Le linee di terapia iniziale negli HIV con i nuovi antiretrovirali Venezia 18.20 Novembre 2009 Prof. Enzo Raise

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EACS Guidelines- Initial Combination Regimen for Antiretroviral-Naïve patient

SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B	A	B	REMARKS
Recommended	NNRTI • EFV[1] • NVP[5] or ritonavir-boosted PI • ATV/r[6] • DRV/r[6] • LPV/r[7] • SQV/r	TDF/FTC ABC/3TC[2-3-4]	- TDF/FTC co-formulated - ABC/3TC co-formulated - EFV/TDF/FTC co-formulated - ATV/r: 300/100 mg qd - DRV/r: 800/100 mg qd - LPV/r:400/100 mg bid or 800/200 mg qd - SQV/r:1000/100 mg bid
Alternative	SQV/r FPV/r RAL[9]	• ZDV/3TC[8] • ddI/3TC or FTC[8]	- SQV/r: 2000/100 mg qd - FPV/r:700/100 mg bid or 1400/200 mg qd - RAL: 400 mg bid - ZDV/3TC co-formulated

1 EFV: not recommended in pregnant women or women with no reliable and consistent contraception; not active on HIV-2 and HIV-1 group O
2 Contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory
3 ABC + NVP contra-indicated, unless HLA B*5701 negative
4 Abacavir should be used with caution in patients with a high cardiovascular risk and/or patients with a viral load higher than 100,000 copies/ml.
5 NVP: Use with extreme caution in women with CD4 >250 and men with CD4 >400/µL; not active on HIV-2 and HIV-1 group O
6 Castle study (LPV/r vs ATV/r) has shown better tolerability of ATV/r and Artemis study (LPV/r vs DRV/r) better efficacy and greater tolerability of DRV/r.
7 ACTG 5142, randomised study showed lower virological efficacy of LPV/r vs EFV. However no PI mutations were seen in the LPV/r failures.
8 Only if unavailable or intolerant to other recommended NRTIs
9 Raltegravir is indicated in combination with other anti-retroviral medicinal products for the treatment HIV-1 infection in adult patients. It has been studied only in combination with TDF/FTC in naïve patients with limited follow-up (48 weeks).

EACS Guidelines, Version 5, November 2009

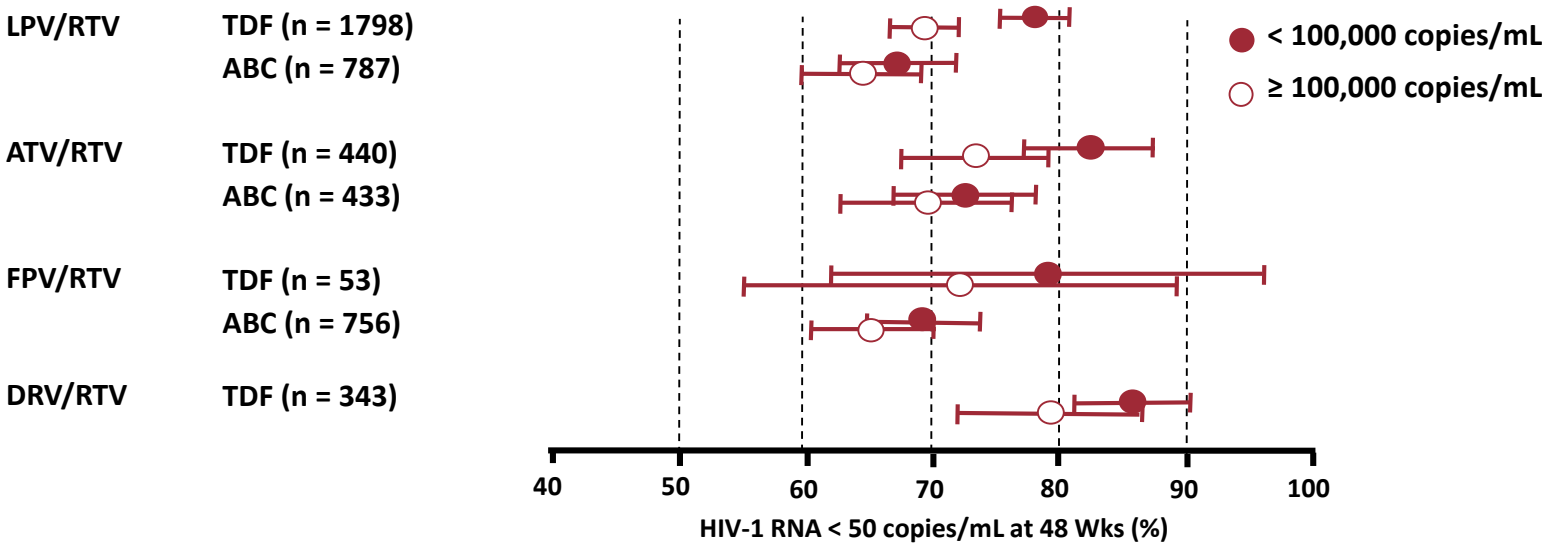
New drugs developed for treatment of HIV naive individuals

- 2nd generation PIs
  - Darunavir/r
  - Atazanavir/GS 9350
- New NNRTIs
  - Rilpivirine (TMC-278)
  - Etravirine
  - Lersivirine (UK-453,061)
- Integrase Inhibitors
  - Raltegravir
  - Elvitegravir/GS 9350
  - GSK 1349572
- CCR5 antagonists
  - Maraviroc
  - Vicriviroc

2nd GENERATION PROTEASE INHIBITORS

PI Efficacy at Higher and Lower Baseline HIV-1 RNA

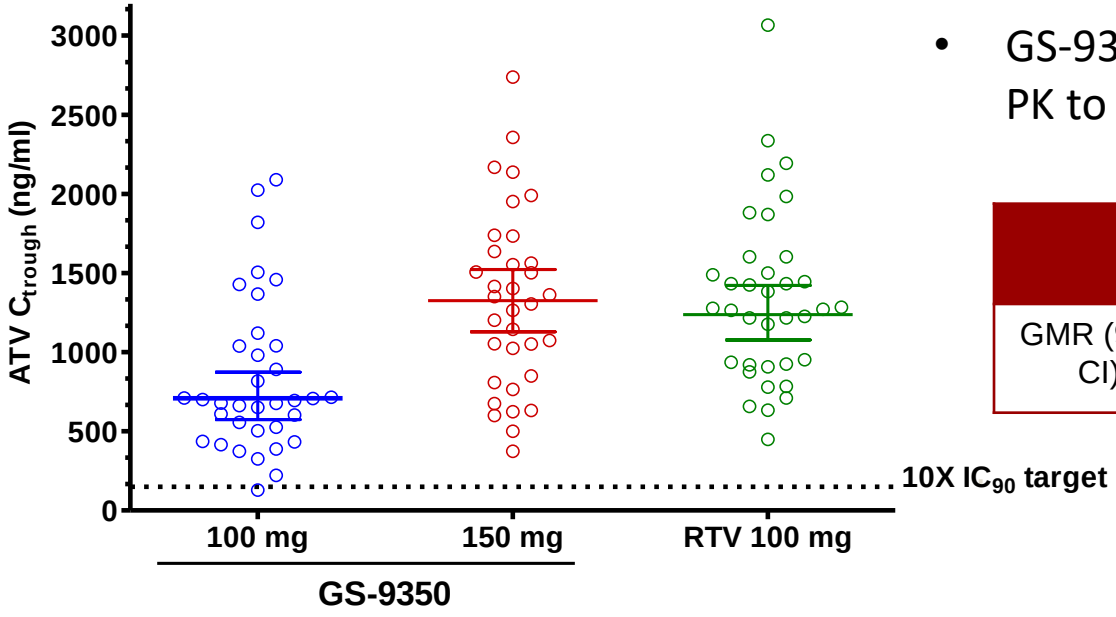
- Systematic review of 21 treatment arms from 12 treatment-naive clinical trials reported from January 2000 - March 2008 (N = 4895)
- Conclusion: significantly ↑ rates of HIV-1 RNA < 50 copies/mL at 48 wks with TDF/FTC vs ABC/3TC by ITT-TLOVR or nearest equivalent endpoint



Hill A, et al. ICAAC/IDSA 2008. Abstract 1254. Graphics reproduced with permission.

ATV+GS-9350 Pharmacokinetics

Mean (CV%) ATV PK (n = 34 - 36)	+ GS-9350 100 mg	+ GS-9350 150 mg	+ RTV 100 mg
AUC_{tau} (ng.hr/mL)	45100 (31)	55900 (28)	55200 (28)
C_{max} (ng/mL)	4420 (21)	4880 (25)	5270 (24)
C_{tau} (ng/mL)	837 (59)	1330 (43)	1340 (41)

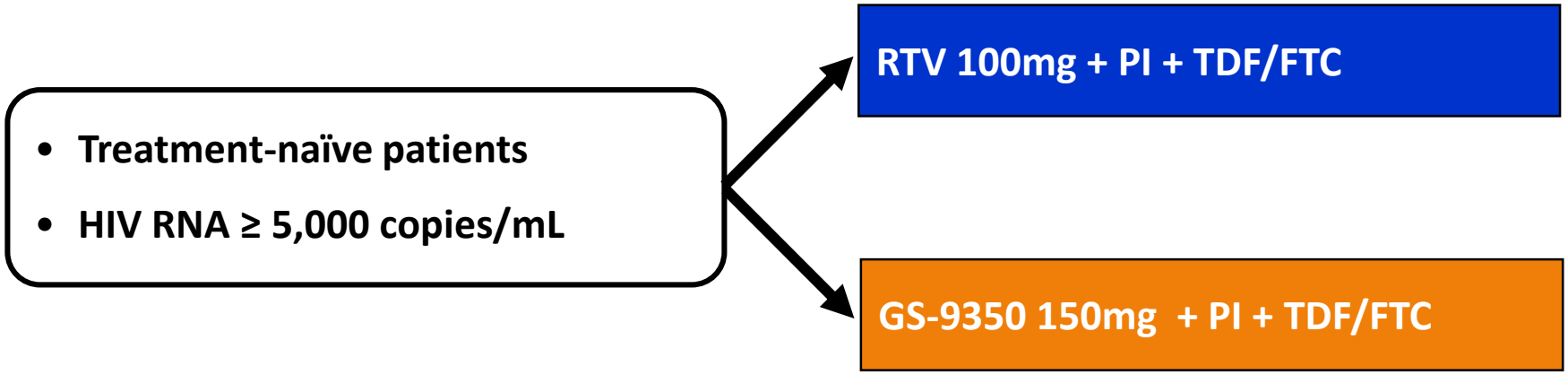


Bars represent geometric mean (±95% CI)

- GS-9350 150 mg provides bioequivalent ATV PK to RTV 100 mg

	AUC_{tau} (ng.hr/ml)	C_{max} (ng/mL)	C_{tau} (ng/ml)
GMR (90% CI)	101 (94.5,108)	92.3 (85.1, 100)	97.6 (88.1, 108)

GS-9350 Phase 3 Study (Proposed)



- N ~ 600, 1:1 randomization, double-blind treatment
  - PI comparator of choice in 1H 2010 → 2012 (launch)
    - ATV, DRV, both?

- Primary endpoint: HIV RNA < 50 copies/mL at week 48 (96 week study)

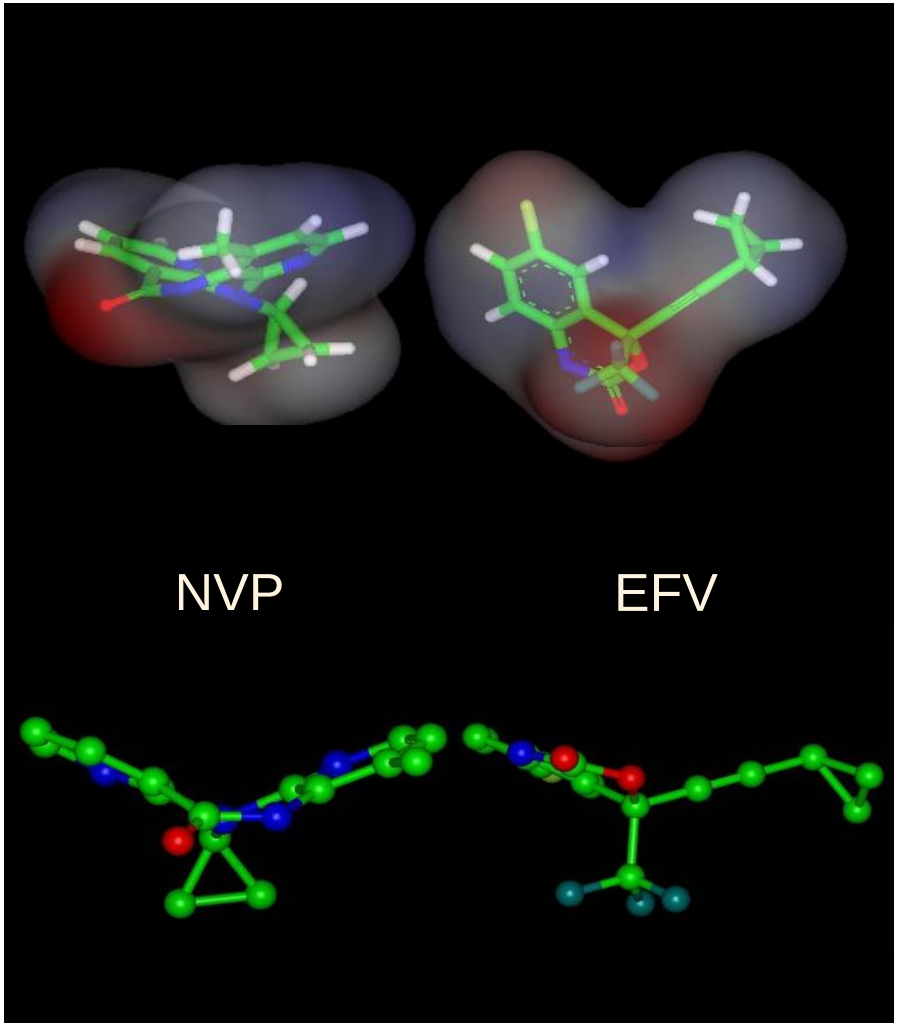
NEW NNRTIs

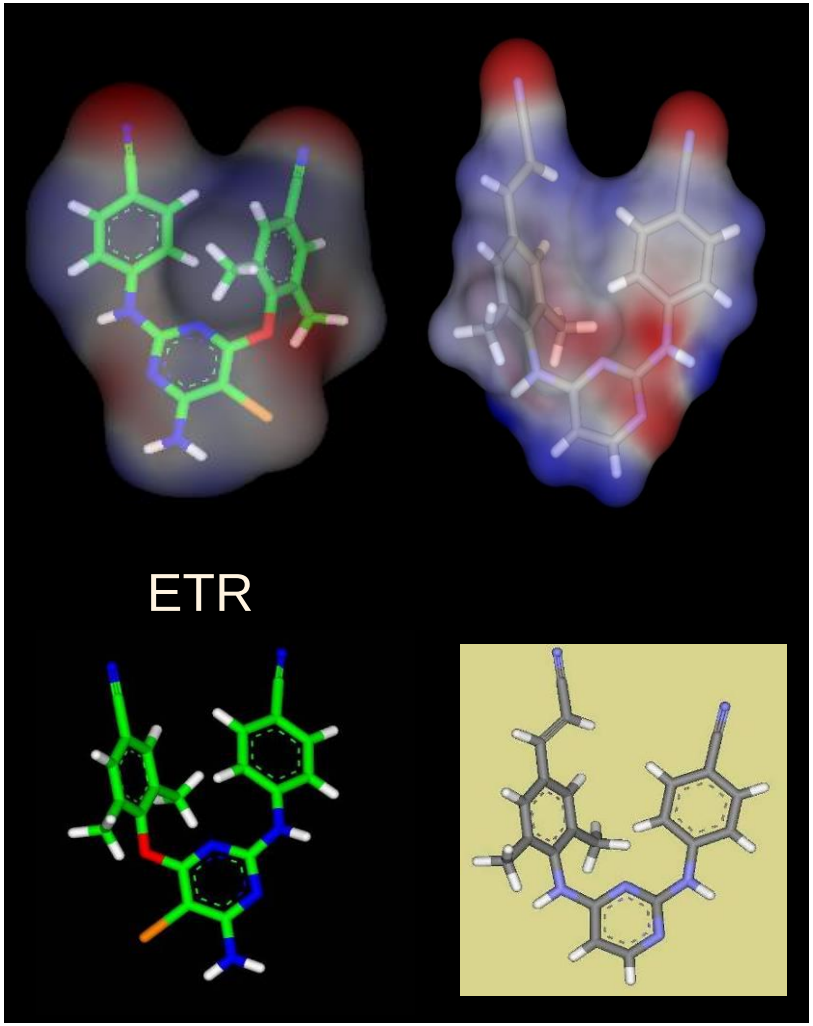
TMC278: need for novel NNRTIs

- **New convenient NNRTIs with better safety and tolerability in NNRTI-naïve patients are needed**
- **Next-generation NNRTIs (DAPYs) have demonstrated potent activity against wild-type and NNRTI-resistant virus[1,2]**
  - **ETR demonstrated an impressive and sustained efficacy profile at Week 48 in treatment-experienced patients[3,4]**
- **TMC278 is being evaluated as a convenient one-tablet, once-daily NNRTI for use in treatment-naïve patients with the potential for use in fixed-dose combinations with other ARVs**

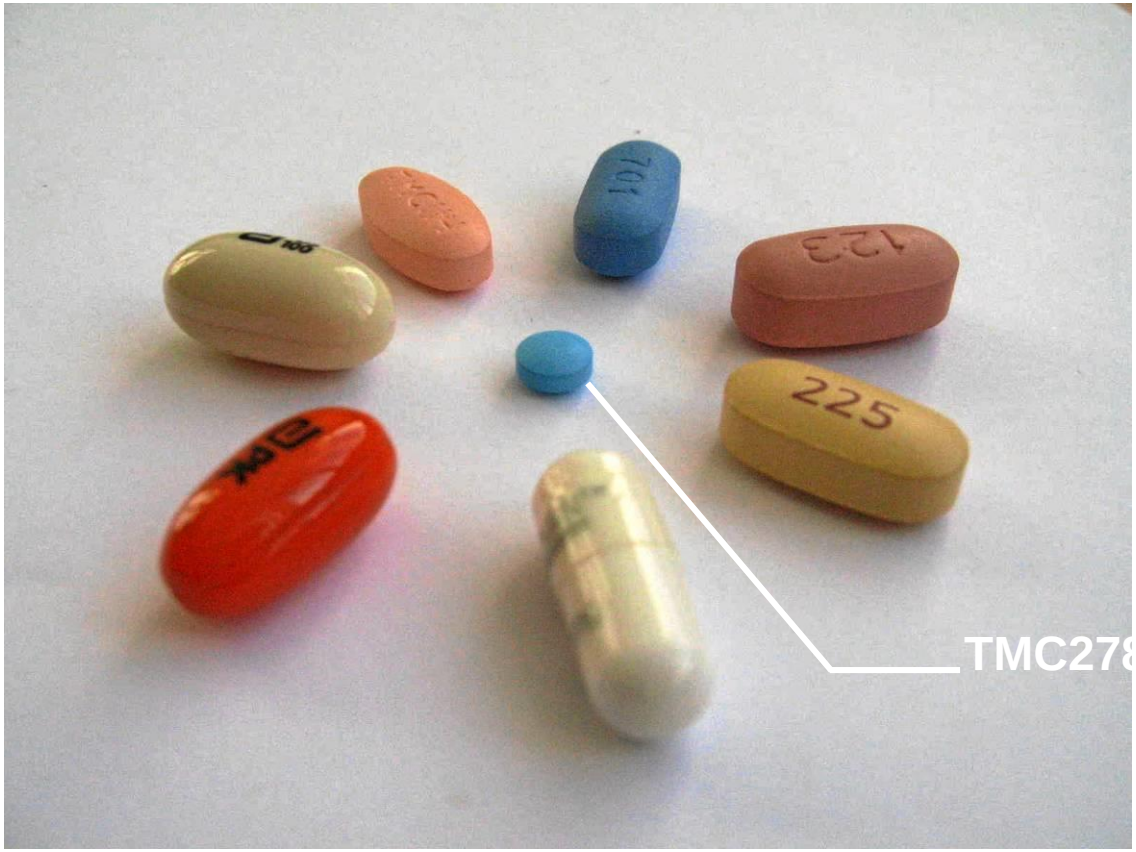
[1]Ludovici DW, et al. Bioorg. Med Chem Lett 2001;11:2235–9
[2]Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
[3]Haubrich R, et al. CROI 2008. Abstract 790
[4]Johnson M, et al. CROI 2008. Abstract 791

Structures of NNRTIs



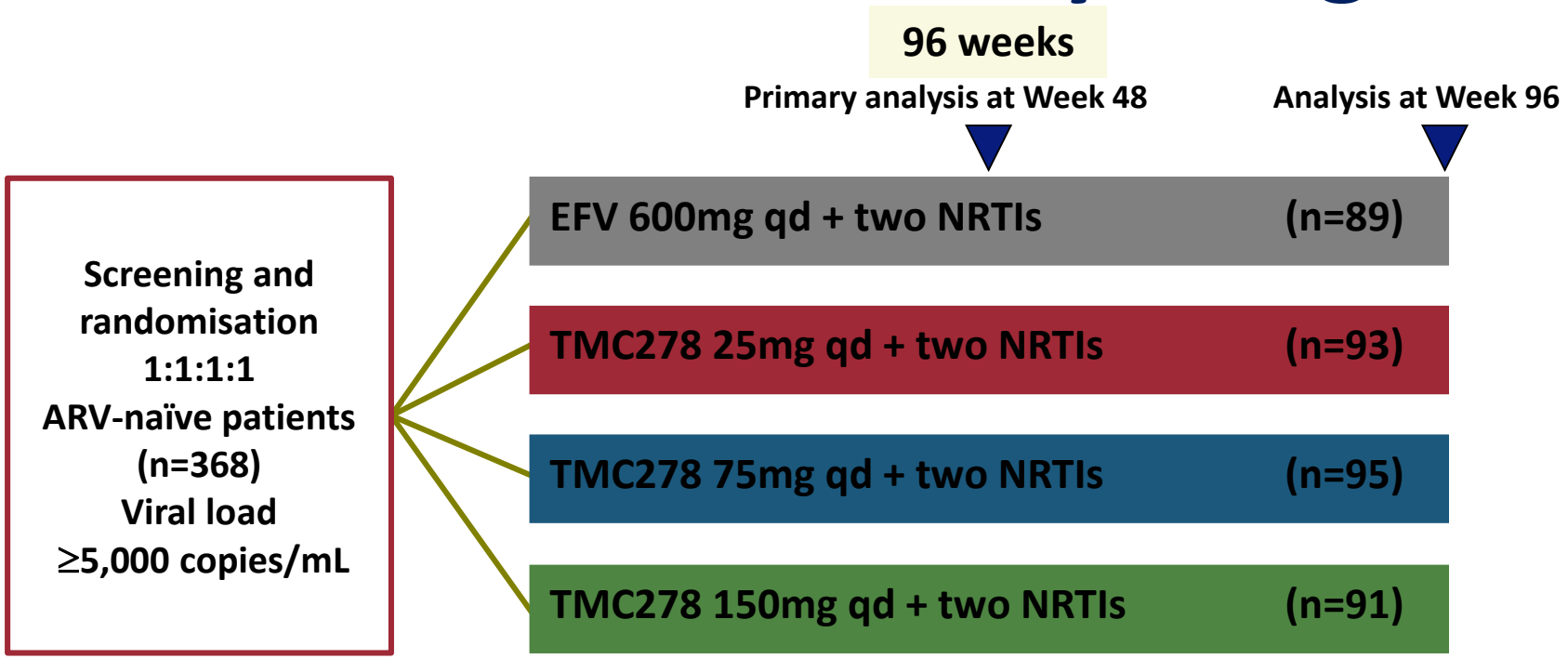


TMC278: given as one small, convenient, once-daily tablet in clinical trials



- **The next-generation NNRTI, TMC278, can be administered as one small, convenient, once-daily pill with the potential for fixed-dose combinations with other agents**

TMC278-C204: study design

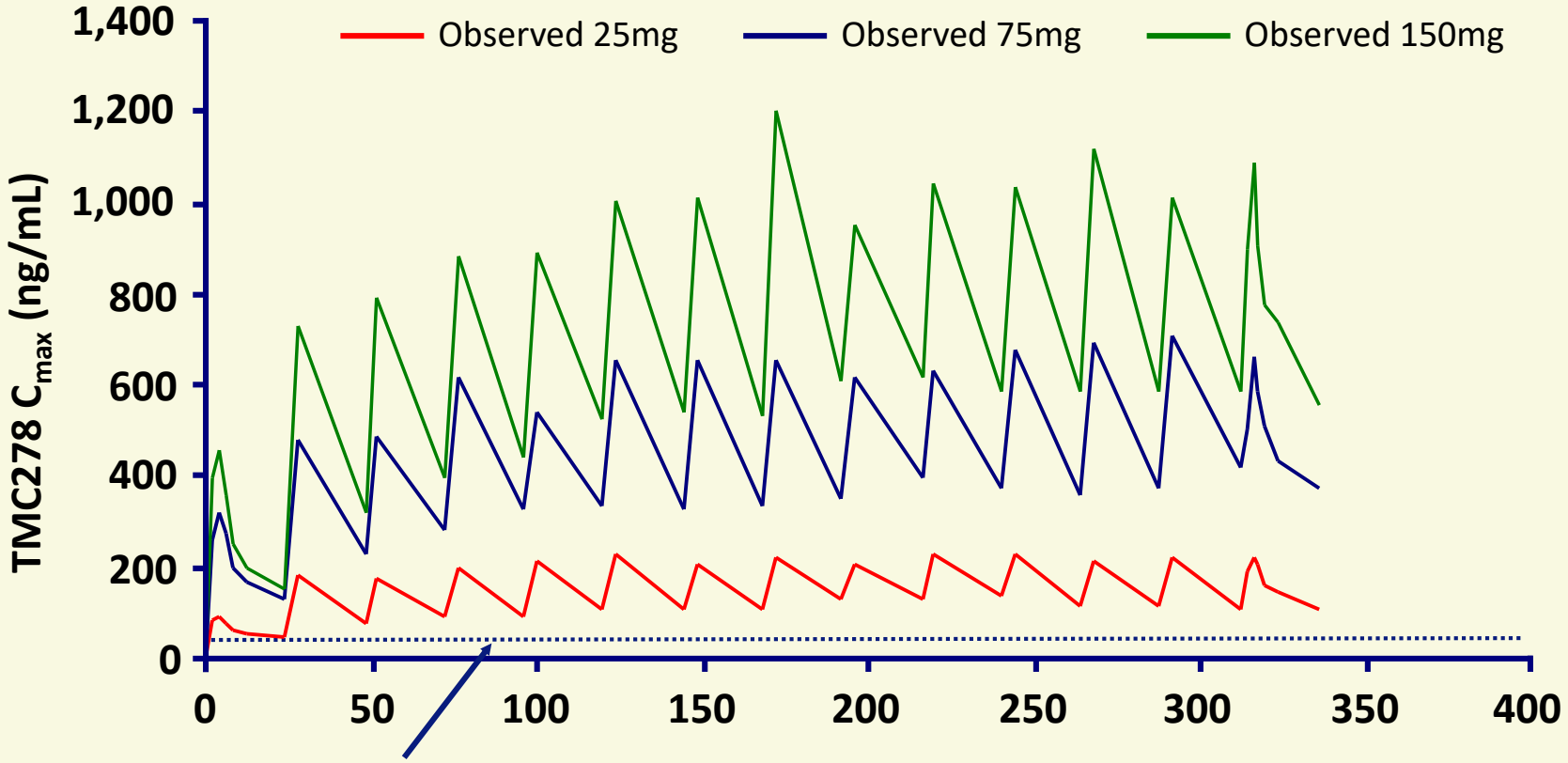


- **Ongoing (extended to 5 years), randomised, active-controlled, dose-ranging, Phase IIb study in ARV-naïve patients**
- **TMC278 blinded for all three groups until Week 96 versus open-label EFV**
- **Primary objective to evaluate the TMC278 efficacy (ITT-TLOVR) and safety dose-response relationship at Week 48**

NRTI backbone chosen by investigator and is either AZT/3TC (75%) or TDF/FTC (25%) administered as fixed-dose combinations where available

Pozniak A, et al. CROI 2007. Abstract 144LB
Yeni P, et al. EACS 2007. Abstract P7.2/08
Santoscoy M, et al. IAC 2008. Abstract TUAB0103
Molina J-M, et al. HIV9 2008. Abstract P002

High TMC278 exposure with qd oral dosing



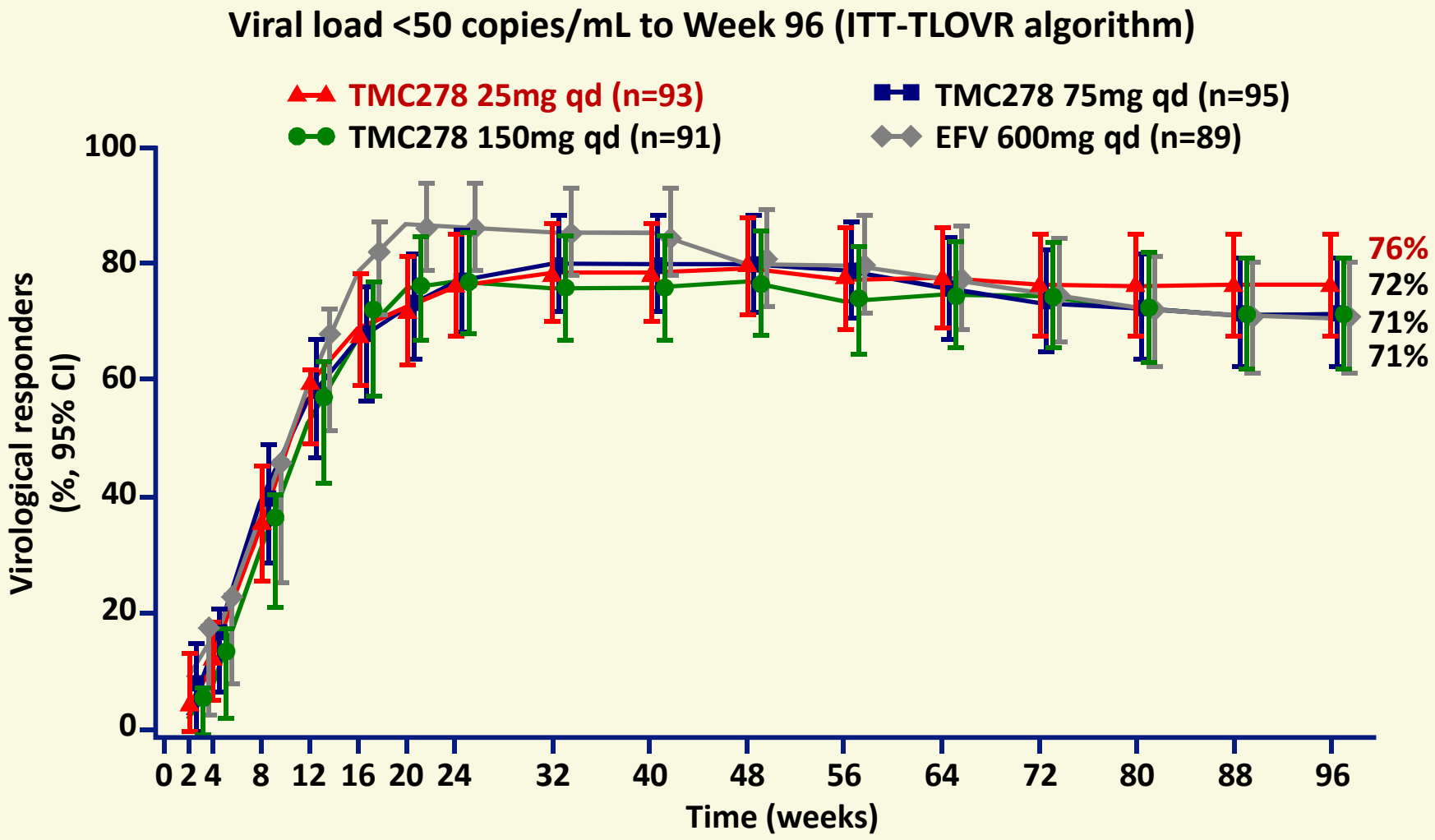
Projected inhibitory levels against wild-type virus (in-vitro data)

Mean $C_{min,ss}$ = 93ng/mL (C204 study)

de Béthune M-P, et al. CROI 2005. Abstract 556

van Heeswijk R, et al. IWCPHIV 2008. Abstract 014

TMC278: high and sustained virological response rate over 96 weeks



Santoscoy M, et al. IAC 2008. Abstract TUAB0103
Molina J-M, et al. HIV9 2008. Abstract P002

Lipid parameters in patients treated with TMC278 or EFV

- No TMC278 dose relationship observed for mean changes in lipid parameters

Mean change from baseline (SD) at 96 weeks

Parameter	EFV 600mg qd	TMC278 25mg qd	TMC278 75mg qd	TMC278 150mg qd	All TMC278
TC (mg/dL)	34 (31)	10 (28)	8 (35)	9 (29)	9 (31)*
LDL-C (mg/dL)	18 (28)	5 (25)	5 (30)	3 (25)	5 (27)*
HDL-C (mg/dL)	11 (12)	6 (10)	7 (11)	6 (12)	6 (11)*
Ratio TC/HDL-C	–0.1 (0.9)	–0.4 (1.3)	–0.5 (1.1)	–0.3 (1.0)	–0.4 (1.1)**
TG (mg/dL)	29 (87)	–8 (75)	–15 (79)	–7 (90)	–10 (81)*

*p<0.01; **p=0.19 for EFV vs TMC278 (non-parametric Wilcoxon rank-sum test, post-hoc analysis)

Santoscoy M, et al. IAC 2008. Abstract TUAB0103
Molina J-M, et al. HIV9 2008. Abstract P002

Incidences of neurological and psychiatric AEs were lower with TMC278 than with EFV

Summary of neurological AEs of interest and psychiatric AEs, irrespective of relationship to treatment‡

Incidence (%)	EFV 600mg qd (n=89)	TMC278 25mg qd (n=93)	TMC278 75mg qd (n=95)	TMC278 150mg qd (n=91)	All TMC278 (N=279)
Neurological (all grades)	60	33	34	31	33*
Grade 1	45	27	28	23	26
Grade 2	14	7	5	8	7
Grade 3	1	0	0	0	0
Psychiatric (all grades)	21	17	17	14	16
Grade 1	10	8	7	10	8
Grade 2	10	9	7	2	6
Grade 3	1	1	2	0	1
Grade 4	0	0	0	2	1

*p<0.01 vs EFV (Fisher's exact test)

‡Well-described neurological (peripheral and central nervous system) and psychiatric AEs associated with current NNRTIs

Molina J-M, et al. HIV9 2008. Abstract P002

Absence of a teratogenic potential from a novel next-generation NNRTI, TMC278

PE7.1/4

M Desmidt,[1] B Willems,[1] P Dom,[1] G Bailey,[1] L De Schaepdrijver,[1] L Lammens,[1] S Lachau-Durand,[2]
F van Velsen,[2] M Martens,[2] W Coussement[1]

[1]Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium; [2]Tibotec BVBA, Mechelen, Belgium

Foetal observations: rats

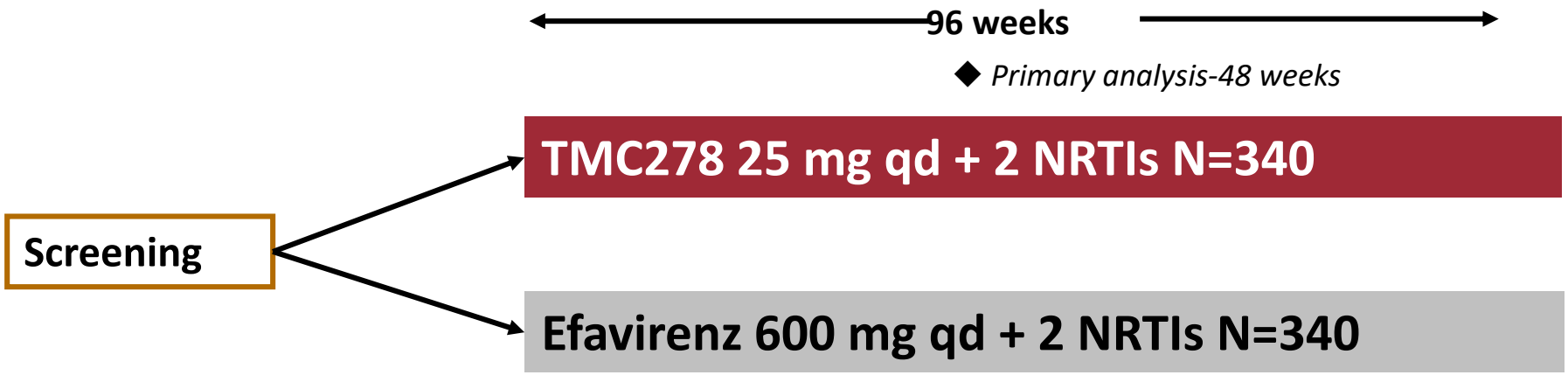
	TMC278 dose level (mg/kg/day)			
Parameters	**0**	**40**	**120**	**400**
Incidence of malformed foetuses	0/288	2/321	0/306	2/307
Individual observations				
Incomplete ossification of sternum bone(s)	1/148	1/166	1/157	7/158*
Reduced ossification of metacarpal bone(s)	0/148	0/166	0/157	5/158*
Dilated renal pelvis	0/140	2/155	5/149*	7/149**

*p<0.05; **p<0.01 vs control

Conclusions

- TMC278 did not show teratogenic potential in rat and rabbit models at exposures 13- to 80-times higher than those seen in HIV-1-infected patients receiving 25mg qd TMC278 at steady-state
  - AUC_{0-24h}: 2.8µg•h/mL (Phase IIb TMC278-C204 study)
  - $AUC_{0-\infty}$: 37µg•h/mL (NOAEL 40mg/kg/day pregnant rats and foetuses)
  - AUC_{0-24h}: 170–232µg•h/mL (NOAEL 10mg/kg/day rabbit foetuses and 20mg/kg/day pregnant rabbits).
- These animal data suggest that further studies of TMC278 in WOCBP are warranted.

THRIVE - TMC278-C215 – Phase III Trial in ARV Naïve Patients



- Randomized, double blind, double dummy
- Non-inferiority, primary efficacy endpoint % of subjects with viral load <50 HIV-1 RNA copies/mL (TLOVR)
- ARV-naïve subjects, primary NNRTI resistance excluded
- Backbone is TVD, EPZ or CBV
- Positive test result for HLA-B*5701 excluded

TVD/TMC-278 Co-formulation

GILEAD SCIENCES ANNOUNCES AGREEMENT WITH TIBOTEC PHARMACEUTICALS TO DEVELOP AND COMMERCIALIZE NEW FIXED-DOSE COMBINATION OF TRUVADA® AND TMC278

-- Product Would Represent Second Truvada-Based Complete Fixed-Dose Regimen --

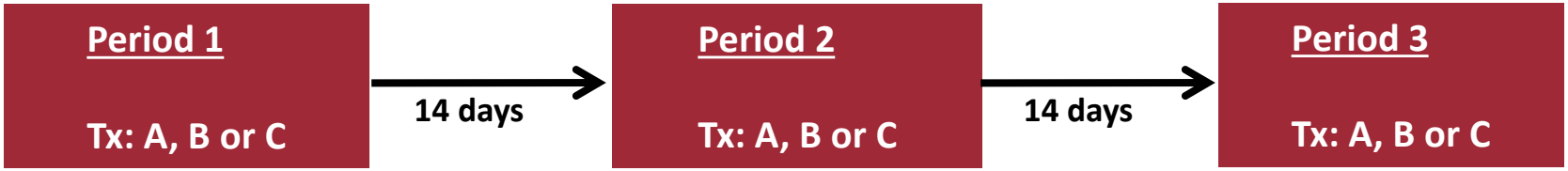
Foster City, CA, July 16, 2009 – Gilead Sciences, Inc. (Nasdaq: GILD) today announced that it has entered into a license and collaboration agreement with Tibotec Pharmaceuticals for the development and commercialization of a new once-daily fixed-dose antiretroviral regimen containing Gilead's Truvada® (emtricitabine and tenofovir disoproxil fumarate) and Tibotec's investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 (rilpivirine hydrochloride, 25 mg) for treatment-naïve HIV-infected individuals. Fixed-dose combinations contain multiple medicines formulated into one tablet and help to simplify HIV therapy.

FTC/RPV/TDF FDC Bioequivalence Study

- **Assess the bioequivalence of two**

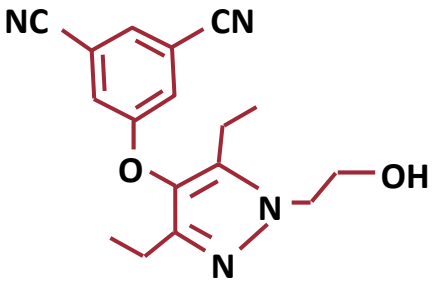
  FTC/RPV/TDF fixed-dose regimen (FDR) tablets vs. FTC + RPV + TDF individual agents

- **Open-label, randomized, 3-way crossover study in HIV negative subjects (N = 48)**
  - **Treatment A: FTC + RPV + TDF (Reference)**
  - **Treatment B: FTC/RPV/TDF FDC (Test Formulation #1)**
  - **Treatment C: FTC/RPV/TDF FDC (Test Formulation #2)**

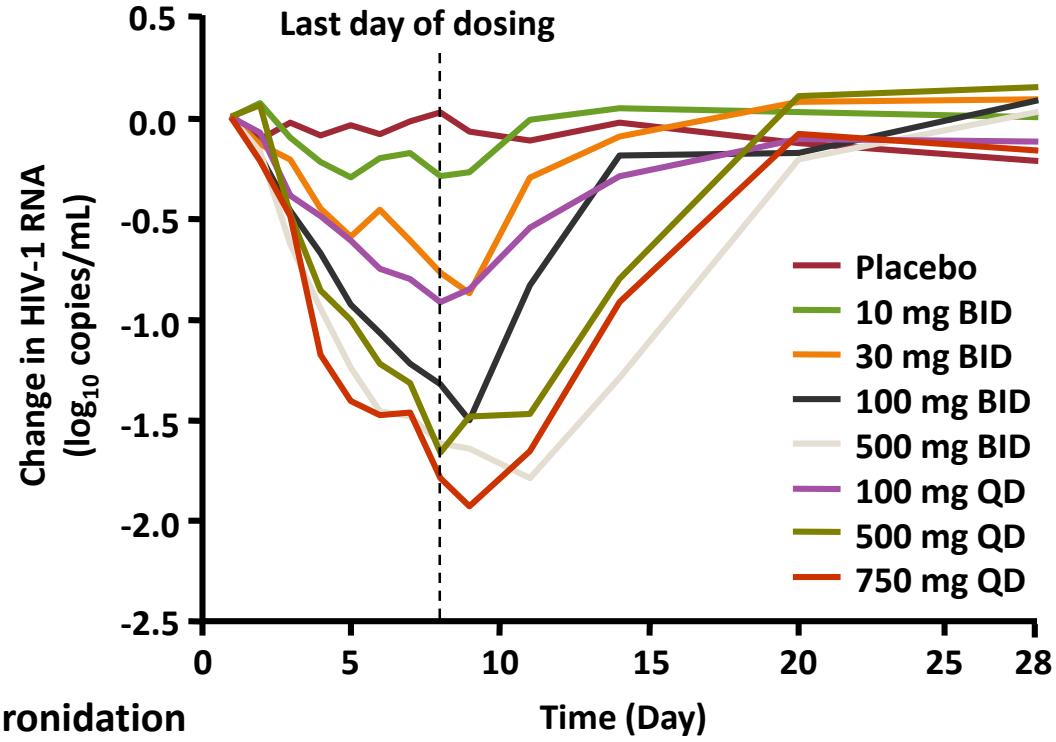


Study drugs administered with food

Antiviral Activity With Varying Doses of Lersivirine (UK-453,061)



- **In vitro characteristics**
  - **IC_{90} of ~12 nM against WT HIV**
- **Phase I pharmacokinetics**
  - **Elimination half-life: 7-11 hours**
  - **Metabolized by CYP3A and glucuronidation**



Corbau R, et al. ICAAC 2007. Abstract 2751.
Fätkenheuer G, et al. IAS 2007. Abstract WESS202.

INTEGRASE INHIBITORS

Raltegravir as First-line Treatment

- **Raltegravir approved for use in treatment-naive HIV-infected patients, by FDA (July 8, 2009) and EUC (September 15, 2009)**
- **Raltegravir noninferior to efavirenz in phase III study in treatment-naive patients[1]**
- **Rationale for use in treatment-naive patients**
  - **Potency**
  - **Does not require ritonavir boosting**
  - **Can be used as basis for NNRTI- and PI-sparing regimens**
  - **Neutral effect on lipids**
- **Current requirement for twice-daily raltegravir dosing a potential drawback vs established first-line regimens**

1. Lennox J, et al. Lancet 2009;374:796-806

Potential Uses of Integrase Inhibitors: Treatment-Naive Patients

Advantages

- Novel mechanism of action
- Efficacy data to 144 wks
- Rapid HIV-1 RNA decay
- Lack of transmitted drug resistance
- Excellent safety and tolerability
- Limited lipid effects
- Limited drug interactions

Disadvantages

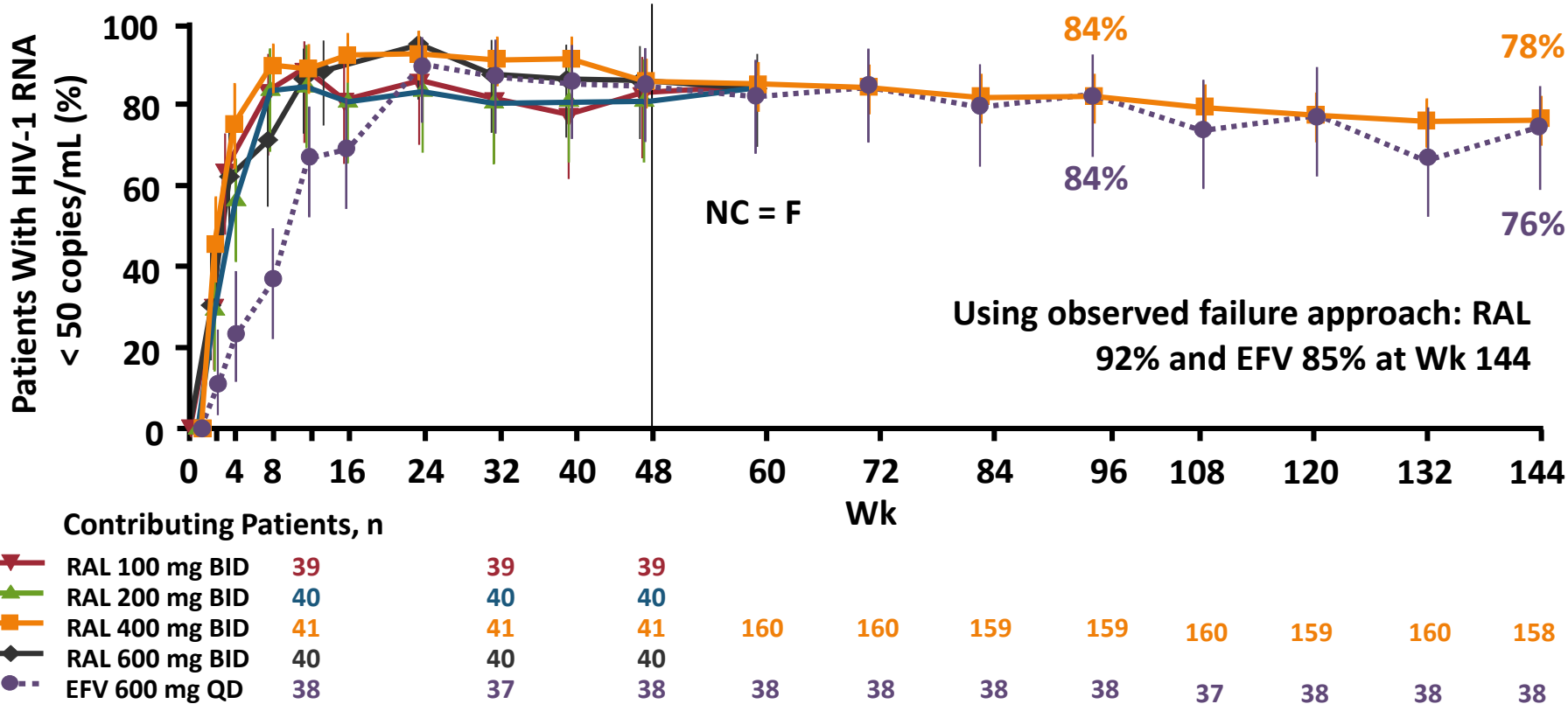
- Twice-daily dosing (RAL, not ELV or S/GSK1349572)
- Currently not in all guidelines
- Cost (unknown for new agents)
- Some drug-drug interactions (varies by drug)
- Fewer data than other agents
- Low barrier to resistance
- Lack of coformulation

Summary of RAL Treatment-Naive Data

- **Phase II (Protocol 004, N = 198): RAL comparable to EFV in virologic efficacy at 144 wks**
  - **HIV-1 RNA < 50 copies/mL: 78% RAL vs 76% EFV**
  - **Fewer CNS adverse events with RAL vs EFV**
  - **RAL had less effect on serum lipids vs EFV**
- **Phase III (STARTMRK, N = 563): non-inferior virologic efficacy of RAL vs EFV at 96 wks**
  - **HIV-1 RNA < 50 copies/mL: 81% RAL vs 79% EFV**
  - **Fewer CNS adverse events with RAL vs EFV**
  - **Lower cholesterol and triglyceride increases with RAL vs EFV**

1. Gotuzzo E, et al. IAS 2009. Abstract MOPEB030.
2. Lennox J, et al. Lancet. 2009;[Epub ahead of print].

Protocol 004: 144-Wk Virologic Response to RAL vs EFV in Naive Pts

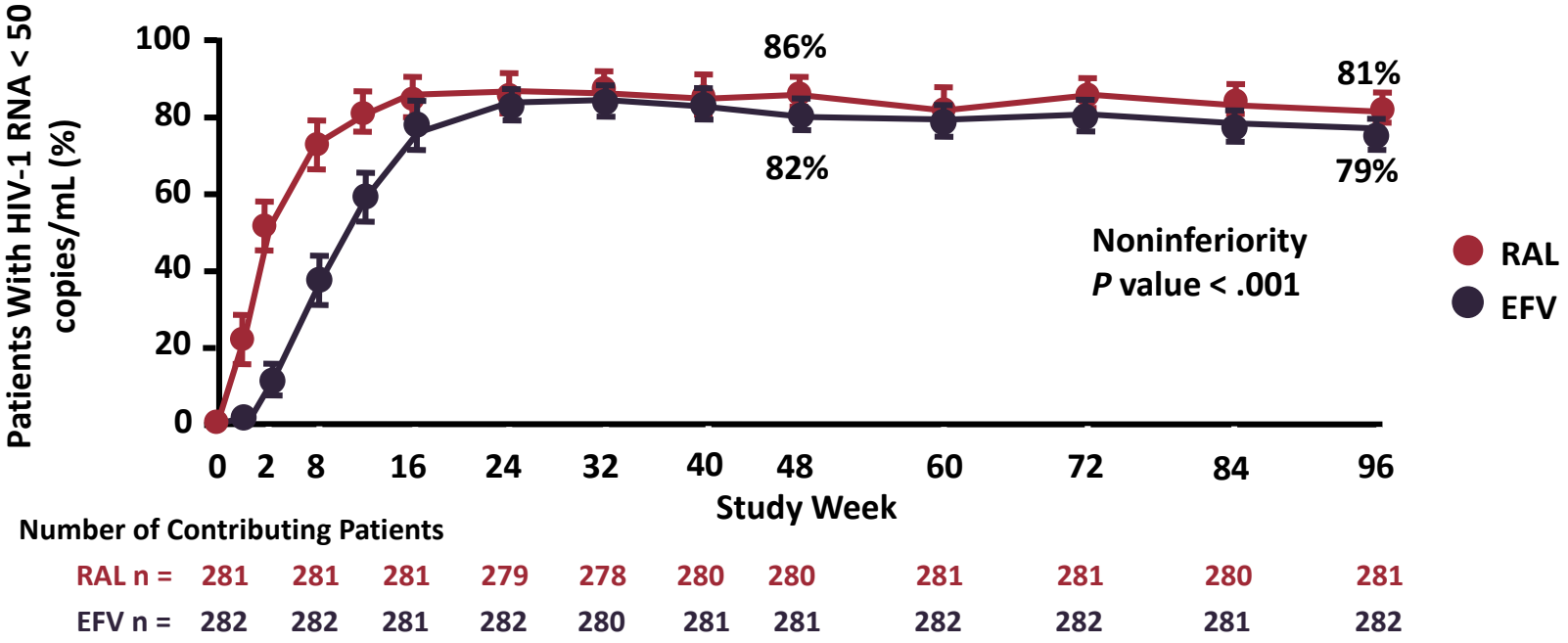


Contributing Patients, n											
RAL 100 mg BID	39	39	39								
RAL 200 mg BID	40	40	40								
RAL 400 mg BID	41	41	41	160	160	159	159	160	159	160	158
RAL 600 mg BID	40	40	40								
EFV 600 mg QD	38	37	38	38	38	38	38	37	38	38	38

*After Wk 48, patients in all RAL groups continued at 400 mg BID.
All patients received TDF/3TC.

Gotuzzo E, et al. IAS 2009. Abstract MOPEB030. Adapted with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

STARTMRK: Virologic and immunologic efficacy at 96 weeks



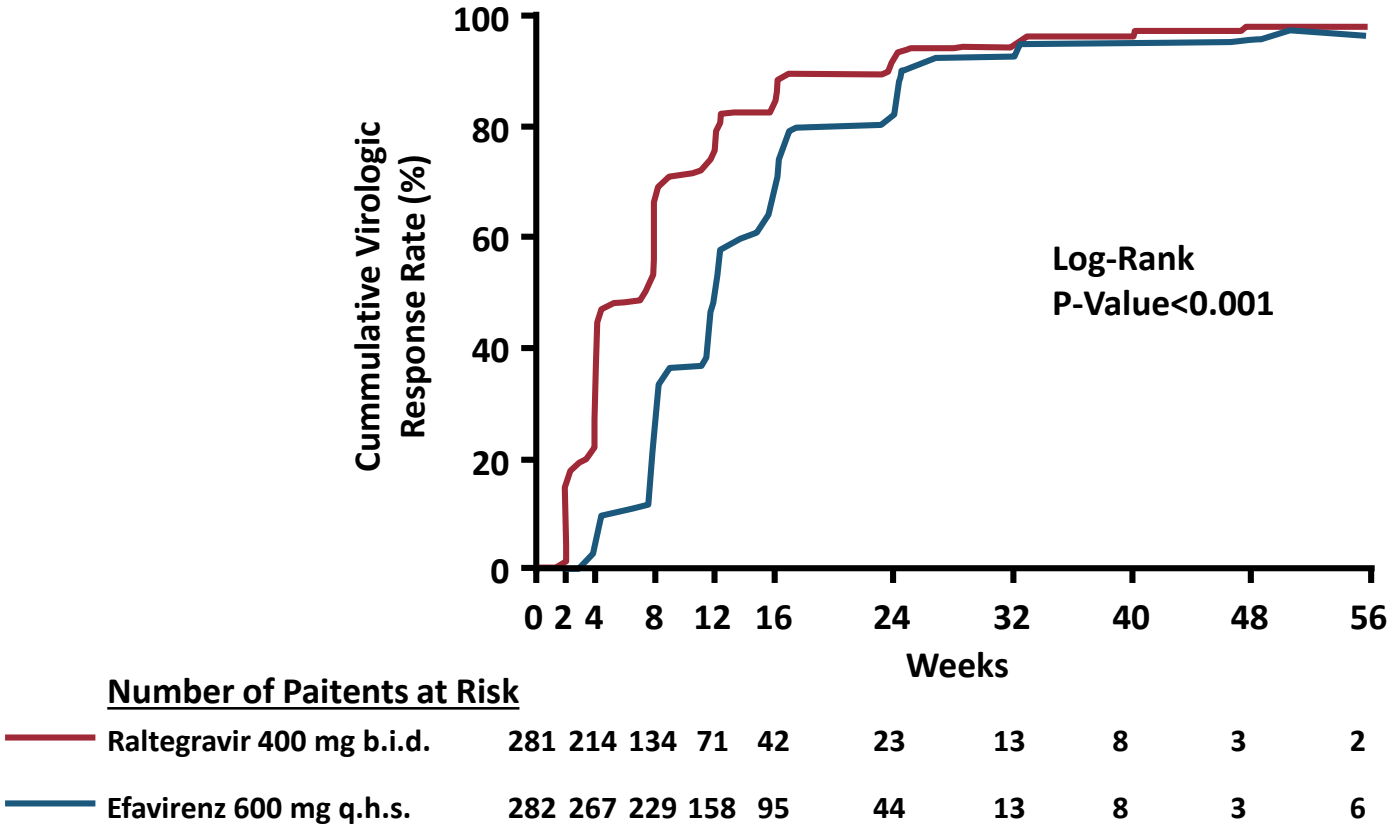
- Significantly shorter time to virologic response with RAL vs EFV (*P* = .001)
- Similar CD4+ cell count increases with RAL vs EFV
  - +240 vs +225 cells/mm^3; Δ: 15 cells/mm^3 (95% CI: -13-42)

Lennox J, et al. ICAAC 2009. Abstract H-924b. Adapted with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

STARTMRK: Significance of Rapid Virologic Decline With Raltegravir

- **Clinical relevance of rapid virologic decline unknown at present**
  - **May partially explain greater CD4+ cell count increase in raltegravir-treated vs efavirenz-treated subjects in STARTMRK**
  - **May prove useful in situations where rapid virologic suppression is particularly desirable**
    - **Example: pregnant women presenting late for prenatal care in order to prevent mother-to-child HIV transmission**

STARTMRK: Time to HIV-1 RNA < 50 copies/mL



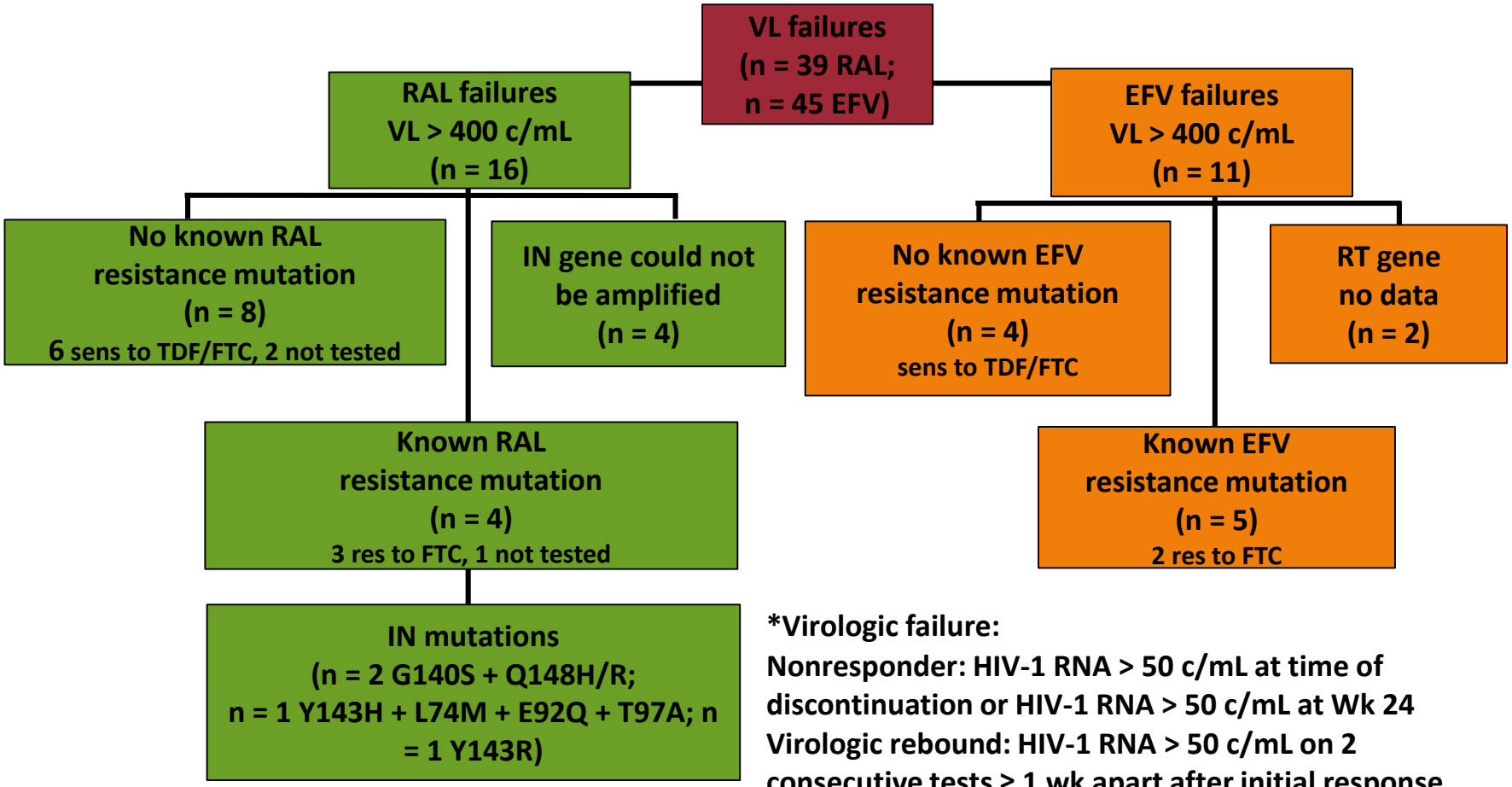
Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a. Reproduced with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

Treatment-Naive Patients for Whom INSTIs May Be Considered

- **Currently, DHHS guidelines do not include INSTIs as preferred options for treatment-naive patients**
- **Possible patients who might be considered**
  - **Patients unable to tolerate NNRTI (rash, CNS toxicity) or PI (any RTV dose)**
  - **High lipids or cardiovascular risk**
  - **Transmitted NNRTI resistance (care must be taken to ensure activity of other regimen components)**
  - **Women who may become pregnant**

DHHS guidelines. Available at: http://aidsinfo.nih.gov.

STARTMRK: Resistance in Patients With Virologic Failure by Week 96*



*Virologic failure:
Nonresponder: HIV-1 RNA > 50 c/mL at time of discontinuation or HIV-1 RNA > 50 c/mL at Wk 24
Virologic rebound: HIV-1 RNA > 50 c/mL on 2 consecutive tests ≥ 1 wk apart after initial response

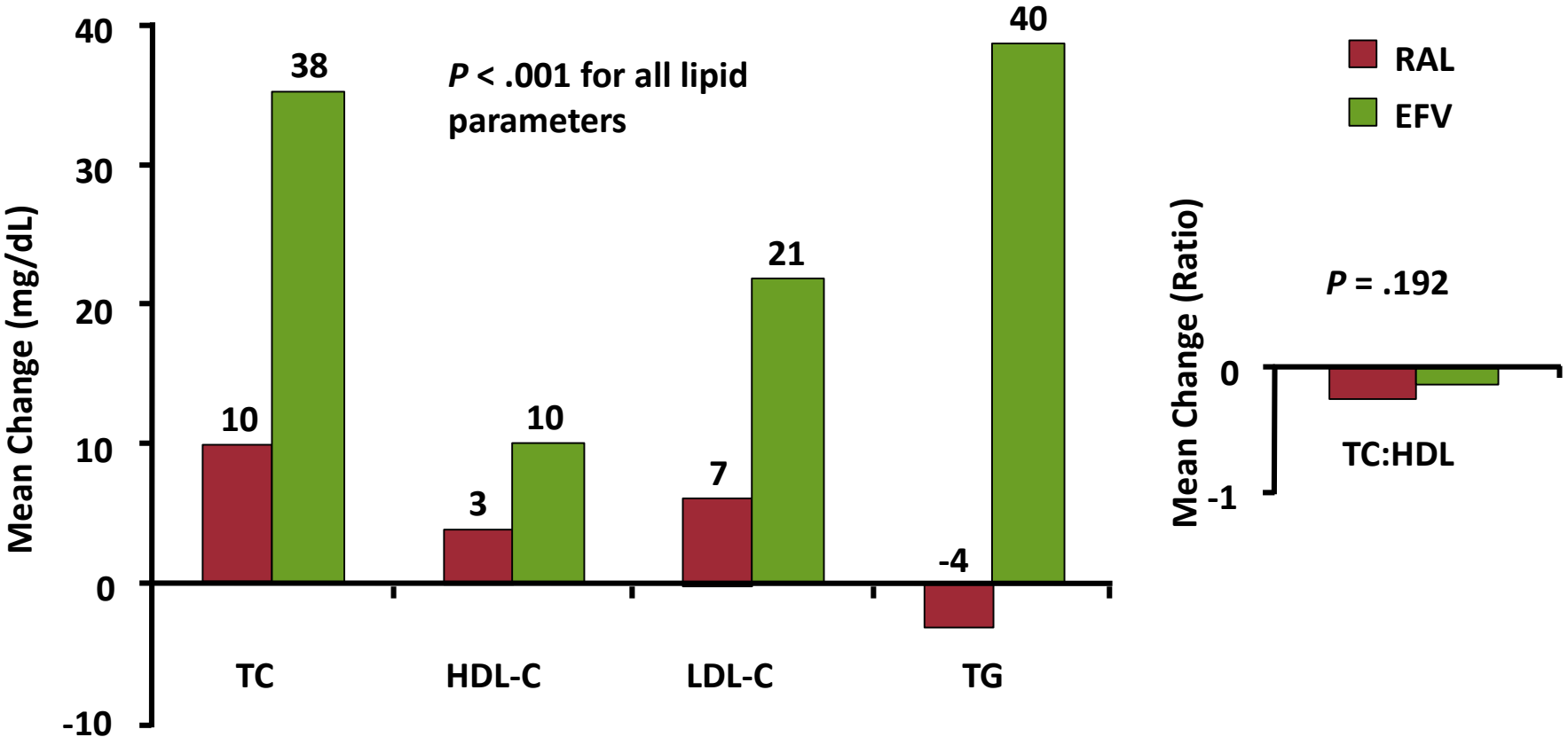
Lennox J, et al. ICAAC 2009. Abstract H-924b.

STARTMRK: Adverse Events at Wk 96

- **Drug-related clinical adverse events more frequent with EFV vs RAL (78% vs 47%; *P* < .0001)**
  - **Serious clinical adverse events in 14% of patients in RAL arm and 12% of patients in EFV arm (*P* = .457)**
- **Fewer patients experienced CNS events by Wk 8 with RAL vs EFV (10.3% vs 17.7%; P = .015)**
- **Malignancies developed in 3 patients in RAL arm vs 11 patients in EFV arm**
  - **Kaposi's sarcoma (n = 7), anal cancer (n = 1), B-cell non-Hodgkin's lymphoma (n = 1), bone cancer (n = 1), lung cancer (n = 1), basal cell cancer (n = 3)**

Lennox J, et al. ICAAC 2009. Abstract H-924b.

STARTMRK: Lipid Changes From Baseline to Week 96



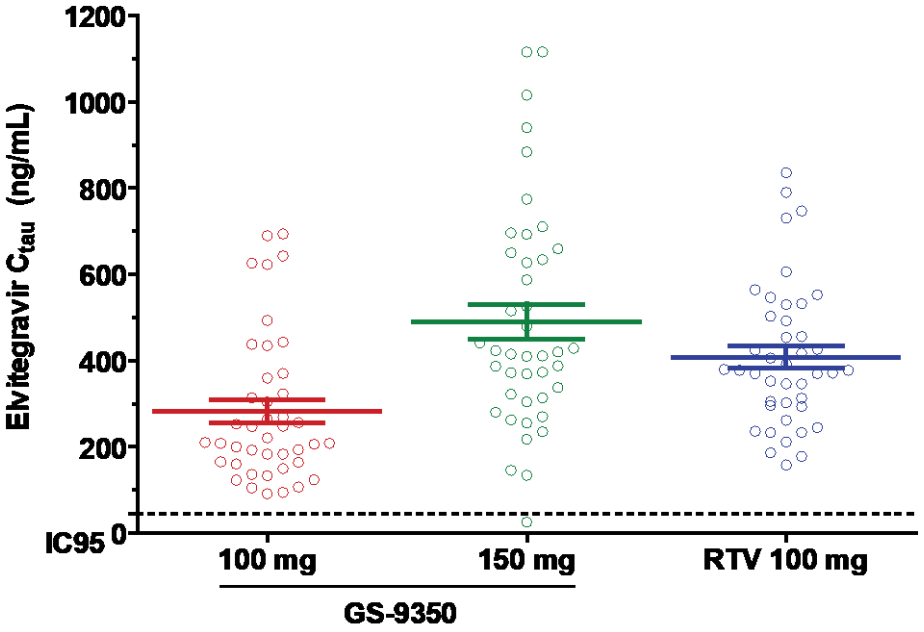
Lennox J, et al. ICAAC 2009. Abstract H-924b.

Elvitegravir (EVG)

- Strand transfer inhibitor of HIV-1 and -2 integrase
- Potent antiviral activity in vitro and *in vivo*
  - PBMC IC_{90} = 1.2 nM
  - 2.0 $\log_{10}$ reduction in HIV-1 RNA as monotherapy
  - 150 mg dose was superior to comparator HIV-1 protease inhibitor in treatment-experienced patients
- Optimal PK and PD in the boosted state
  - 150 mg dose provides trough concentration > 10-fold above the protein binding adjusted IC_{50}
  - **RTV 100 mg or GS9350 150mg maximally boosts EVG**

EVG+GS-9350 Pharmacokinetics

Mean (CV%) EVG PK (n = 42)	GS-9350 100 mg FDC	GS-9350 150 mg FDC	+ RTV 100 mg
AUC_{tau} (ng.hr/mL)	21100 (25.4)	27000 (29.4)	22500 (23.4)
C_{max} (ng/mL)	2250 (26.3)	2660 (27.6)	2500 (32.1)
C_{tau} (ng/mL)	282 (60.4)	490 (52.9)	409 (40.5)

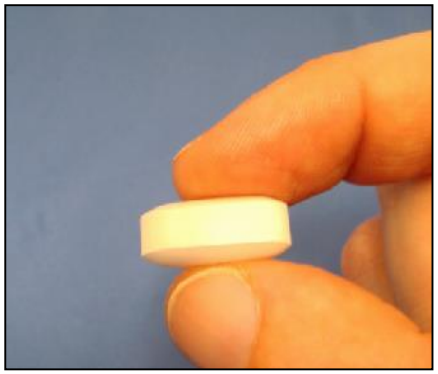


Bars represent geometric mean (±95% CI)

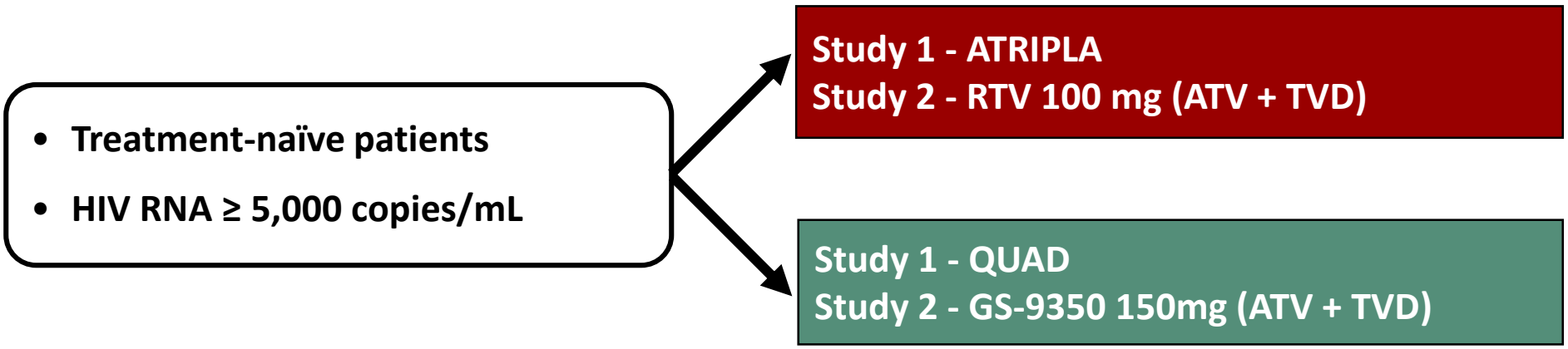
- **High EVG trough concentrations maintained w/ GS-9350 150 mg**
  - **11-fold above the protein binding-adjusted IC_{95} (44.5 ng/mL)**
  - **Low within-subject variability (15% CV)**

The “QUAD” Tablet

- Elvitegravir (EVG 150mg)
- Emtricitabine (FTC 200mg)
- Tenofovir DF (TDF 300 mg)
- GS-9350 (150mg)
- Smaller than ATRIPLA

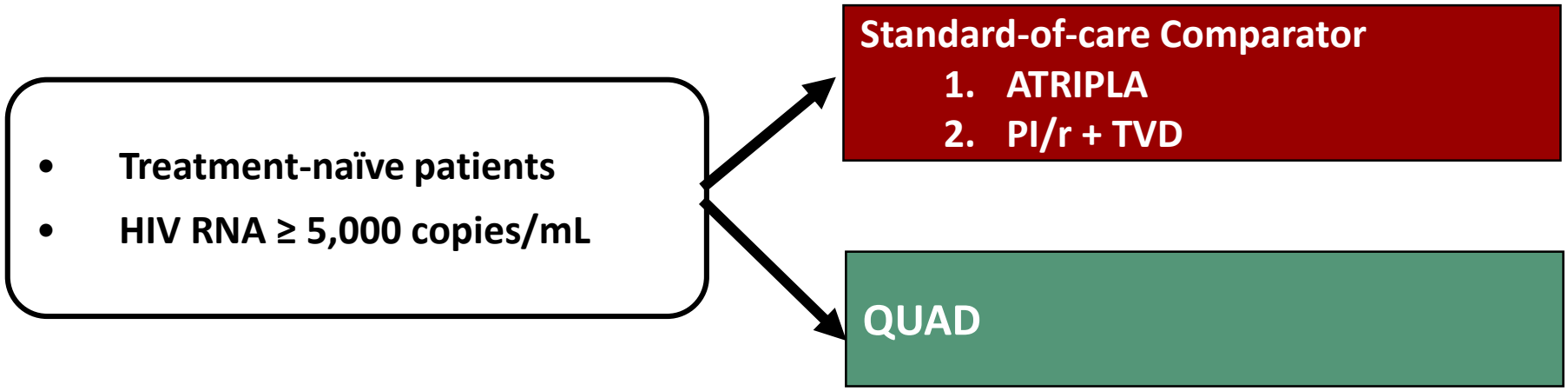


QUAD - Ongoing Phase 2 Studies



- N = 75, 2:1 randomization, double-blind, placebo controlled
- Primary endpoint: HIV RNA < 50 copies/mL at week 24 (48 week study w/ extension)
  - QUAD vs. ATRIPLA (GS-US-236-0104)
    - Completely enrolled
  - GS-9350 vs. RTV (GS-US-216-0105)
    - Completely enrolled

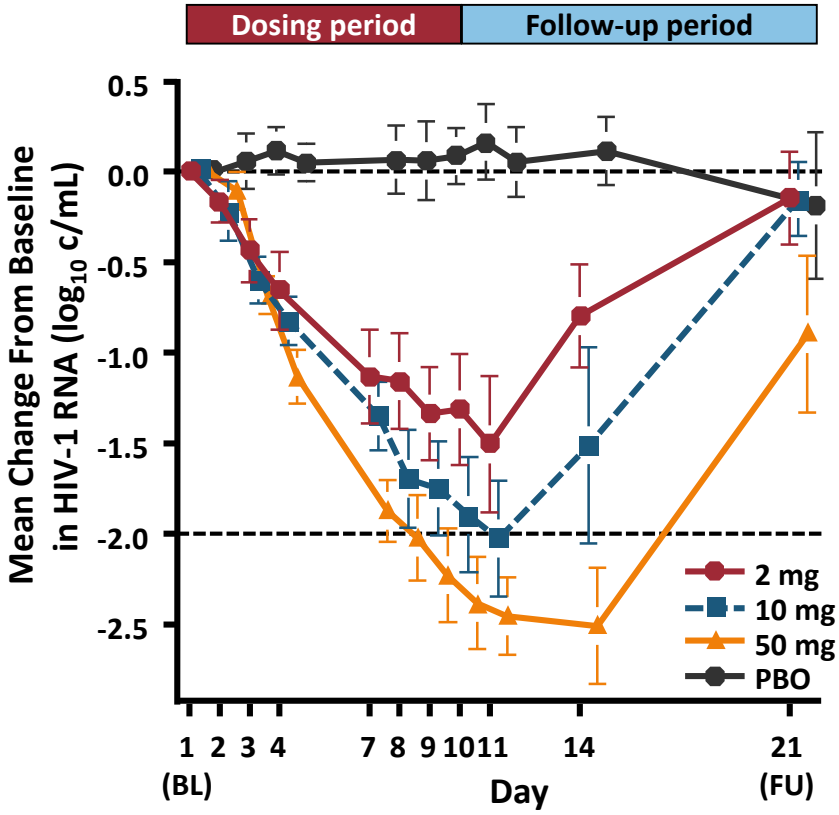
QUAD Phase 3 Studies (Proposed)



- Two registrational studies
  - N ~ 700, 1:1 randomization, double-blind, placebo controlled
  - Primary endpoint: HIV RNA < 50 copies/mL at week 48 (96 week study)
- Study 1: QUAD vs. ATRIPLA
- Study 2: QUAD vs. PI/r + TVD
  - PI comparator of choice in 1H 2010 → 2012 (launch)
    - ATV, DRV, both?

S/GSK1349572: Monotherapy With New INSTI in INSTI-Naive Pts

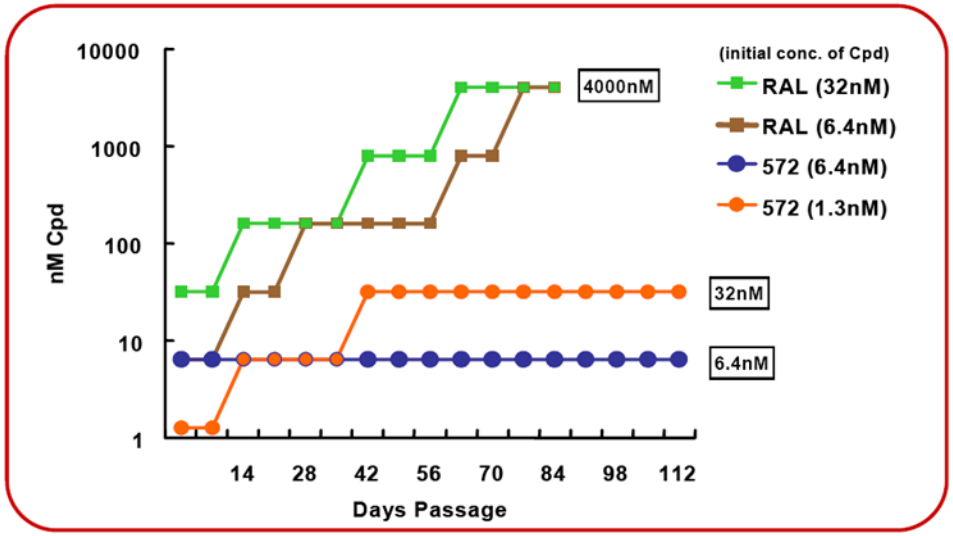
- Randomized, placebo-controlled, double-blind, 10-day monotherapy trial in INSTI-naive pts (either ARV naive or experienced) with CD4 cell count ≥ 100 cells/mm^3, HIV-1 RNA ≥ 5000 c/mL, and no HIV treatment for 12 wks[1]
- 3 cohorts of approximately 10 subjects (8 active, 2 PBO)
  - S/GSK1349572 given at 2 mg, 10 mg, 50 mg, each QD
- S/GSK1349572 highly effective in reducing HIV-1 RNA: 2.5 $\log_{10}$ copies/mL at Day 10 with 50-mg dose
- Exposure-response curve supports QD dosing with no boosting[2]



HIV-1 RNA < 50 c/mL, n	S/GSK1349572		
	2 mg QD (n = 9)	10 mg QD (n = 9)	50 mg QD (n = 10)
	1	0	7

1. Lalezari J, et al. IAS 2009. Abstract TUAB105.
2. Song I, et al. IAS 2009. Abstract WEPEB250. Graphic used with permission.

In vitro Passage Selected Virus Was Able to Replicate Under Higher Raltegravir (RAL) Concentrations than for S/GSK1349572



- HIV-1 IIIB was passaged in medium containing increasing concentrations of S/GSK1349572 or RAL.
- Viruses with RAL-resistant mutation(s) replicated in the presence of RAL at the higher concentration of 4,000nM.
- Genotypic assay identified that N155H, Q148K, or Q148R were selected during passages with RAL by day 28 or 42, and resulted in phenotypic resistance (FC=19, >23, or 8) against RAL.
- HIV was unable to replicate under an initial concentration of 32nM S/GSK1349572, and no replication was observed under 160nM during passage.
- These *in vitro* passage data demonstrate the potential for a higher genetic barrier for S/GSK1349572 when compared to RAL.

Sato A, et al. EACS 2009 – 12th European AIDS Conference 11-14 November 2009, Cologne, Germany. Abst. PE7.1/1

Integrase Mutations Generated by Passage of Virus in the Presence of S/GSK1349572, Raltegravir (RAL), or Elvitegravir (ELV)

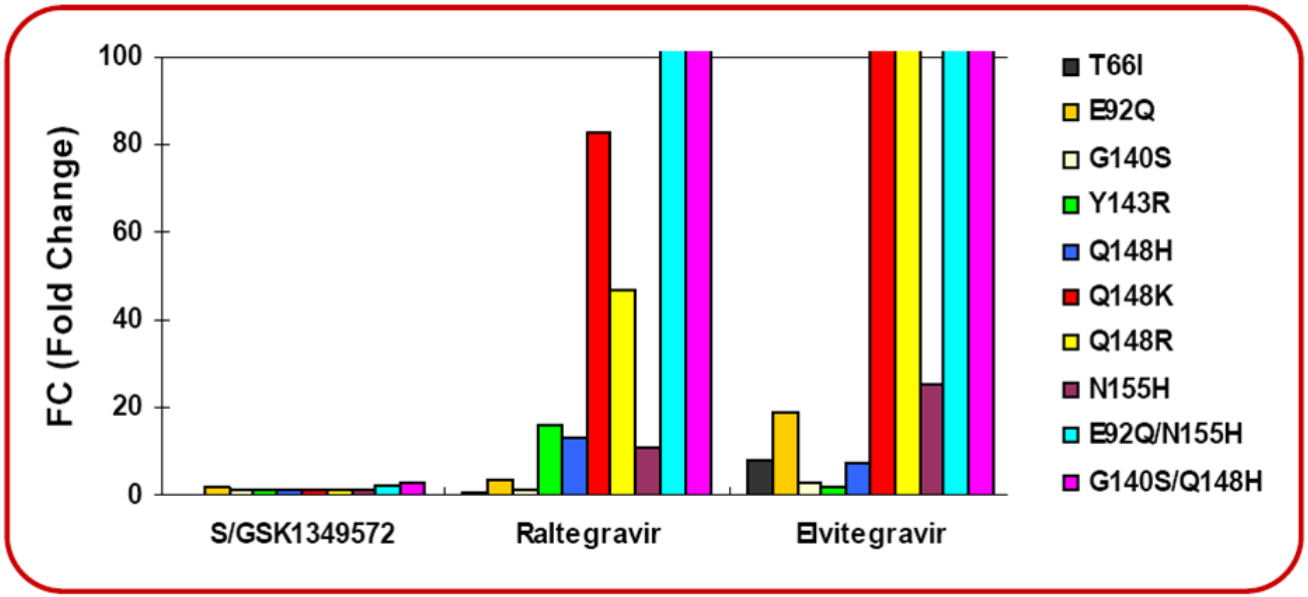
Raltegravir (84 days)	Elvitegravir (56 days)	S/GSK1349572 (56 days)
T124A Q148K* Q148R E138K/Q148K E138K/Q148R G140S/Q148R N17S/Q148K/G163R G140C/Q148K/G163R E138K/Q148K/G163R E92Q/E138K/Q148K/M154I N155H/I204T V151I/N155H T124A/V151I/N155H (FC=6 – >138)	T66I E92Q T124A P145S Q148K Q148R T66I/T124A T66K/T124A E92V/T124A P145S/T124A Q146L/T124A Q148R/T124A T66I/V72A/A128T T66I/E92Q/T124A T66I/T124A/Q146L (FC=2 – 497)	T124A T124A/S153F **S/GSK1349572 (84 days)** T124A S153Y T124A/S153Y L101I/T124A/S153F **S/GSK1349572 (112 days)** T124A S153Y T124A/S153Y L101I/T124A/S153F (FC=1.2 – 4.1)

• Red text indicates substitutions seen in clinical trials

- T124A is polymorphic and S/GSK1349572 has wild type potency versus site directed T124A mutants.
- Highly resistant mutants with high fold change (FC>100) were isolated in the presence of RAL and ELV; many of these mutations have been observed in the clinic in patients failing RAL and ELV-based regimens.
- In the presence of S/GSK1349572, highly resistant mutants were not isolated. Multiple mutations in INI selected during S/GSK1349572 passage only conferred low fold change (maximum FC=4.1).
- Data may be consistent with higher genetic barrier of S/GSK1349572 when compared to RAL and ELV.

Sato A, et al. EACS 2009 – 12th European AIDS Conference 11-14 November 2009, Cologne, Germany. Abst. PE7.1/1

Susceptibility of INI Resistant Molecular Clones to S/GSK1349572



- Fold change (FC) of each clone was determined in comparison with the IC_{50} value for the wild type virus NL432.
- S/GSK1349572 demonstrated low fold change in activity against RAL and ELV-resistant site directed molecular clones.
- Although cross-resistance between RAL and ELV was observed, S/GSK1349572 was active against this panel of INI-resistant mutants.

Sato A, et al. EACS 2009 – 12th European AIDS Conference 11-14 November 2009, Cologne, Germany. Abst. PE7.1/1

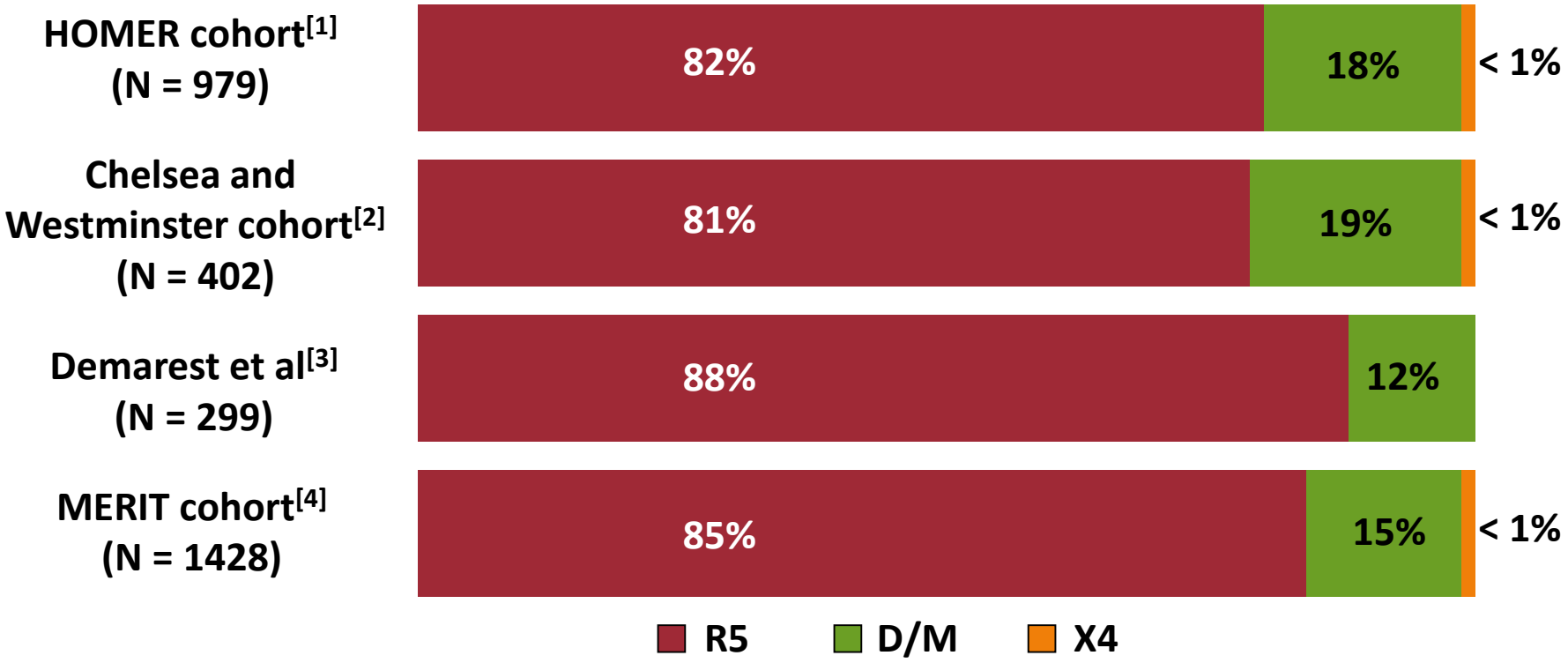
CCR5 INHIBITORS

Viral Tropism Testing in Treatment-Naive Patients

- Tropism testing recommended prior to MVC use
- MVC not approved for first-line therapy
- Tropism may change over time, so testing should be conducted immediately before MVC use
- Tropism testing requires HIV-1 RNA > 1000 copies/mL
  - Possibility that samples stored before treatment initiation may be useful if patient cannot tolerate suppressive first-line regimen and switch to MVC considered
    - Assumes viral tropism does not change during virologic suppression but this has not been established

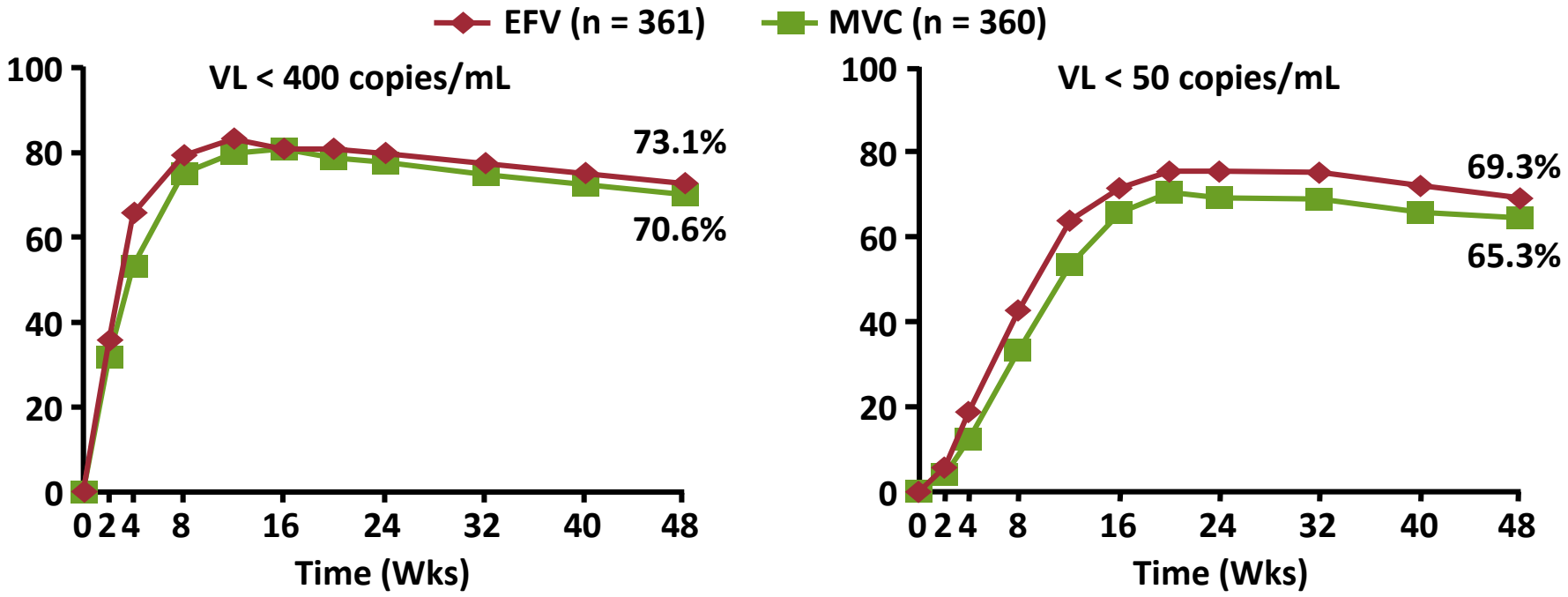
HIV Tropism in Antiretroviral-Naive Populations

- R5-only virus in 80% to 90% of patients, with D/M or X4 virus in remainder



1. Brumme ZL, et al. J Infect Dis. 2005;192:466-474. 2. Moyle GJ, et al. J Infect Dis. 2005;191:866-872. 3. Demarest J, et al. ICAAC 2004. Abstract H-1136. 4. Coakley E, et al. Intl Wkshp on Targeting HIV Entry 2006. Abstract 8.

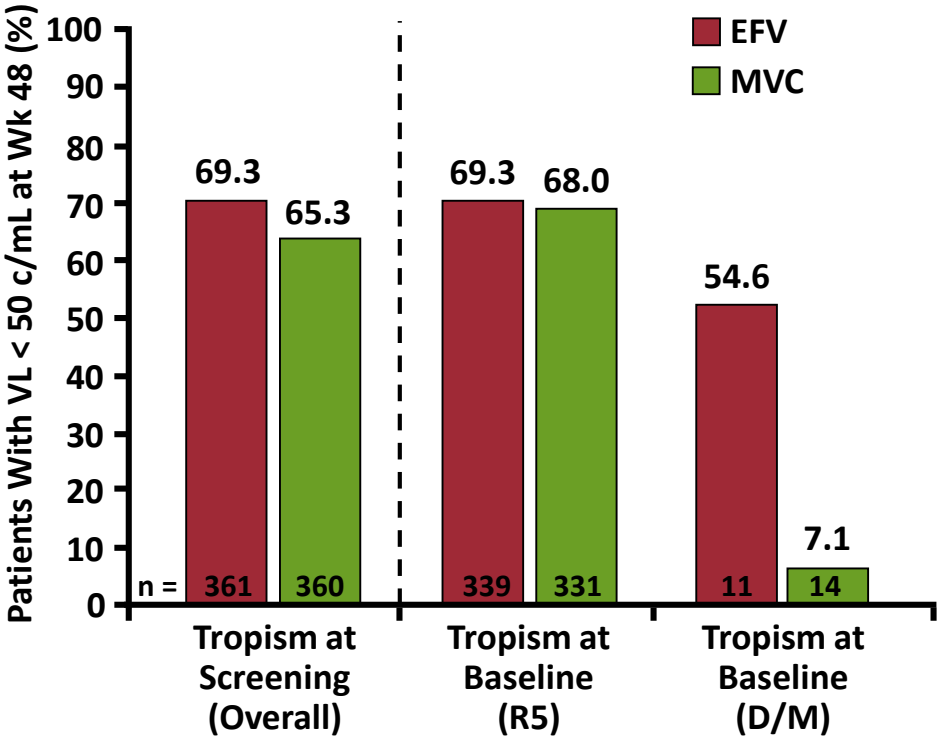
MERIT: Patients With VL < 400 and < 50 copies/mL by Week 48 (ITT)



- MVC was noninferior to EFV for < 400 copies/mL but not < 50 copies/mL endpoint
- CD4+ cell count increases were significantly higher in patients receiving MVC vs EFV (+170 vs +144 cells/mm^3)

Saag M, et al. IAS 2007. Abstract WESS104.

MERIT Substudy: Viral Suppression at Week 48 by Baseline Tropism

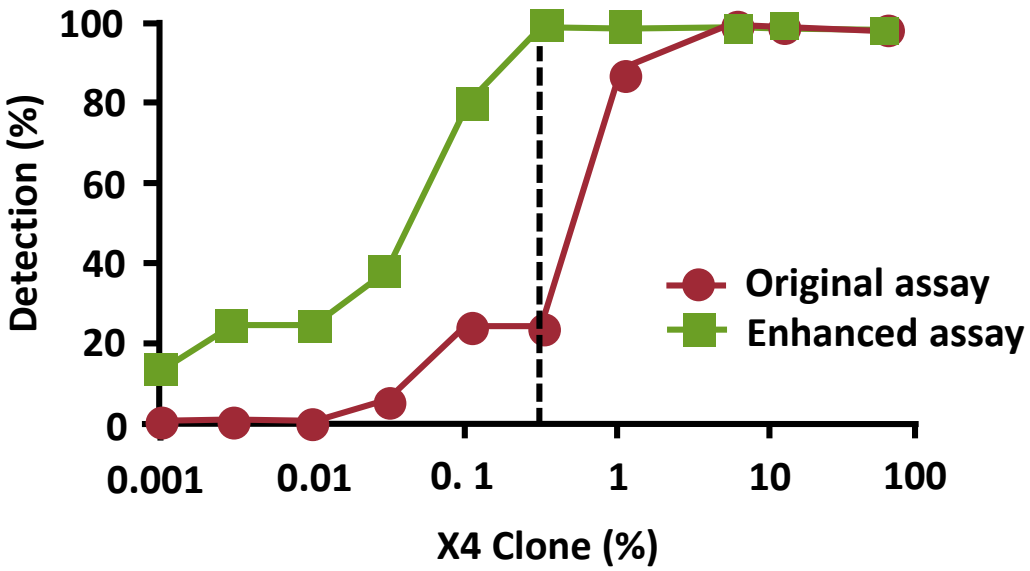


- Change in detected HIV-1 tropism from R5 at screening to D/M at baseline and potentially adherence may explain some MVC failures
  - 3.5% of patients experienced change in detected tropism between screening and baseline
  - 50.0% of pts with R5 virus at baseline and without confirmed X4 at failure had plasma MVC concentrations below limit of detection
- Tropism changes more common in patients with lower mean CD4+ cell count at screening as well as with clade B or other/undetermined HIV-1 subtype vs clade C

Heera J, et al. CROI 2008. Abstract 40LB.

Enhanced Phenotypic Tropism Assay for Detection of CXCR4-Using Virus

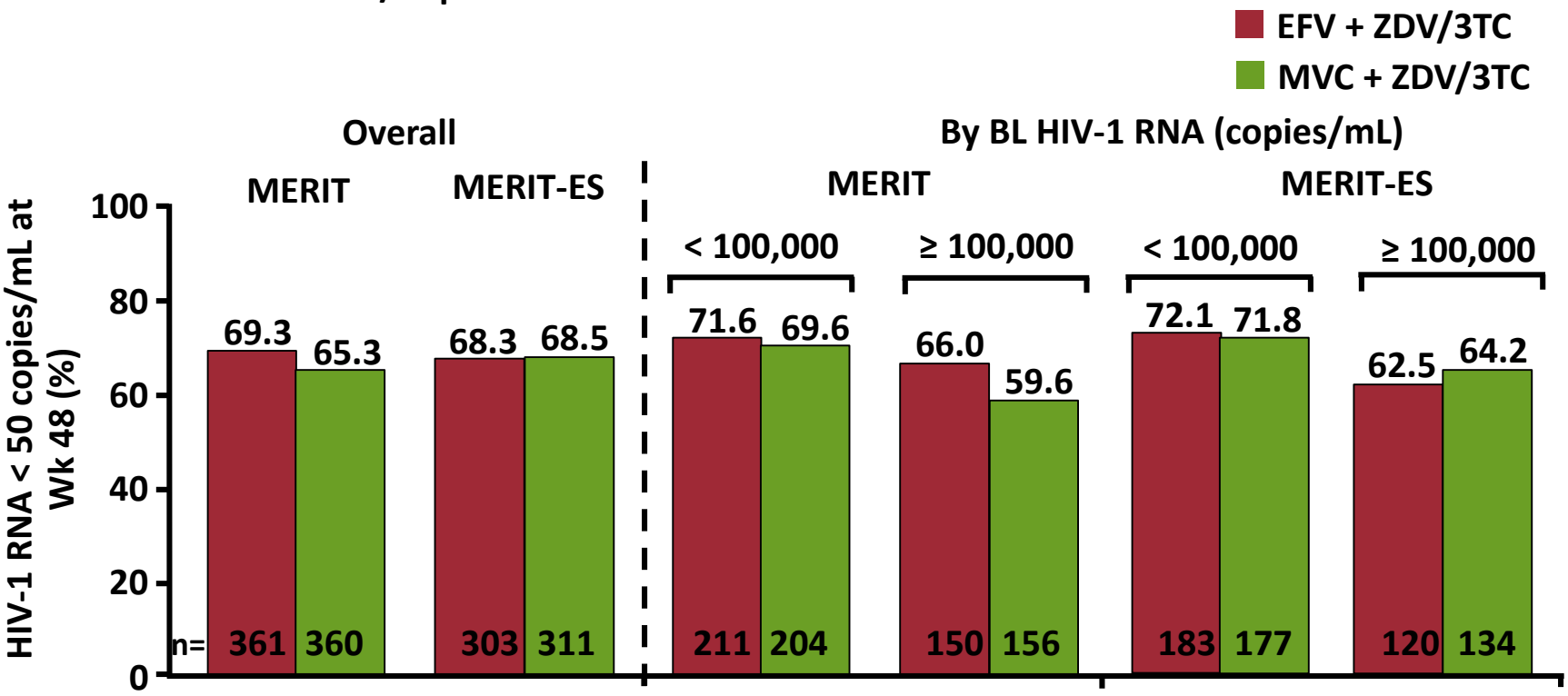
- **Enhanced assay highly sensitive in detecting CXCR4-using HIV variants comprising 0.3% of viral populations**



Trinh L, et al. ICAAC/IDSA 2008. Abstract 1219.

Reanalysis of Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced phenotypic tropism assay resulted in reclassification of 15% of pts from R5 to D/M at screening
  - Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M pts excluded

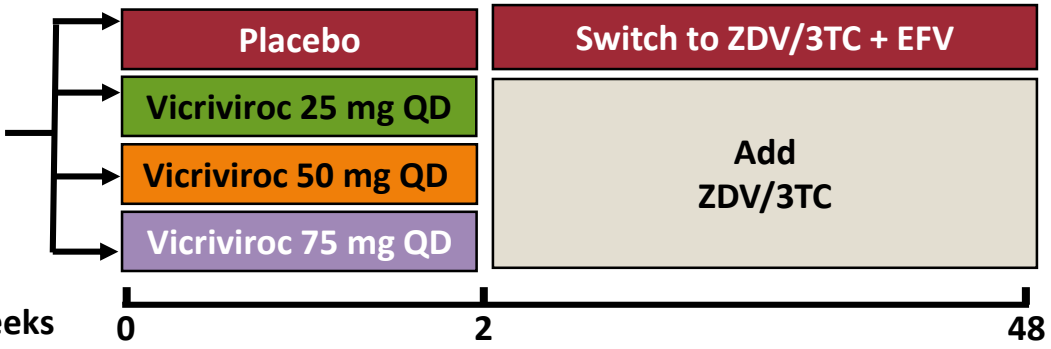


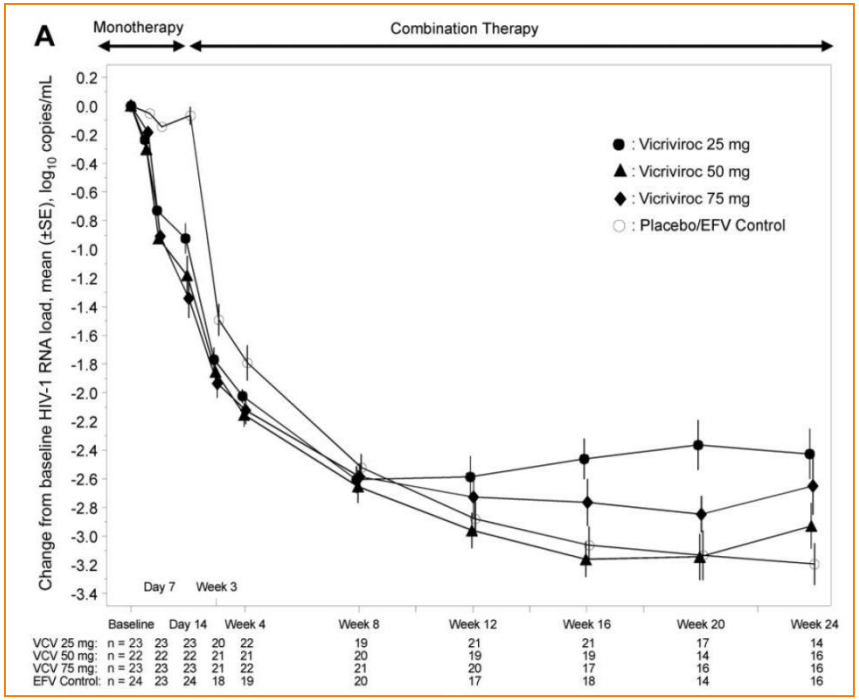
Saag M, et al. ICAAC/IDSA 2008. Abstract 1232a. Graphics reproduced with permission.

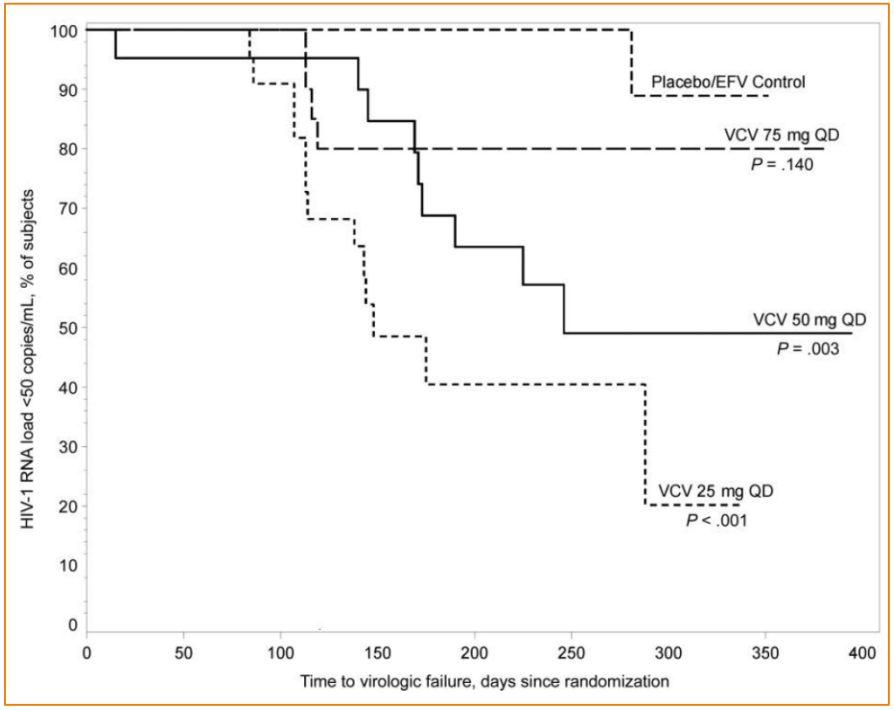
Phase II Study of VCV vs. EFV (both plus Combivir) in Treatment-naïve subjects (P03802)

- **Phase II study, randomized, placebo-controlled trial**

Treatment-naive subjects CCR5-tropic virus
CD4+ count > 150 cells/mm³
HIV-1 RNA ≥ 3000 copies/mL
No baseline resistance
to regimen compounds (N = 92)







Landovitz RJ et al. JID 2008

Summary

- Main advantages of new drugs in ARV first-line: sparing toxicities, improving sequencing, prolonging long-term success
- Integrase inhibitors and possibly new NNRTIs as more promising drug classes
- CCR5 antagonists still limited by tropism distribution and efficacy concern
- Fixed-dose combinations characterizing most of new drug options
- How to preserve still effective options in the sequencing and impact of costs as main problems to be solved