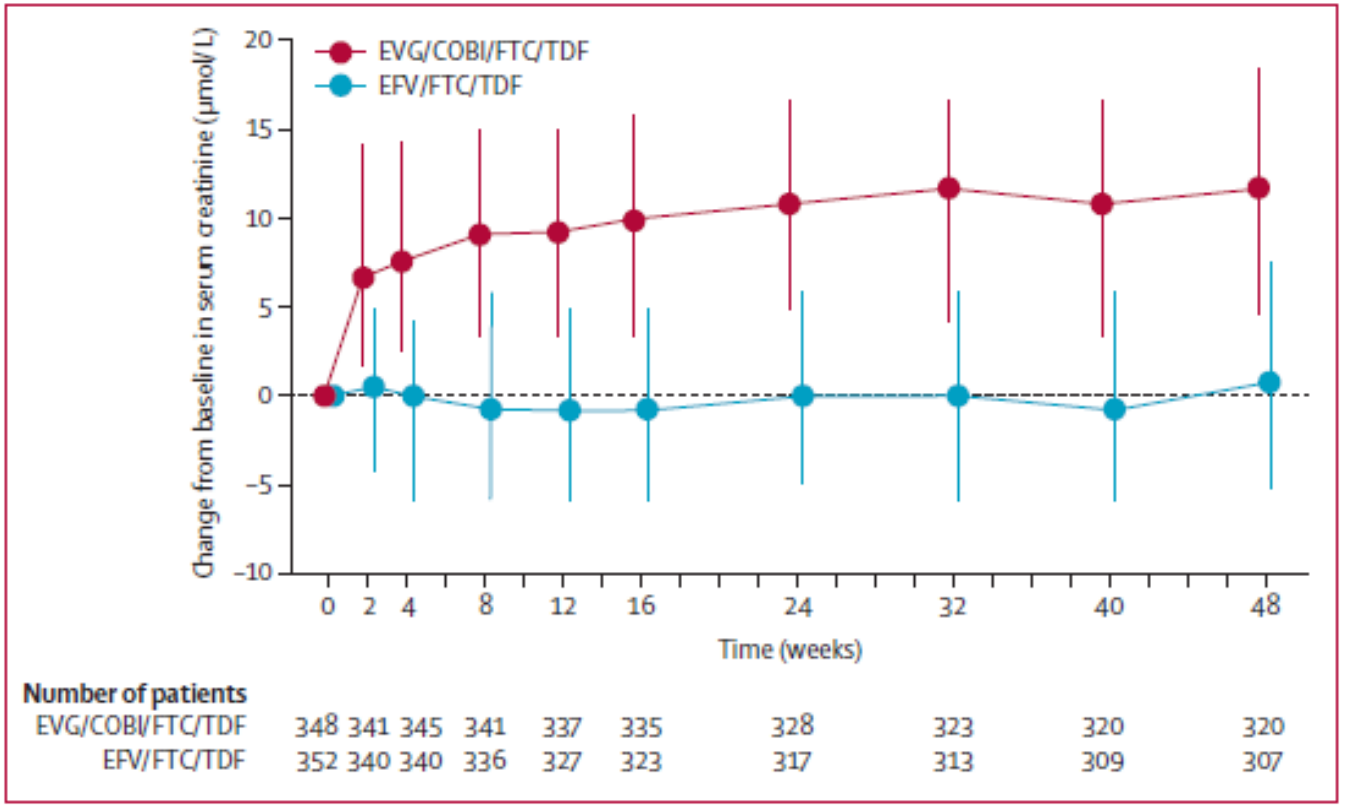
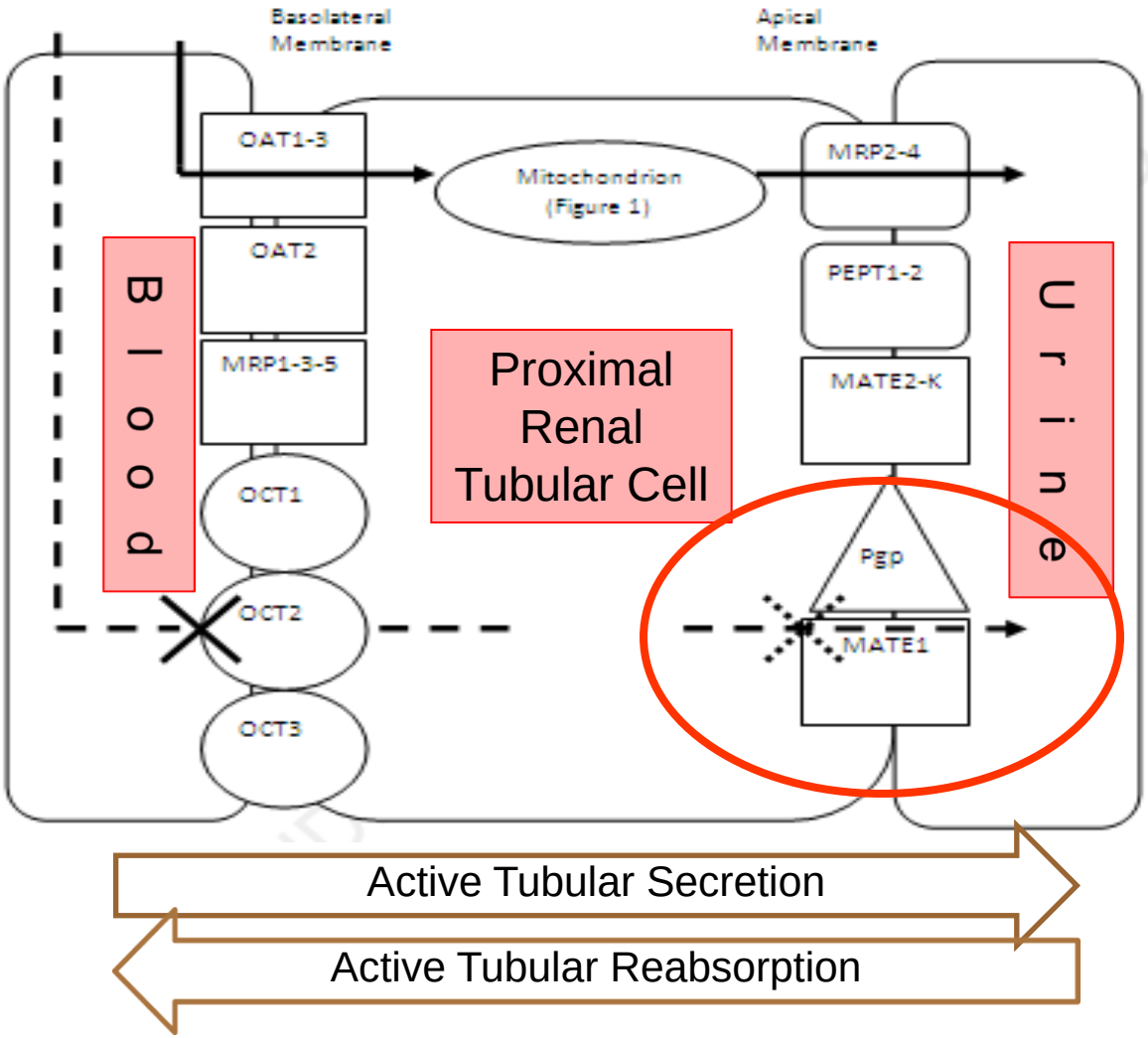


***Figure 5*: Change of serum creatinine concentration from baseline**
Bars are IQR. Data are for the safety population.

(Sax P et al. Lancet 2012)

Renal Tubular Transporters



MATE-1, multidrug and toxin extrusion transporter-1

COB inhibition

Creatinine

OCT2:	Cimetidine
	Trimethoprim
	Quinidine
	Dolutegravir
OAT1-3:	Probenecid
PGP:	Quinidine
MATE-1:	Cimetidine
	Chloroquine
	Cobicistat

Urinary Creatinine is secreted by tubule at approximately 10% of total amount

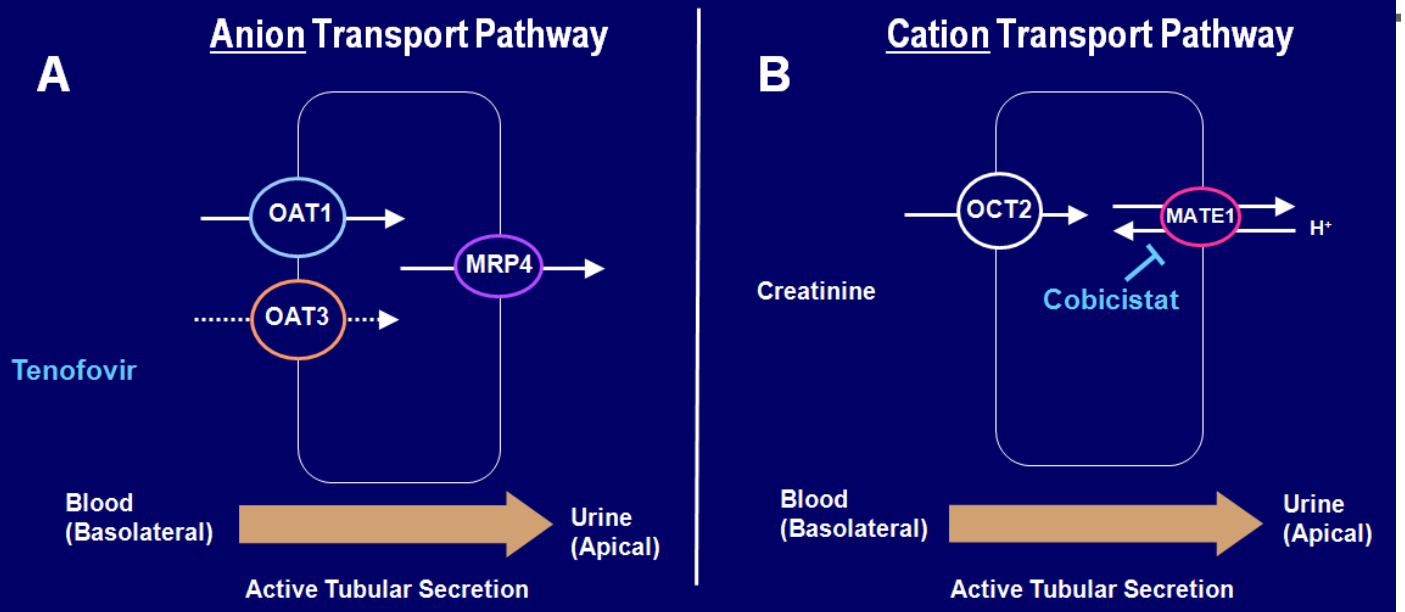
Creatinine is an endogenous substrate of OCT2 (uptake in tubule cells)[1]

Creatinine efflux in urine seems mediated by MATE1 and MATE2-K[2]

1.Urakami Yet al., Pharm Res 2004;21(6):976-981; 2. Imamura Y et al., Clin. Pharmacol. Ther 2001;89:81-88

COBI's Effect On Creatinine Tubular Secretion

Distinct Renal Tubular Transport Pathways of TFV and Creatinine



(A) The active tubular secretion of tenofovir is mediated by organic anion pathway (OATs and MRP4).

(B) Cobicistat interacts with organic cation pathway involved in the active secretion of creatinine (MATE1)

Stray KM, et al. ICAAC 2012; San Francisco, CA. #H-892

Effect of Cobicistat on Actual GFR and CrCl in Healthy Subjects

Population

- Cohort 1: 36 healthy [CrCl ≥ 80 ml/min per 1.73 m^2] subjects given COBI or RTV or placebo for days 1-7
- Cohort 2: 18 mild-moderate renal function [CrCl 50-79 ml/min per 1.73 m^2] given COBI for days 1-7

Measurements

- eGFR $_{[CG, MDRD]}$ and aGFR [iohexole] at days 0, 7 and 14
- mGFR, SCr, BUN, sodium, phosphate

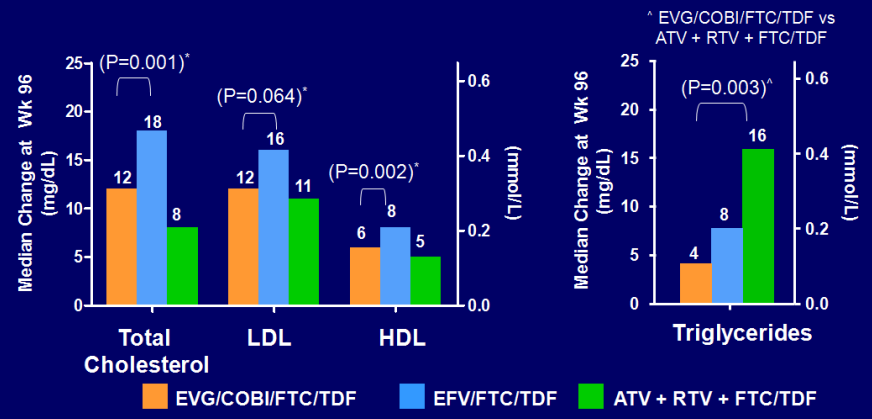
Results

- Cohort 1 showed statistical significant variations in SCr [increase - $p<.05$] and eGFR $_{CG}$ [-9,9 ml/min per 1.73 m^2 – $p<.05$] at day 7
- Cohort 2 showed statistical significant variations in SCr [increase - $p<.05$] and eGFR $_{CG}$ [-11,9 ml/min per 1.73 m^2 – $p<.05$] at day 7
- At day 14 the values were not different from day 0
- Both Cohorts didn't show any difference between days 7 an 0 when the aGFR method was used

(German P et al., J Acquir Immune Defic Syndr 2012)

Integrated Study 102 and 103 - Week 96

Change from Baseline in Fasting Lipids



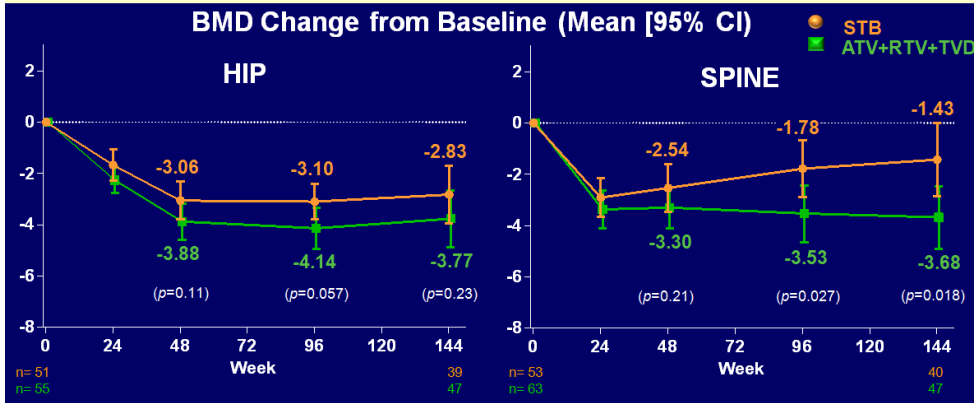
No difference in change in TC:HDL ratio at Week 48 or 96

* *P*-value for EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Zolopa A, et al. CROI 2013; Atlanta, GA. #553

Study 103 (STB vs. ATV+RTV+TVD) – Week 144

Changes in Bone Mineral Density



	STB (n=353)		ATV+RTV+TVD (n=355)	
	W96	W144	W96	W144
Fracture Events*, (n)	4 (1%)	+6 (+2%)	14 (4%)	+5 (+1%)

* Majority of fractures were due to traumatic injury, except 2 cases in ATV+RTV+TVD[2]

1. Clumeck N, et al. EACS 2013. Brussels, Belgium. #LBPS7/2 2. Data on file, Gilead Sciences, Inc.

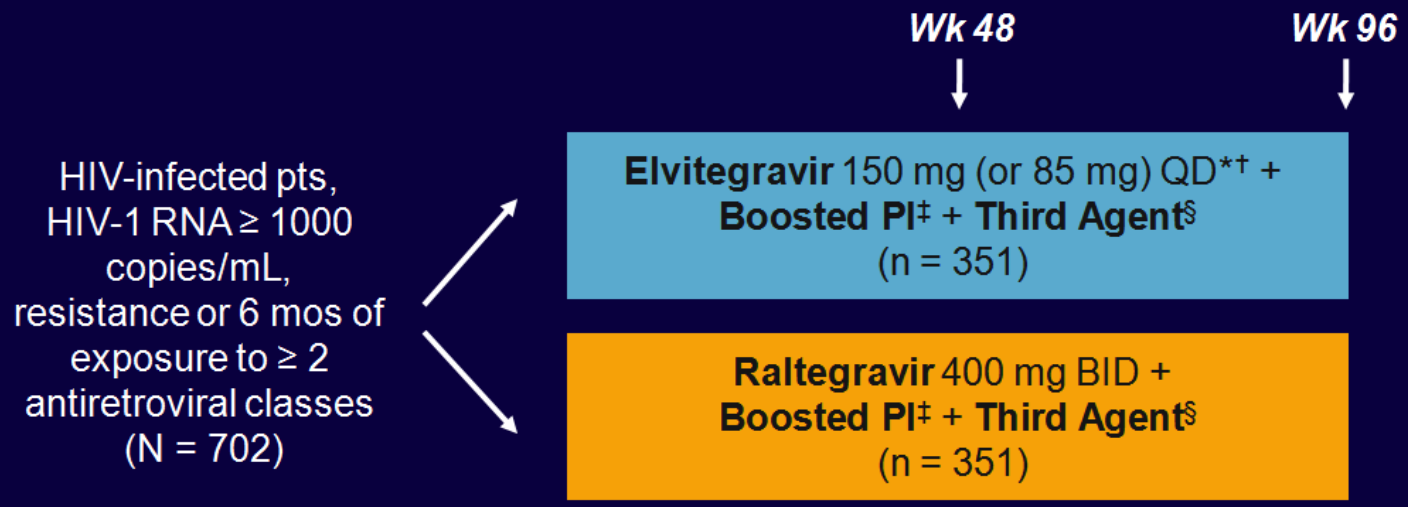
INSTI RAMs

Site-Directed Mutant Viruses	Fold Change in EC_{50} Values Relative to WT [a]				
	INSTI			NRTI	
	EVG	RAL	DTG	FTC	TFV
WT	1.0	1.0	1.0	1.0	1.0
T66A	7.6	0.9	0.3	0.8	1.0
T66I	9.7	0.9	0.3	0.8	1.0
T66K	40	8.0	1.7	1.0	0.8
E92G	9.0	1.5	1.0	1.1	1.1
E92Q	26	4.5	1.3	1.1	1.1
T97A	2.4	1.2	0.5	1.0	1.0
Y143C	1.1	3.4	0.8	1.1	1.0
Y143H	1.2	2.1	0.9	1.2	1.0
Y143R	2.1	18	1.3	1.1	1.1
S147G	4.1	1.1	1.0	1.2	1.1
Q148H	4.9	15	0.4	1.1	1.2
Q148K	94	37	1.5	1.1	1.0
Q148R	92	29	1.1	1.0	1.1
N155H	30	12	1.3	1.0	1.0

(Abram ME et al., Antimicrob Agents Chemother 2013)

Study 145: Elvitegravir vs Raltegravir in Treatment-Experienced Patients

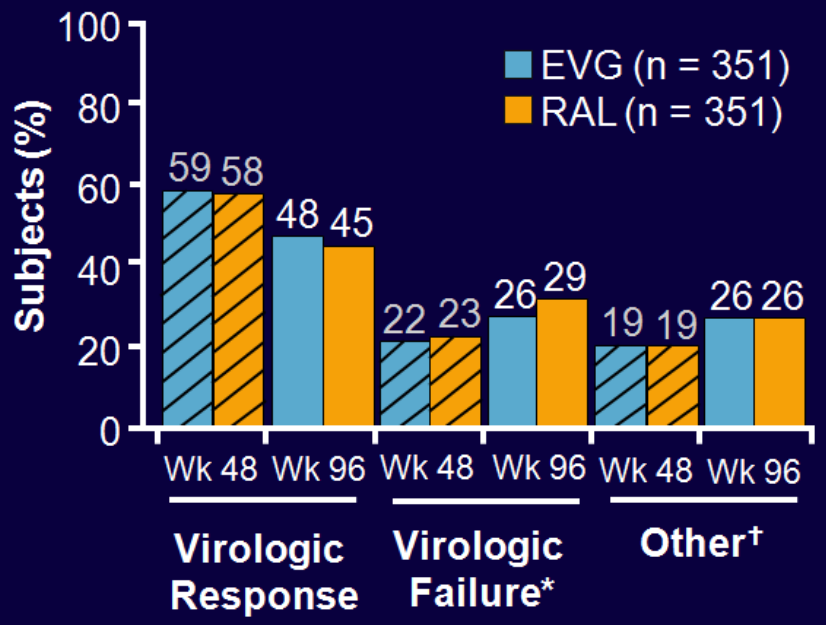
- Randomized, placebo-controlled phase III study



*EVG currently unavailable as single agent.
†EVG dose reduced to 85 mg QD for pts receiving ATV/RTV or LPV/RTV as part of background regimen.
‡Background regimen to include fully active RTV-boosted PI, selected using resistance testing.
§Selected from ENF, ETR, MVC, or NRTI. Option of also adding FTC or 3TC for pts with M184V/I.

Molina J, et al. Lancet Infect Dis. 2012;12:27-35.

Study 145: EVG Noninferior to RAL at Wks 48 and 96



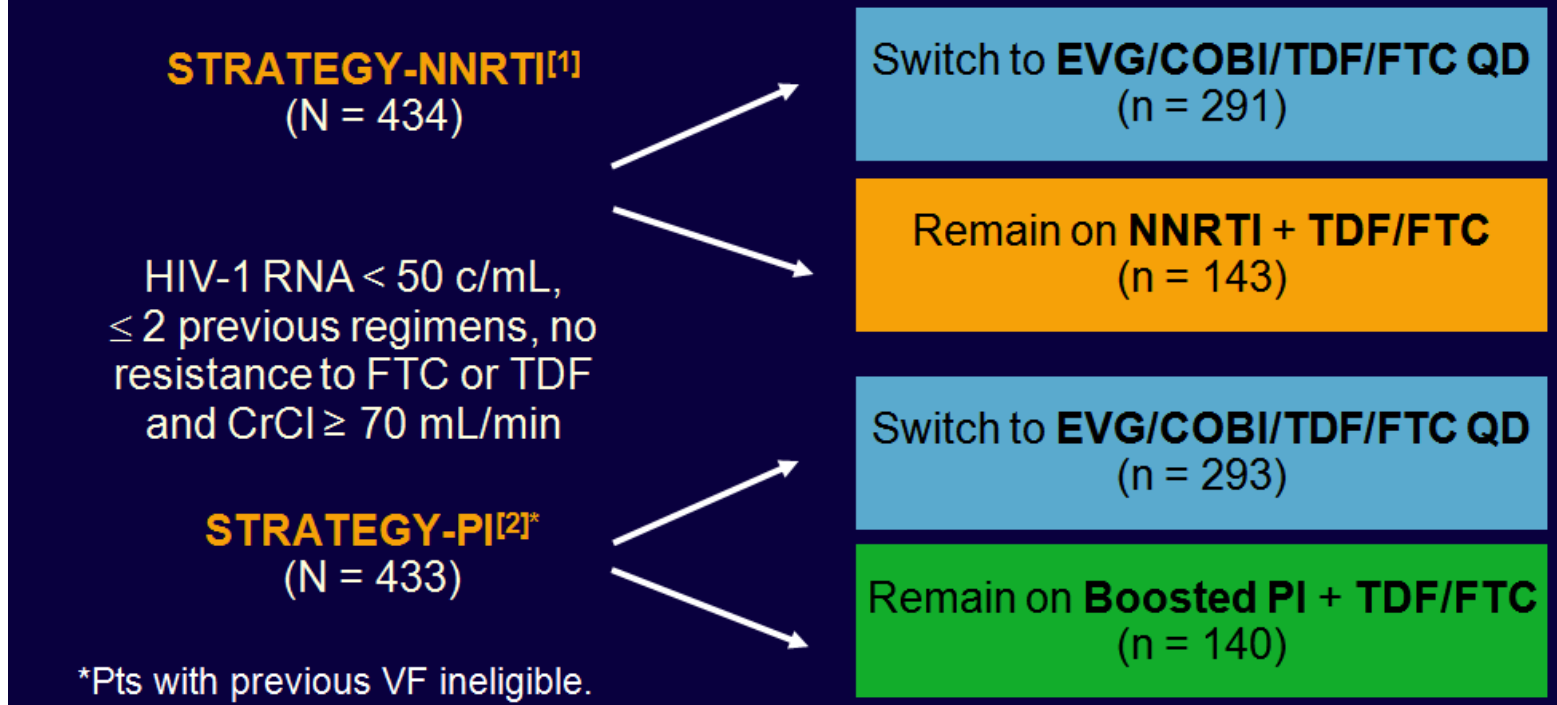
*VF includes never suppressed, rebound, switch of BR, and d/c due to lack of efficacy.
†Others include death, discontinuation due to AE, investigator's discretion, lost to follow-up, pregnancy, protocol violation, subject noncompliance, withdrawal of consent.

- Similar incidence of resistance at VF with EVG vs RAL
  - Integrase resistance: 6.6% vs 7.4%
  - OBR resistance: 7.4% vs 7.1%
- Both regimens well tolerated
  - Higher rates of diarrhea with EVG at Wks 48 and 96
  - Discontinuations: 3% vs 4%

Elion R, et al. J Acquir Immune Defic Syndr. 2013;63:494-497.

STRATEGY Trials: Switch to EVG/COBI/TDF/FTC in Suppressed Pts

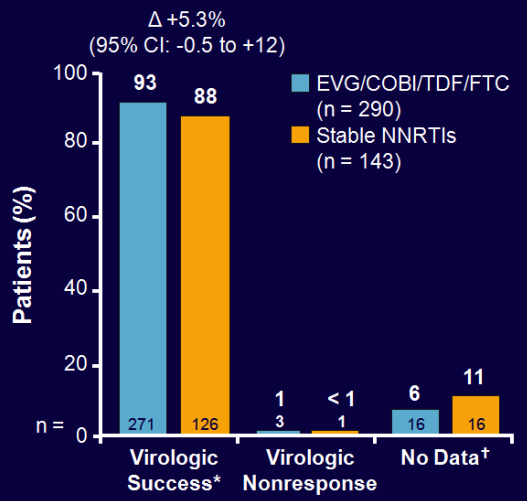
- Randomized, open-label switch studies in pts virologically suppressed on an NNRTI- or boosted PI–based regimen (both with TDF/FTC) for ≥ 6 mos
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



*Pts with previous VF ineligible.

1. Pozniak A, et al. CROI 2014. Abstract 553LB. 2. Arribas J, et al. CROI 2014. Abstract 551LB.

STRATEGY-NNRTI: Change to EVG/COBI Noninferior to Stable NNRTIs at Wk 48

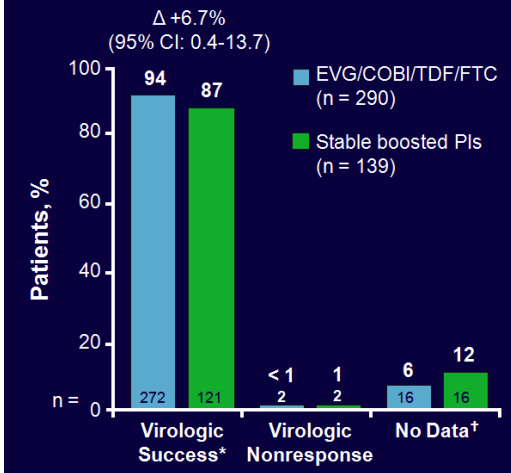


*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

- Regimens: EFV, 78%; NVP, 17%; RPV, 4%; ETR, < 1%; 74% on EFV/TDF/FTC; 91% on first regimen
- Results similar across all baseline virologic and demographic subgroups
- 3 pts with VF in EVG/COBI arm and 1 in NNRTI arm
  - No pts with resistance in either arm
- 5 in the switch arm and 1 in the NNRTI arm discontinued due to adverse event

Pozniak A, et al. CROI 2014. Abstract 553LB. Reproduced with permission.

STRATEGY-PI: Change to EVG/COBI Better Than Maintaining bPIs at Wk 48



*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

- Regimens: ATV, 40%; DRV, 40%; LPV, 17%; FPV, 3%; SQV, < 1%; 79% on first regimen
- Results similar across all baseline virologic and demographic subgroups
- 2 pts with VF in each arm but no pts with resistance in either arm
- 5 in the switch arm and 2 in the boosted PI arm discontinued due to adverse event
- Lipids in switch pts
  - ↓ TGs vs all bPIs
  - ↓ TC, TG, HDL-C vs LPV/RTV
  - ↑ HDL-C vs DRV/RTV

Arribas J, et al. CROI 2014. Abstract 551LB.

Study 123: RAL to STB Switch Week 48

Study Design

Phase 3b, Open-Label, Multicenter, 48-Week Study

Suppressed for ≥6 months on 1st ARV regimen
First ARV regimen RAL+TVD
Screening HIV-1 RNA <50 c/mL
No historical genotypic resistance
eGFR > 70 mL/min

RAL + TVD
Multi-Pill BID Regimen
N=48

→

STB
Single-Tablet Regimen

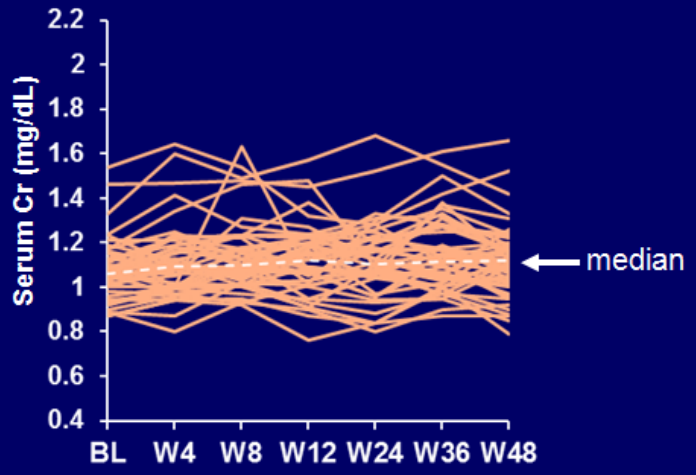
Wk 12 **Wk 24** **Wk 48**

Primary Endpoint: HIV-1 RNA <50 c/mL at Week 12

Secondary Endpoints: Efficacy and safety of STB over 24 and 48 weeks

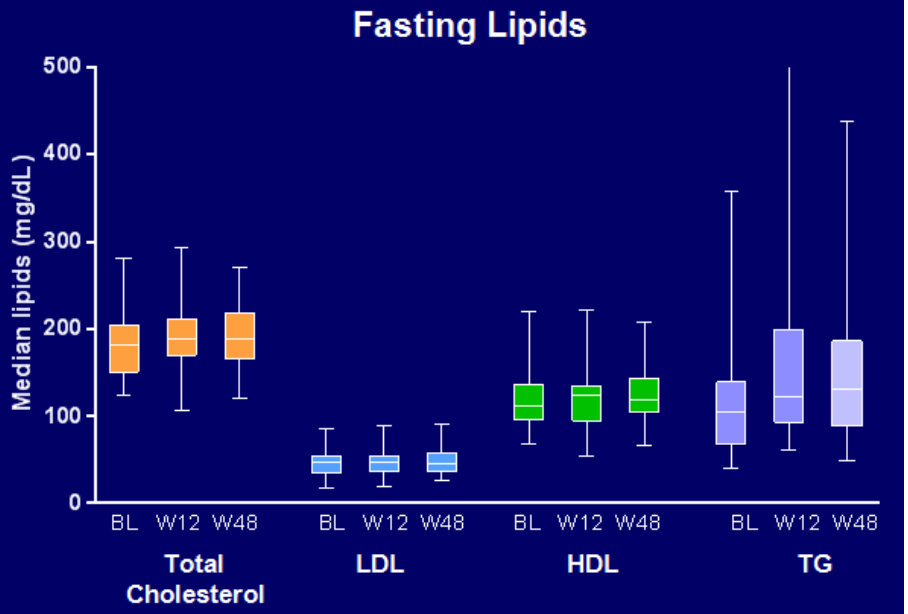
Study 123: RAL to STB Switch Week 48

Changes in Renal Function or Fasting Lipids



eGFR (mL/min) Median (min, max)	STB (N=48)
Baseline	105 (80, 170)
Week 4	102 (70,188)
Week 12	101 (75,171)
Week 24	102 (67,182)
Week 48	101 (67, 176)

eGFR = estimated GFR calculated by Cockcroft Gault formula



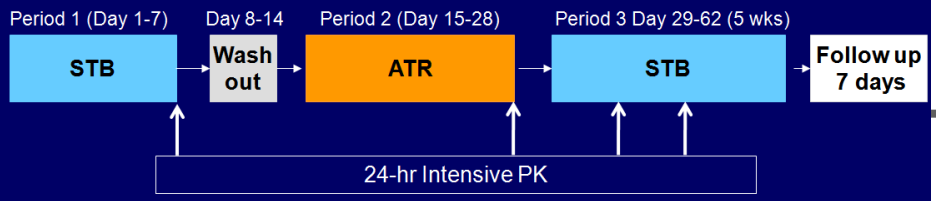
When simplifying from BID RAL+TVD to STB, all patients remained virologically suppressed and there were no clinically significant changes in

- **Serum Cr or eGFR**
- **TC, LDL, HDL or TGs**

Mills A, et al. EACS 2013; Brussels, Belgium. #PE7/5

Study 120: ATR to STB Switch PK Analysis
Study Design

Open-label, fixed-sequence, multiple-dose pharmacokinetic study
of HIV-1 negative patients (n = 32; 8 subjects CYP2B6 poor metabolizer genotype*)



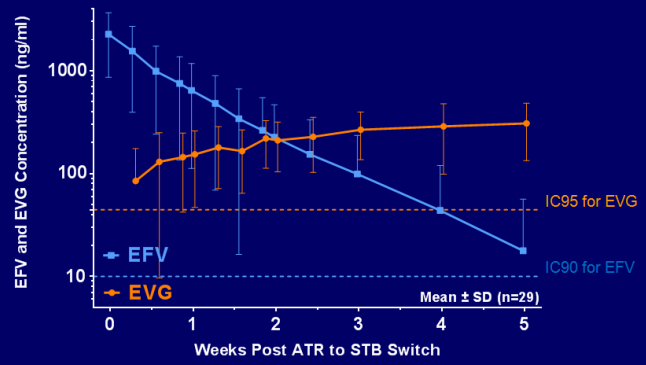
- **PK determinations for**
  - **EVG, EVG metabolites (GS-9200 glucuronide) and (GS-9202 oxidative), COBI, FTC, TFV and EFV**
- **Overlapping metabolic pathways**
  - **EFV: inducer of CYP3A and UGT**
  - **EVG: primarily metabolized by CYP3A and secondarily by UGT1A1/3**
  - **COBI: inhibitor of CYP3A**

STB = Stribild® = EVG/COBI/FTC/TDF
ATR = Atripla® = EFV/FTC/TDF

Cohen C, et al. ICAAC 2013. Denver, CO. #H-658

Study 120: ATR to STB Switch PK Analysis
EFV and EVG PK Post-Switch

Open-label, fixed-sequence, multiple-dose pharmacokinetic study
of HIV-1 negative patients (n = 32; 8 subjects CYP2B6 poor metabolizer genotype*)



- Following switch from ATR to STB, there were lower EVG exposures at Week 2 due to CYP3A and UGT induction by EFV
- EVG and/or EFV exposure at all times were associated with potent antiviral activity
- COBI exposures comparable and TFV, FTC PK unaffected (not shown)

Cohen C, et al. ICAAC 2013. Denver, CO. #H-658

Drugs contraindicated with Elvitegravir/Cobicistat

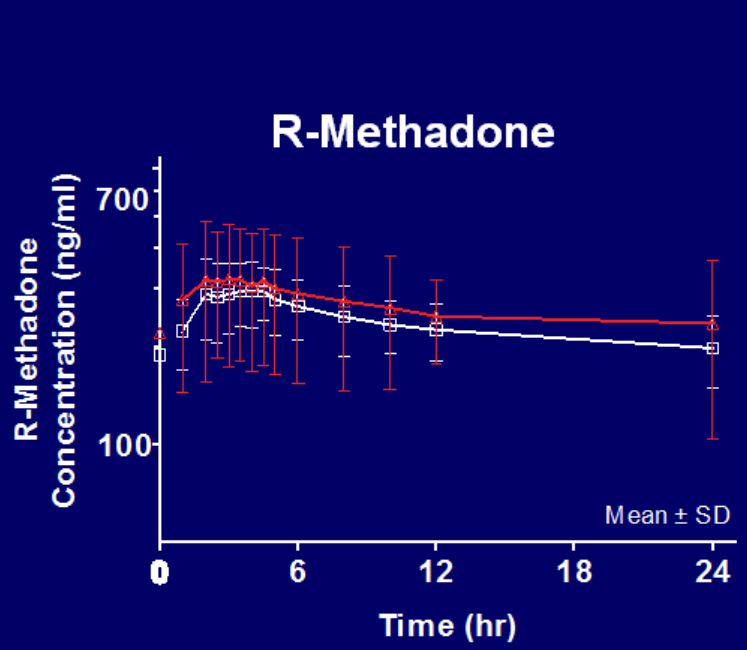
Drug Class	Drug Name
Alpha 1 adrenoceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone, Quinine
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoin*
Antimycobacterial	Rifampicin*
Ergot derivatives	Dihydroergotamine, Ergometrine, Ergotamine
GI motility agent	Cisapride
Herbal products	St John's wort (*Hypericum perforatum)**
HMG CoA reductase Inhibitors	Lovastatin, Simvastatin
Neuroleptic	Pimozide
PDE 5 Inhibitor	Sildenafil (for pulmonary arterial hypertension)
Sedative/hypnotics	Triazolam, oral midazolam

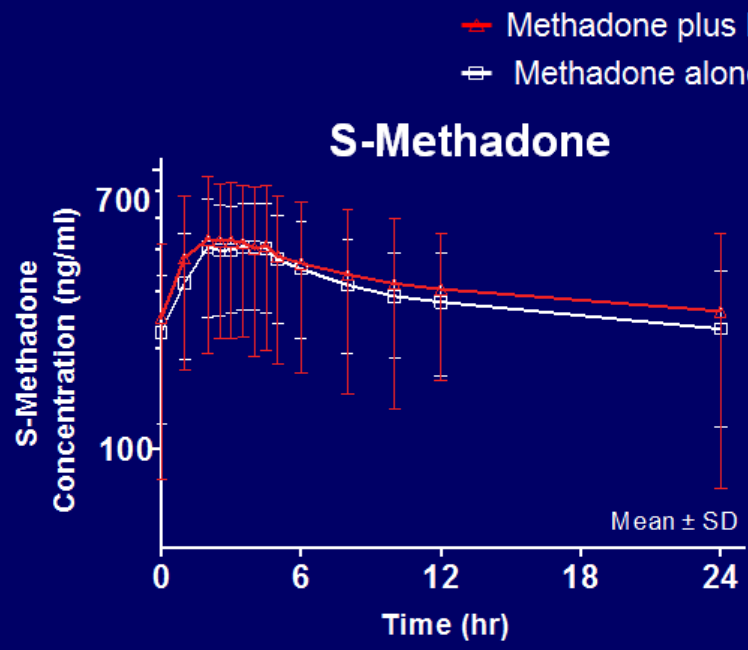
Please refer to the SPC for further interactions

1.Stribild SPC 2013

Methadone

EVG + COBI + Methadone





R-methadone (active enantiomer) PK unaffected by EVG + COBI co-administration, indicating lack of inductive effects of EVG/co on CYP2C19

S-methadone (inactive enantiomer) PK unaffected by EVG + COBI co-administration, indicating lack of inductive effects of EVG on CYP2B6

EVG/COBI/FTC/TDF is not expected to alter methadone plasma concentration after co-administration

Bruce R, et al. ICAAC 2012; San Francisco. A-1250 **Note that pharmacodynamic was unaffected thus no dose modification is necessary**

Elvitegravir summary: advantages and disadvantages

Advantages

- Only INSTI currently available as a 1-pill once-daily regimen
- Noninferior to EFV and ATV/RTV in initial therapy
- Maintains antiviral activity as well as comparators across HIV-1 RNA and CD4+ cell count strata
- Fewer adverse effects than EFV and ATV/RTV
- Appears to be effective switch regimen for patients on first-line RAL
- Noninferior to RAL in treatment-experienced patients

Disadvantages

- Not recommended for patients with eGFR < 70 mL/min
- Must be taken with food
- Cobicistat inhibits tubular secretion of creatinine, increasing Cr levels
- Risk of resistance at VF, especially in treatment-experienced patients
- When VF occurs with resistance, 2-class resistance is common
- Many COBI-related drug–drug interactions
- Currently only available in FDC, limiting regimen flexibility

…and the future

Dolutegravir

Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study

- Randomized, double-blind trial
- North America, Australia, Europe
- 822 naive patients
- DTG versus RTG + TDF/FTC or ABC/3TC

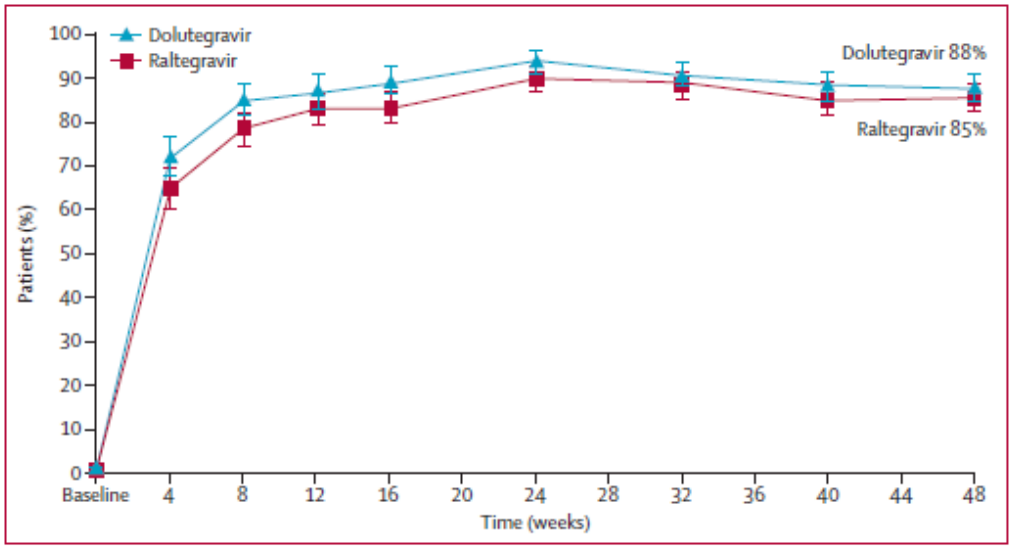


Figure 2: **Proportion of patients with HIV-1 RNA less than 50 copies per mL**
Error bars show 95% CIs.

(Raffi F et al., Lancet 2013)

Dolutegravir Renal Safety

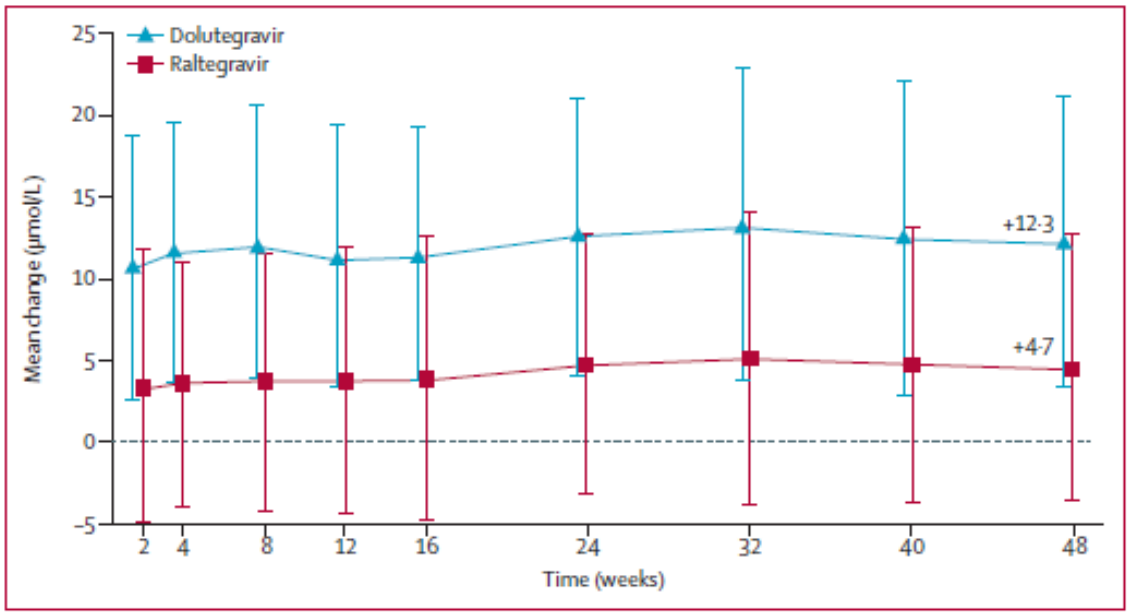
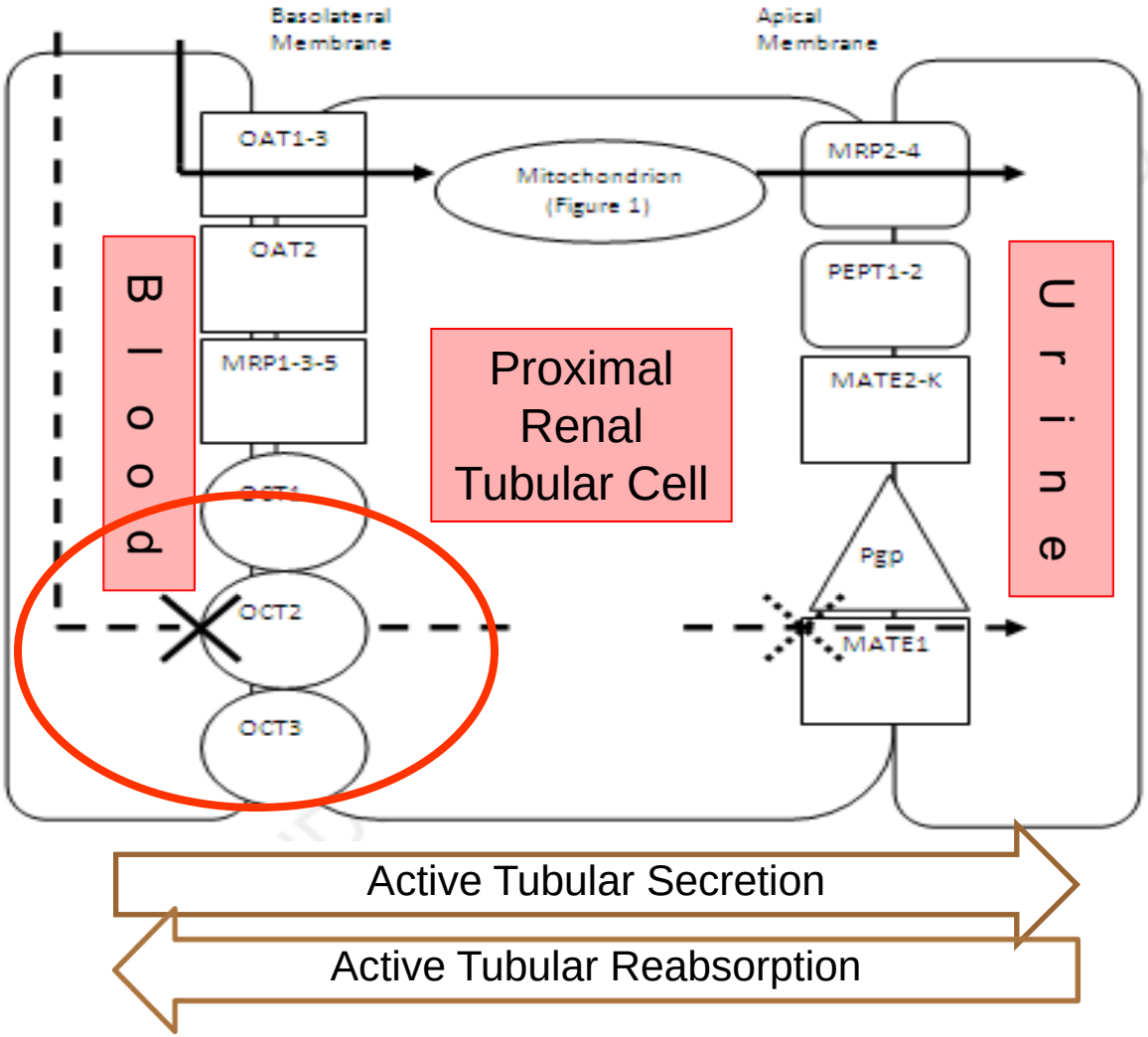


Figure 4: **Mean change from baseline in serum creatinine**
Error bars show SD.

(Raffi F et al., Lancet 2013)

Renal Tubular Transporters



OCT-2, organic cation transporter-2

DTG inhibition

Creatinine

OCT2:	Cimetidine
	Trimethoprim
	Quinidine
	Dolutegravir
OAT1-3:	Probenecid
PGP:	Quinidine
MATE-1:	Cimetidine
	Chloroquine
	Cobicistat

Urinary Creatinine is secreted by tubule at approximately 10% of total amount

Creatinine is an endogenous substrate of OCT2 (uptake in tubule cells)[1]

Creatinine efflux in urine seems mediated by MATE1 and MATE2-K[2]

Urakami Yet al., Pharm Res 2004;21(6):976-981; 2. Imamura Y et al., Clin. Pharmacol. Ther 2001;89:81-88

A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects

- Randomized trial in healthy [CrCl ≥ 80 ml/min per 1.73 m^2] subjects to assess DTG effect on CrCl and GFR
- Subjects (n = 38) received **DTG 50 mg** (**q24h** or **q12h**) or **placebo** for 14 days
  - Along with single infusions of iohexol and para-aminohippurate [PAH] on **Days -1, 7, 14**
  - *Iohexol allows for assessment of actual GFR*
  - *Para-aminohippurate allows for assessment of renal plasma flow*
  - 24 h CrCl, albumin, total protein, β2-microglobulin, NGA, RBP, cystatin-c were also measured

Table 3

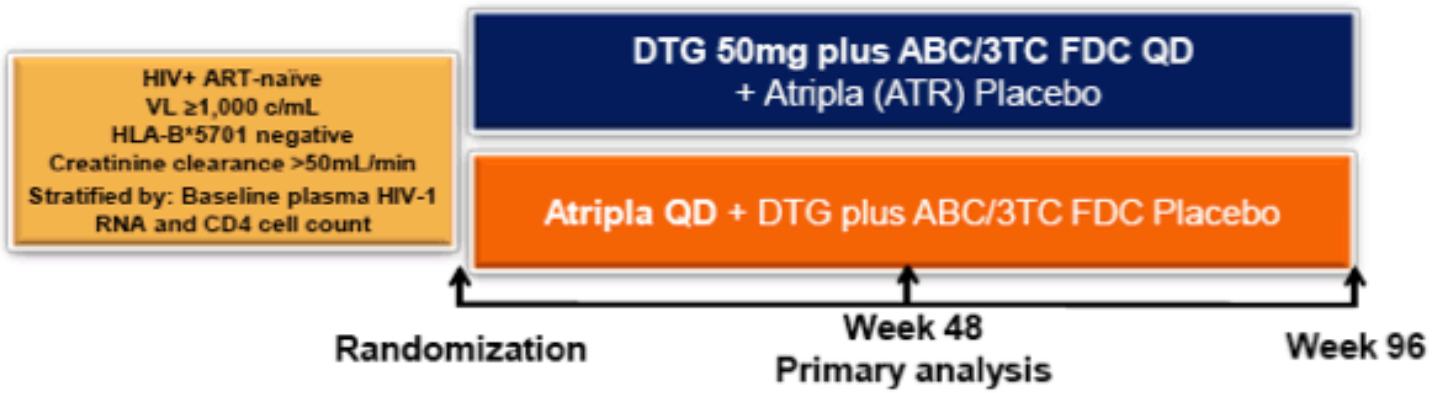
Placebo-adjusted comparison between day 14 and day –1 body surface area-normalized iohexol clearance, PAH clearance and creatinine clearance*

	Iohexol clearance	PAH clearance	Creatinine clearance
Day 14/Day –1 DTG 50 mg once daily to day 14/day –1 placebo	0.993 (0.915, 1.078)	1.029 (0.921, 1.150)	0.900 (0.808, 1.002)
Day 14/Day –1 DTG 50 mg twice daily to day 14/day –1 placebo	1.045 (0.963, 1.135)	0.969 (0.866, 1.083)	0.861 (0.772, 0.960)

DTG, dolutegravir; PAH, para-aminohippurate; *Data presented are geometric mean ratio (90% confidence interval).

(Koteff J et al., Br J Clin Pharmacol 2013)

Study Design

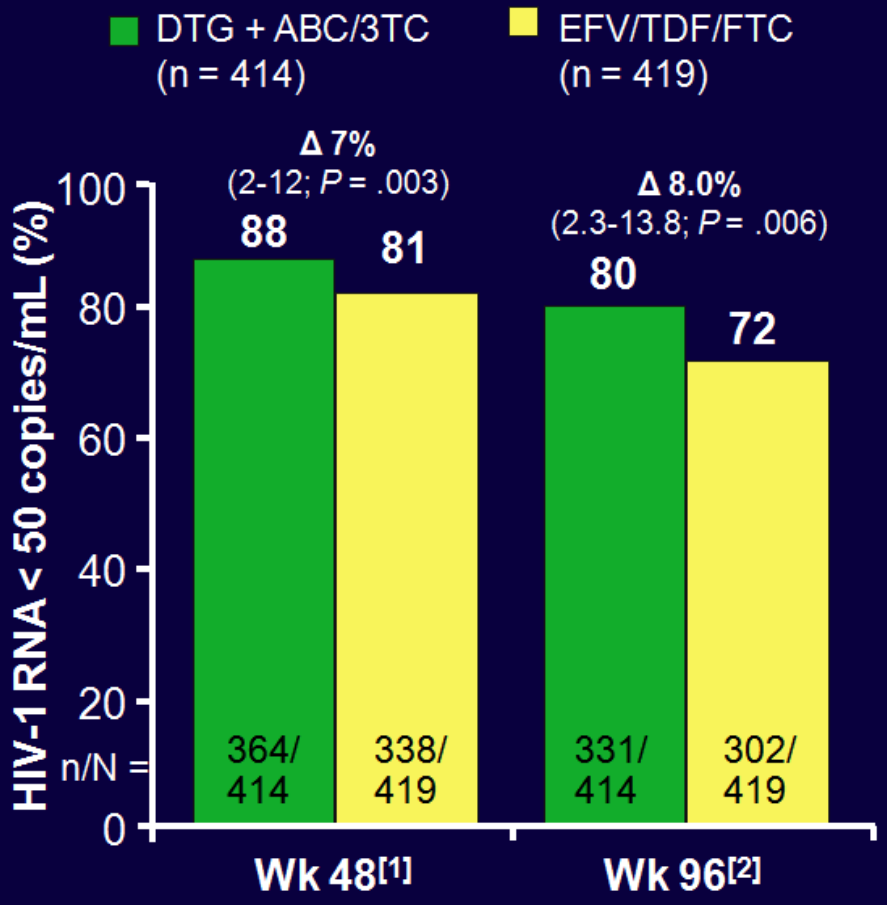


Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% non-inferiority margin with pre-specified tests for superiority

Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

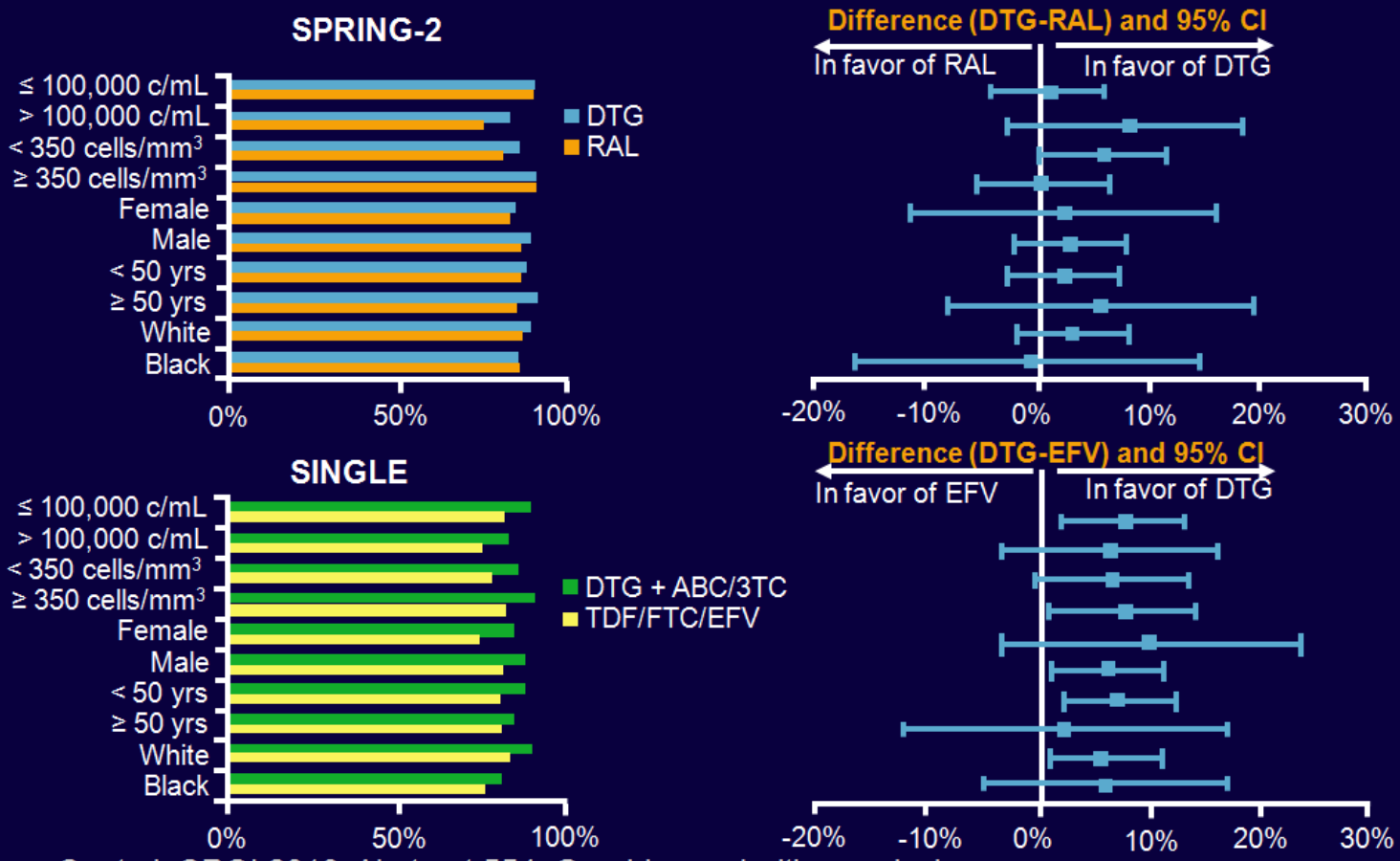
SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC at Both Wk 48 and 96



- Treatment-related study d/c: 3% in DTG vs 11% in EFV arm
  - No new treatment-related AEs in either arm btwn Wks 48-96
- VF at Wk 96: 25 (6%) in each arm
- 0 pts with resistance in DTG arm; 1 pt with NRTI and 6 pts with NNRTI resistance in EFV arm
- CD4+ cell count increase at Wk 96 greater with DTG: +325 vs +281 cells/mm^3 (P = .004)

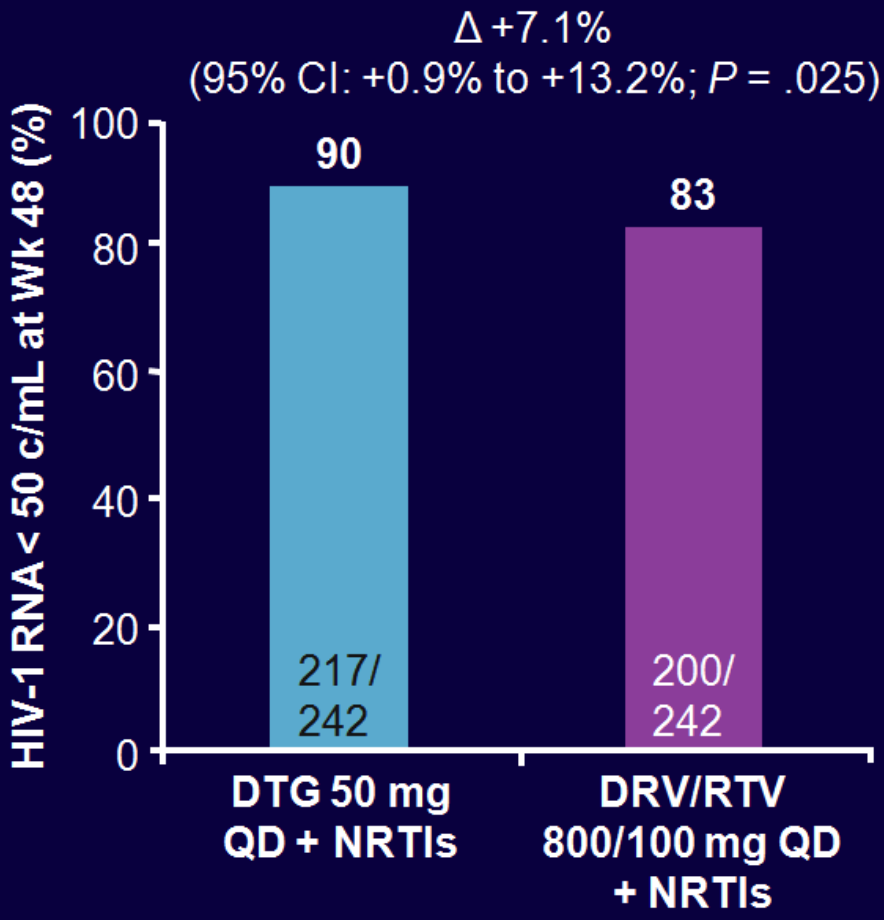
1. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.
2. Walmsley S, et al. CROI 2014. Abstract 543.

Subgroup Analyses of SPRING-2 and SINGLE: Virologic Suppression at Wk 48



Brinson C, et al. CROI 2013. Abstract 554. Graphic used with permission.

FLAMINGO: DTG vs DRV/RTV + 2 NRTIs in Naive Patients at Wk 48



- DTG superior to DRV/RTV at Wk 48 primary efficacy endpoint
  - Treatment-related study d/c: 2% in DTG arm vs 4% in DRV/RTV arm
- VF at Wk 48: < 1% (n = 2) in each arm
- Similar CD4+ cell count increase at Wk 48:
  - +210 cells/mm³ in each arm

Feinberg J. et al. ICAAC 2013. Abstract H1464a.

Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study

- Week 48, phase III, randomized, double-blind study
- 715 ARV experienced, integrase inhibitor-naive patients with HIV RNA ≥400 cp/mL and ≥2 class resistence
- DTG 50 mg bid or RTG 400 mg bid + placebo + OBR (≥1 effective agent)
- **Superior rate of virological success and lower incidence of resistance at VF with DTG**

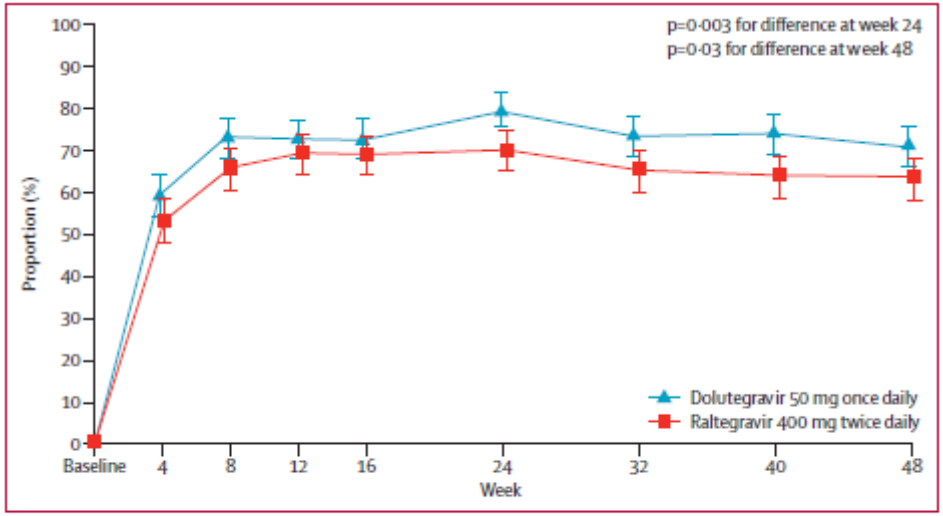


Figure 2: **Snapshot analysis of proportion of patients with plasma HIV-1 RNA lower than 50 copies per mL, by visit**
Error bars show 95% CIs, derived using the normal approximation. Analysis included all participants randomly assigned to treatment groups who received at least one dose of study drug, excluding participants at one site with

	Dolutegravir (n=354)	Raltegravir (n=361)	Difference (95% CI; p value)
Week 24 interim analysis	281 (79%)	252 (70%)	9·7% (3·4 to 15·9; p=0·003)*
Per-protocol population	263/323 (81%)	245/339 (72%)	9·3% (3·0 to 15·7)*
Week 48			
Virological success	251 (71%)	230 (64%)	7·4% (0·7 to 14·2; p=0·030)*
Virological non-response	71 (20%)	100 (28%)	..
Data in window not <50 copies per mL	35 (10%)	48 (13%)	..
Discontinued for lack of efficacy	19 (5%)	35 (10%)	..
Discontinued for other reason while not <50 copies per mL	7 (2%)	7 (2%)	..
Change in ART	10 (3%)	10 (3%)	..

(Cahn P et al., Lancet 2013)

Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study

- Single arm, open-label, phase III study
- 183 experienced patients with INI-resistant virus
- Failing regimen + DTG 50 mg bid for 7 days then OBT with ≥1 fully active drug + DTG for 24 weeks

Table 2. Primary Efficacy Results (ITT-E Population)

Parameter	DTG 50 mg BID (N = 183)
Change from baseline in plasma HIV-1 RNA at day 8 (LOCFDB)	
Plasma HIV-1 RNA level, $\log_{10}$ c/mL	
Baseline, mean (SD)	4.26 (0.93)
Change from baseline, mean (SD)[a,b]	−1.43 (0.61)
95% CI	−1.52, −1.34
Subjects with plasma HIV-1 RNA <50 c/mL at Week 24, n (%)[c]	
Virological success (HIV-1 RNA <50 c/mL)	126 (69)
Virological nonresponse	50 (27)
Data in window ≥50 c/mL	28 (15)
Discontinued for insufficient viral load response[d]	9 (5)
Discontinued for other reasons while not <50 c/mL	3 (2)
Change in background ART	10 (5)
No virological data at Week 24	7 (4)
Discontinued due to AE/death[e]	5 (3)
Discontinued for other reasons	2 (1)

(Castagna A et al., J Infect Dis 2014)

Dolutegravir summary: advantages and disadvantages

Advantages

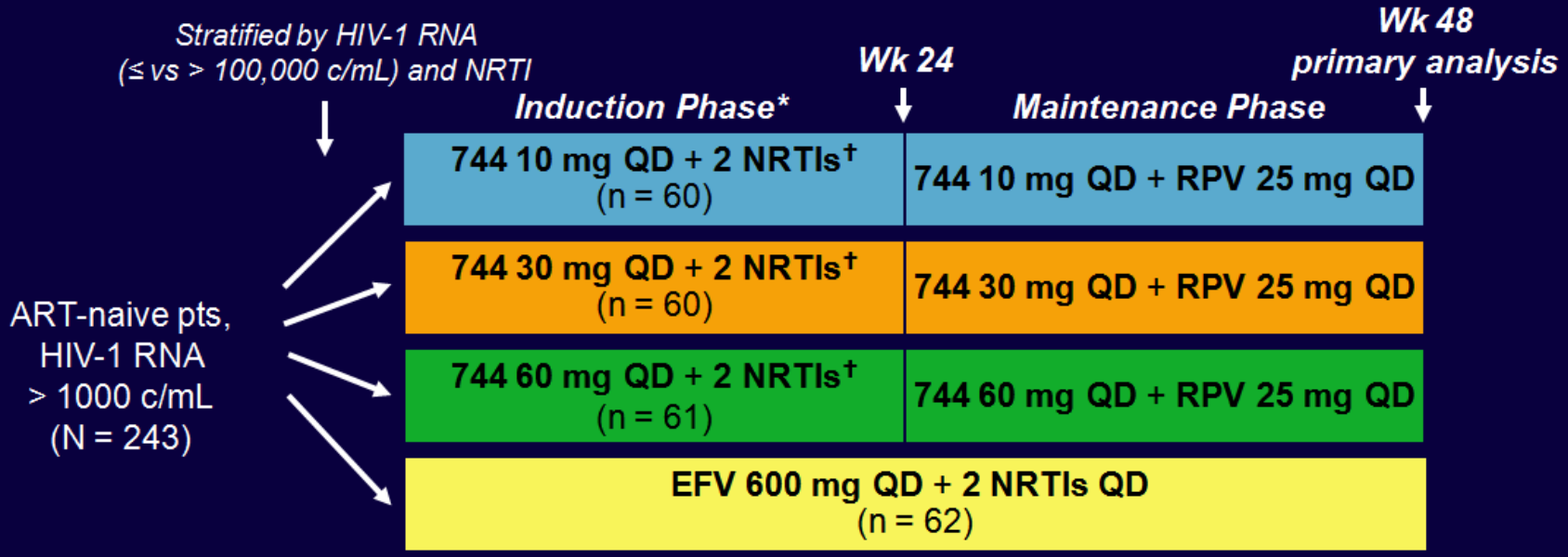
- Once-daily administration
- Small mg dose and tablet size
- Noninferior to RAL and superior to EFV and DRV/r in naïve patients
- Maintains comparable or better virologic activity to EFV, RAL, DRV/RTV across low and high HIV-1 RNA
- Fewer CNS and rash events vs EFV
- No IN resistance mutations at VF in naive patients
- Few drug–drug interactions

Disadvantages

- Not yet available as part of FDC
- Inhibits tubular secretion of creatinine, increasing Cr levels
- Relatively little clinical experience and shortest duration of follow-up when compared with RAL (especially) and EVG

LATTE: GSK1265744 as Part of ART in Naive Pts: Results of 24-Wk Induction

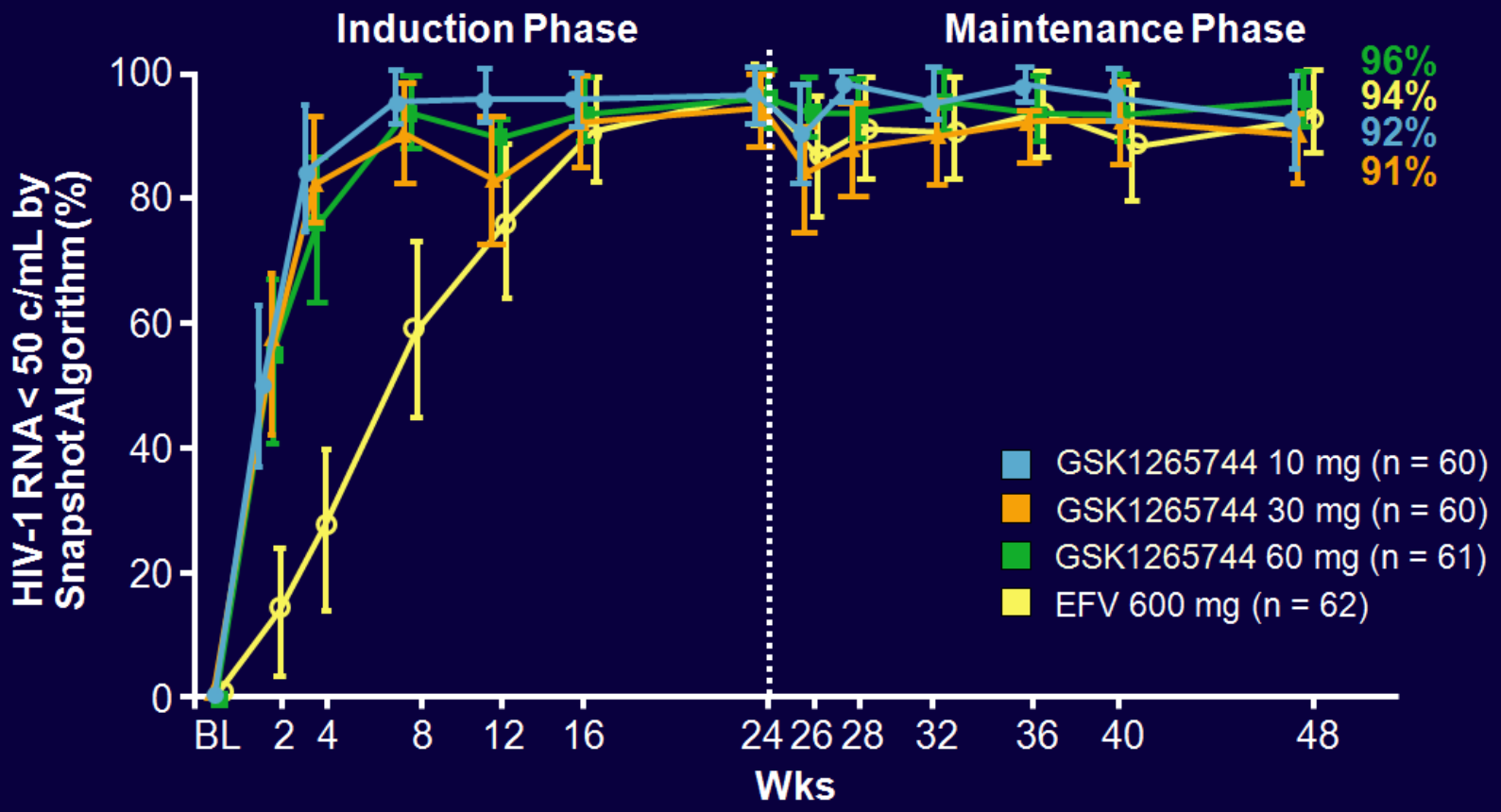
- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



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

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB.

LATTE: Virologic Success During Induction and Maintenance Phases



- 2 pts with PDVF during maintenance; both with INSTI mutations at BL

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB

Integrase Inhibitors in DHHS Guidelines

	Preferred Regimens	Alternative Regimens
NNRTI	▪ EFV/TDF/FTC (AI)	▪ EFV + ABC/3TC (BI) ▪ RPV/TDF/FTC (BI) or RPV + ABC/3TC (BIII)
Boosted PI	▪ ATV/RTV + TDF/FTC (AI) ▪ DRV/RTV + TDF/FTC (AI)	▪ ATV/RTV + ABC/3TC (BI) ▪ DRV/RTV + ABC/3TC (BIII) ▪ FPV/RTV + (TDF/FTC or ABC/3TC) (BI) ▪ LPV/RTV + (TDF/FTC or ABC/3TC) (BI)
INSTI	▪ **RAL + TDF/FTC** (AI) ▪ **EVG/COBI/TDF/FTC*** (AI) ▪ **DTG + ABC/3TC** (AI) ▪ **DTG + TDF/FTC** (AI)	▪ **RAL + ABC/3TC (BIII)**

*in patients with estimated CrCL $\geq$ 70 mL/min

(DHHS Guidelines. February 2013. DHHS Recommendation on INSTIs. October 2013)

Recommended Regimens(*)

A drug from column A should be combined with the drugs listed in column B(**)

A	B	Remarks
NNRTI	**NRTI**	
EFV(i) RPV(ii)	ABC/3TC(vii) or TDF/FTC	ABC/3TC co-formulated TDF/FTC co-formulated EFV/TDF/FTC co-formulated RPV/TDF/FTC co-formulated
PI/r		
ATV/r(iv) DRV/r(iv)	ABC/3TC(vii) or TDF/FTC	ATV/r: 300/100 mg qd DRV/r: 800/100 mg qd
INSTI		
RAL	TDF/FTC or ABC/3TC	RAL: 400 mg bd

Alternative Regimen Components

PI/r	Remarks
FPV/r LPV/r(v) SQV/r	700/100 mg bd or 1400/200 mg qd 400/100 mg bd or 800/200 mg qd 1000/100 mg bd
NNRTI	
NVP(iii)	
NRTI	
ddI/3TC or ddI/FTC(viii) TDF-3TC ZDV/3TC	ZDV/3TC co-formulated
CCR5 inhibitor	
MVC(vi)	Only if CCR5 tropic HIV(viii)
INSTI	
EVG + COBI	TDF/FTC co-formulated(ix)

(EACS Guidelines, October 2013)

	REGIME	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Preferiti	TDF/FTC+EFV	[AI]	[1-9]
	ABC/3TC+EFV (se HIV-RNA < 100.000 cp/mL)	[AI]	[4-6,10]
	TDF/FTC/RPV (utilizzabile solo se HIV-RNA < 100.000 cp/mL)	[AI]	[11-13]
	TDF/FTC+ATV+r	[AI]	[6,14-18]
	ABC/3TC+ATV+r (se HIV-RNA < 100.000 cp/mL)	[AI]	[4,5]
	TDF/FTC+DRV+r	[AI]	[19-22]
	[illegible]	[illegible]	[illegible]
	TDF/FTC+RAL	[AI]	[25-28]
	ABC/3TC+RAL	[AII]	[29-31]
	TDF/FTC/EVG/COBI	[AI]	[32-34]
	TDF/FTC+DTG	[AI]	[23,29,30]
	ABC/3TC+DTG	[AI]	[23,29,30,35]
Alternativi	TDF/FTC+LPV/r	[BI]	[7,36]
	ABC/3TC+LPV/r	[BI]	[17-22,37-40]
	TDF/FTC+NVP	[BI]	[9,14-16]

(Linee Guida Italiane, Novembre 2013)

Integrase nhibitors for initial therapy: conclusions

- While there are many options for initial therapy, regimens that include an integrase inhibitor have many favorable characteristics
  - all are potent, well tolerated, favorable metabolic profile
  - rates of transmitted (baseline) drug resistance to INSTIs presumed to be low
  - much clinical experience with long-term follow-up (RTG)
  - few drug–drug interactions (RAL, DTG)
  - resistance rarely reported with DTG
  - available as single-pill regimen (EVG)
- Integrase inhibitor–based regimens may be appropriate for many (if not most) treatment-naive patients

Integrase inhibitors for treatment-experienced patients: conclusions

- INSTIs appropriate for many treatment-experienced pts
  - for INSTI-naive pts, all INSTIs should be active
    - DTG superior to RAL, EVG noninferior to RAL
  - for INSTI-experienced pts, DTG superior to RAL
    - Cross-resistance between EVG and RAL
- Difficult to use EVG due to current FDC-only regimen, lack of data combining FDC with other ARVs
- Much clinical experience with RAL as component of new regimens for pts with NRTI, NNRTI, PI experience
- DTG represents a new option for INSTI-experienced pts
  - BID dosing recommended for those with INSTI resistance

Grazie per l'attenzione!