6th Infectivology Today®

L'infettivologia del 3° millennio: AIDS ed altro

VI Convegno Nazionale

15- 16 -17 maggio 2014

Centro Congressi Hotel Ariston
Paestum (SA)

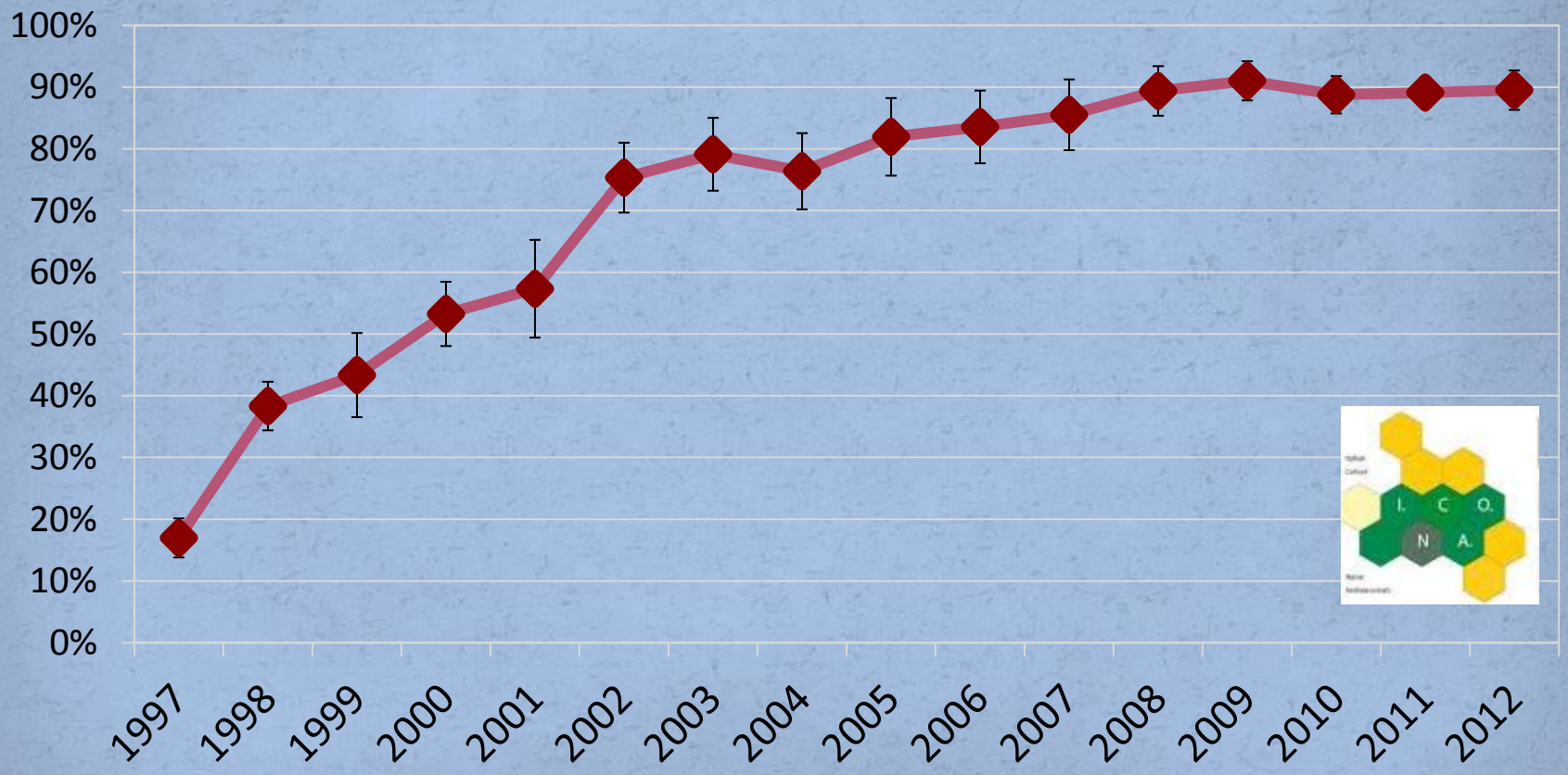
6th Infectivology Today®

"Nuove molecole ad azione anti-HIV"

Annalisa Saracino
Clinica Malattie Infettive
Università di Bari

Paestum (Sa) 15- 16 -17 maggio 2014

Proportion of patients with a HIV-RNA ≤80 cp/mL at 12 months from starting their first ART regimen



Available Antiretrovirals 2014

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

New Classes

Fusion Inhibitors

- Enfuvirtide

R5 Inhibitors

- Maraviroc

Integrase Inhibitors

- Raltegravir
- Elvitegravir
- Dolutegravir (2014)

Fixed-dose Combinations

AZT/3TC
ABC/3TC
TDF/FTC
AZT/3TC/ABC
TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/ELV/COB

www.emea.europa.eu

What's New in Coformulated Agents and Regimens

Co-formulated regimens including approved agents:

Current

- **EFV/FTC/TDF – ATRIPLA**
- **RPV/FTC/TDF -EVIPLERA**
- **EVG/COBI/FTC/TDF - STRIBILD**

Future

- **ABC/3TC/DLV**

Coformulated regimens using investigational agents:

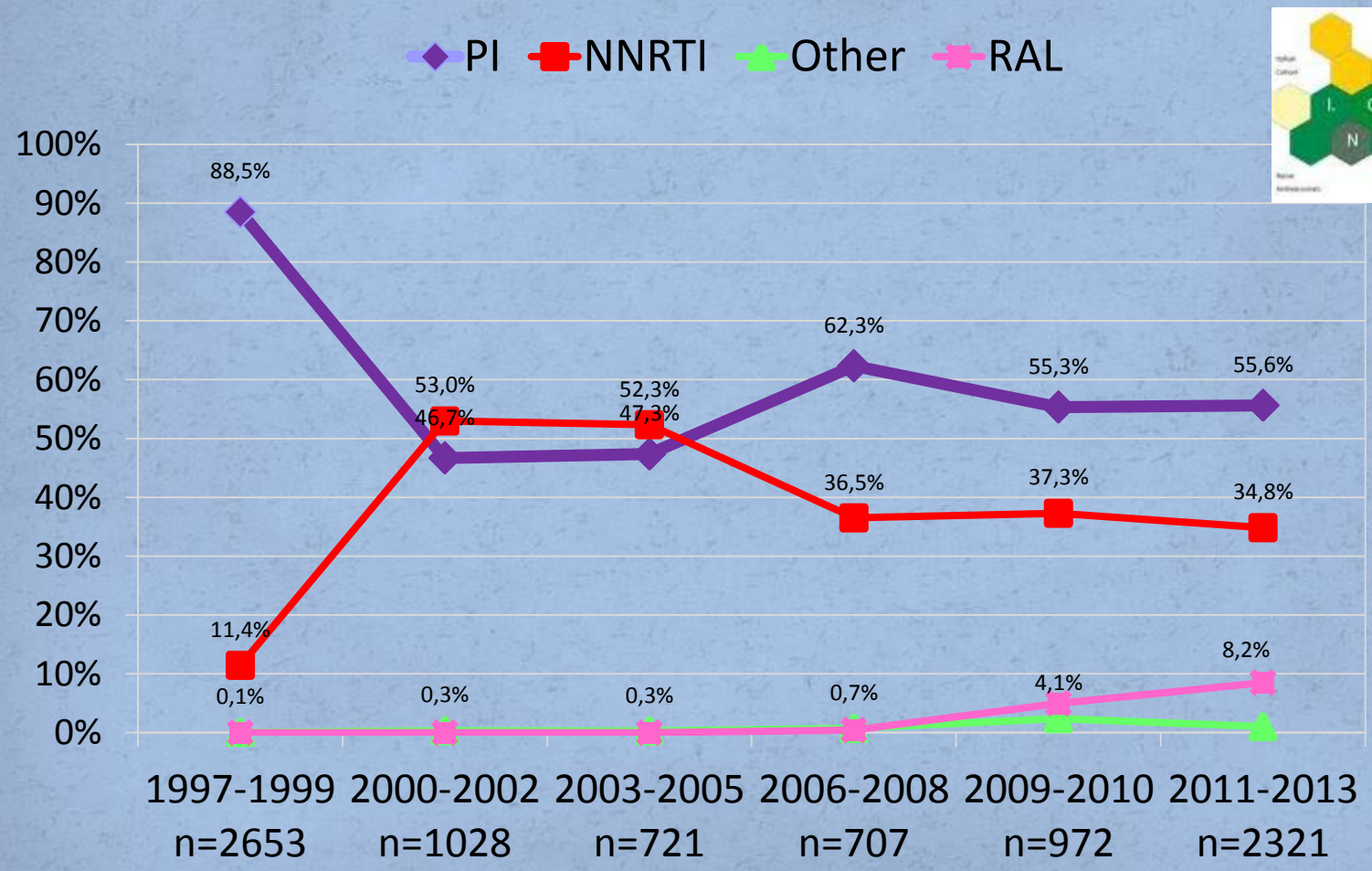
- **EVG/COBI/TAF/FTC**
- **DRV/COBI/TAF/FTC**

PIs coformulated with cobicistat as the pharmacologic booster:

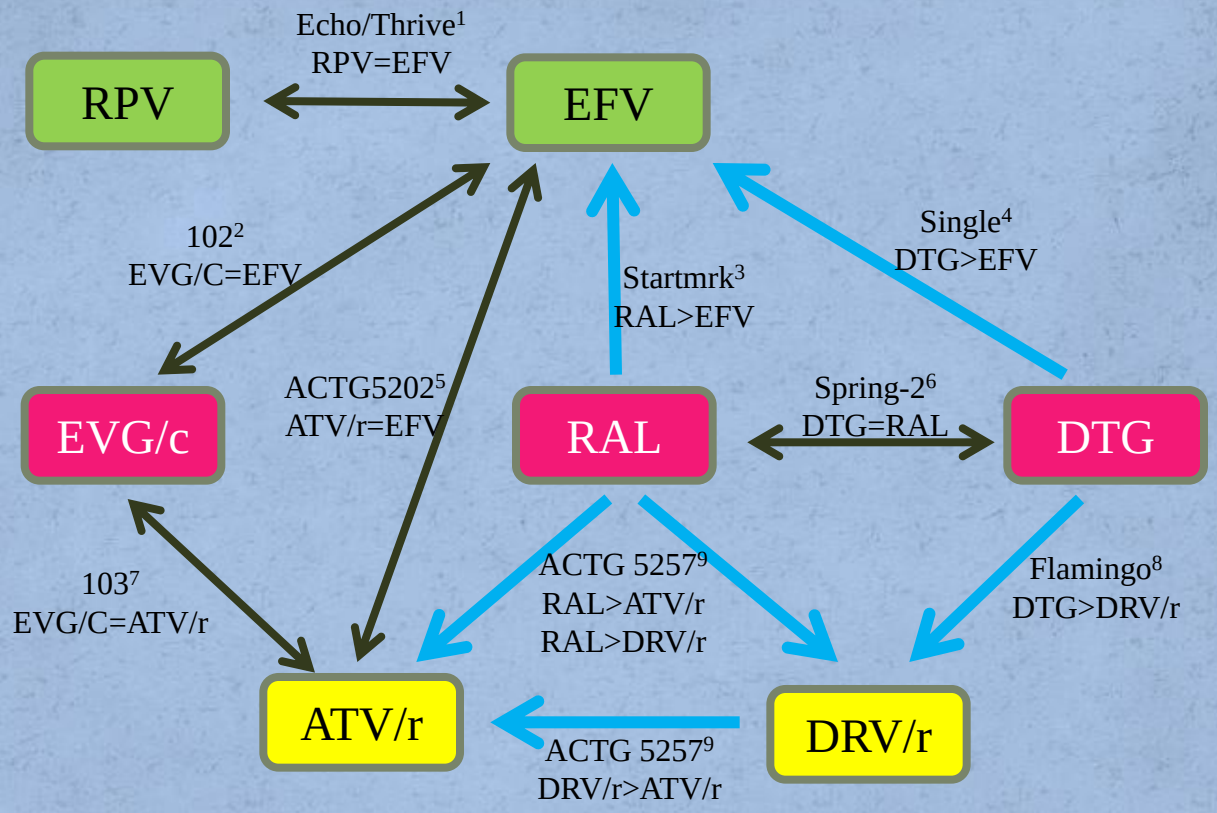
- **ATV/COBI**
- **DRV/COBI**

Novel integrase inhibitors

Proportion of ART classes in first line regimens according to calendar period of starting

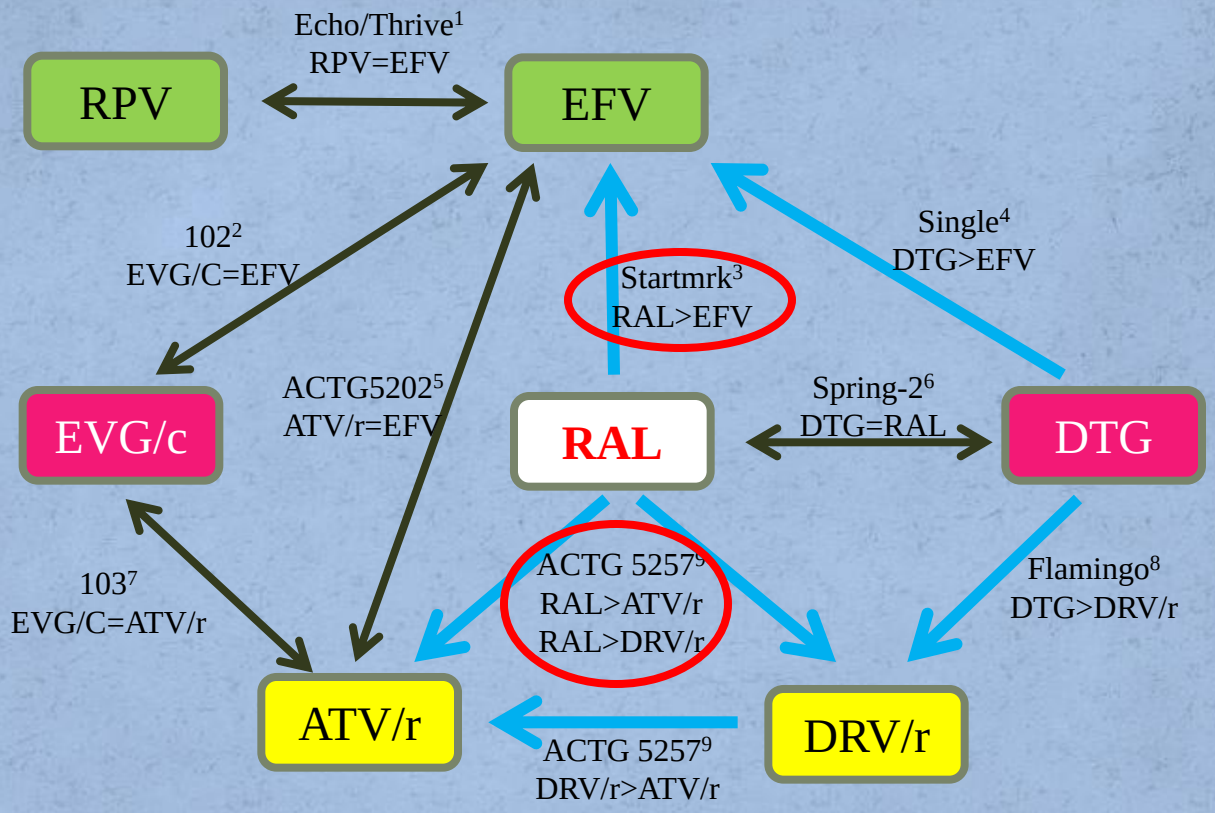


Increasing evidence for integrase inhibitors in ART-naive patients



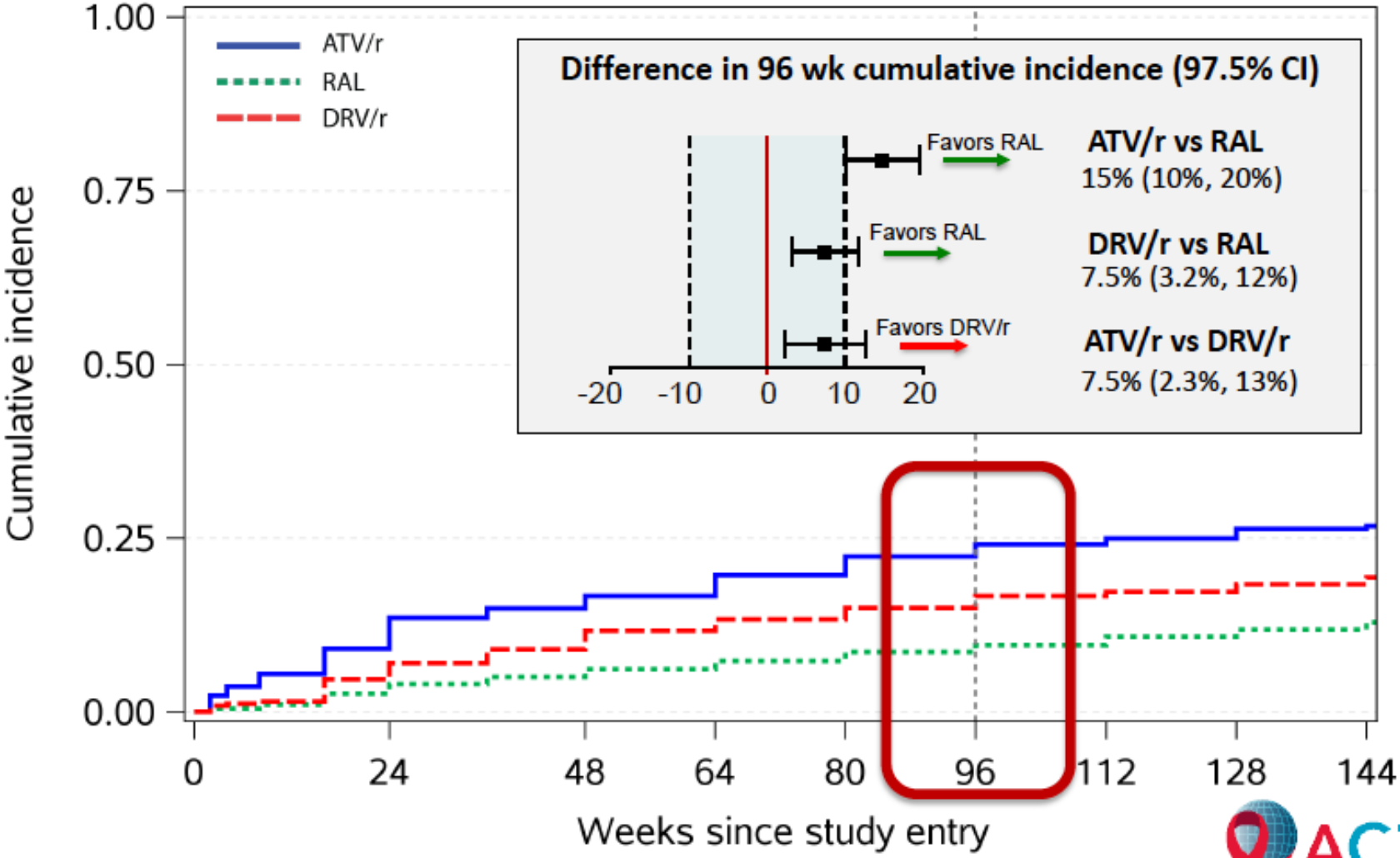
1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

Increasing evidence for integrase inhibitors in ART-naive patients



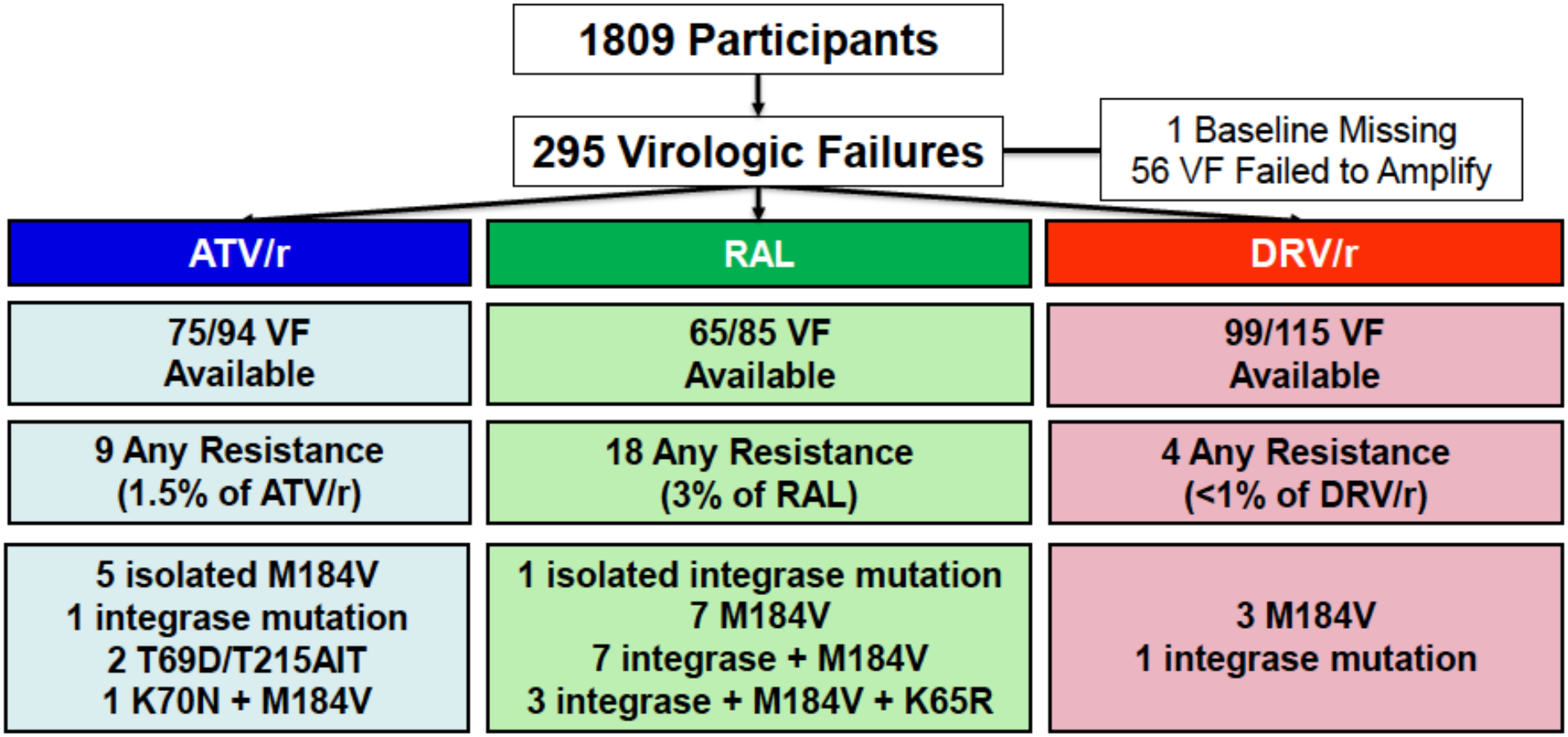
1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

Cumulative Incidence of Virologic or Tolerability Failure



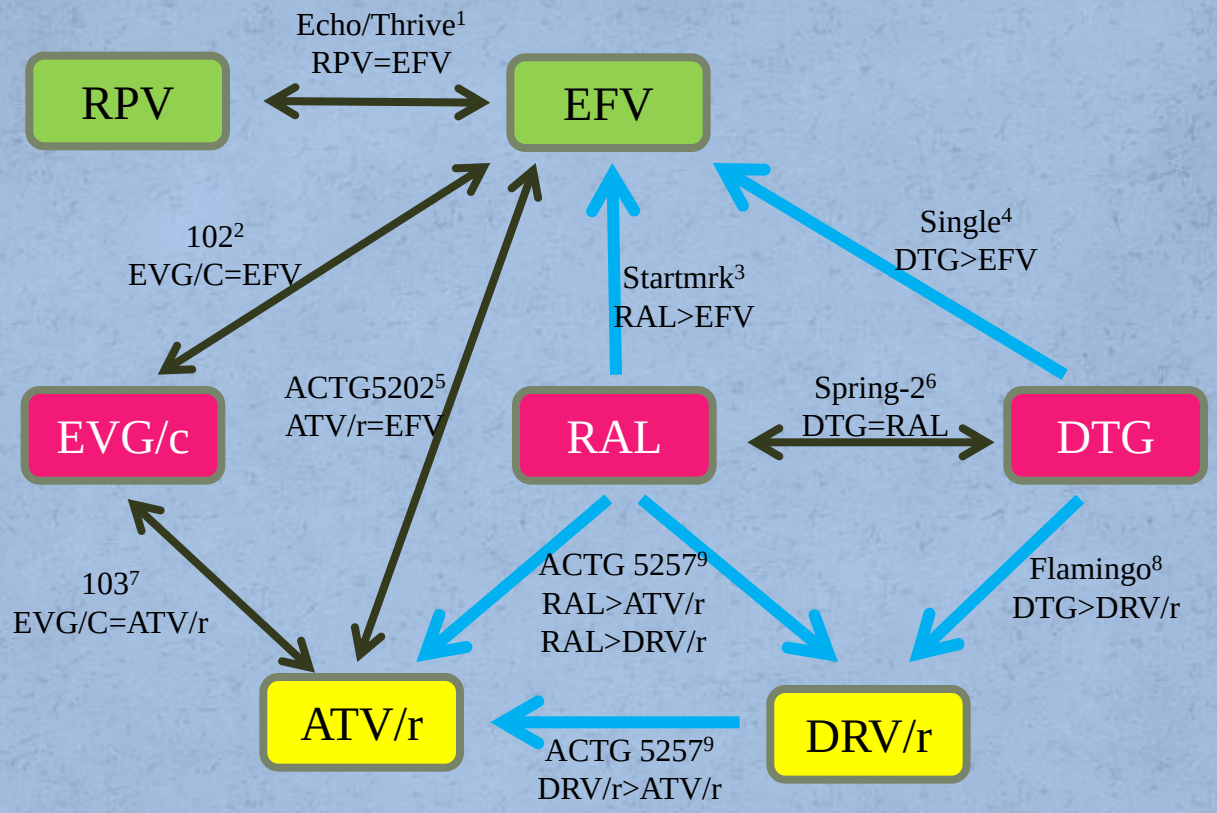
ACTG
AIDS CLINICAL TRIALS GROUP

Resistance to Study Agents



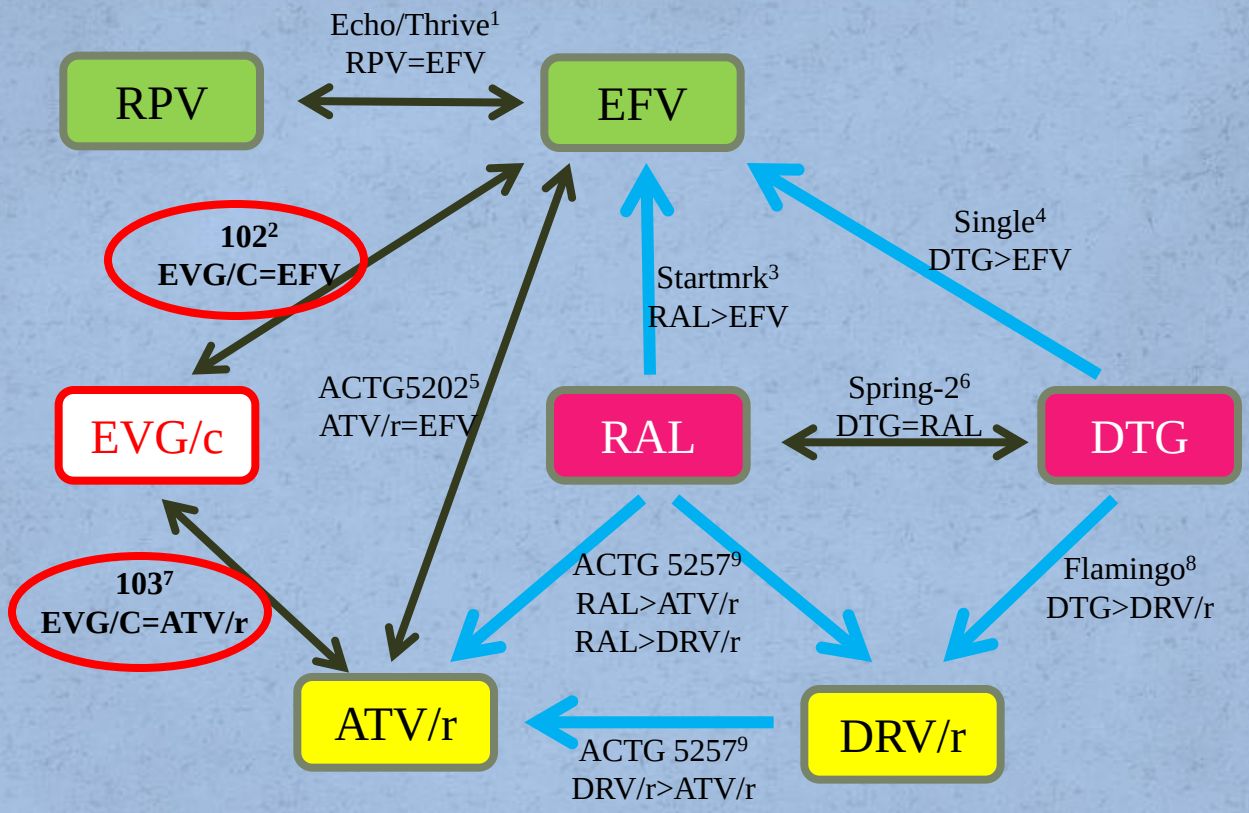
- All arms associated with **significant loss of BMD** through Wk 96
- Significantly greater loss in the combined PI arms than in the RAL arm

Increasing evidence for integrase inhibitors in ART-naive patients



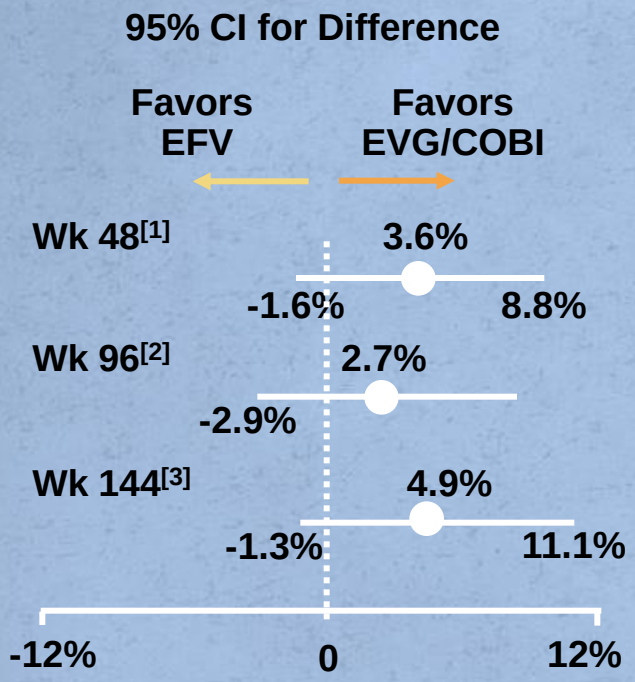
1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

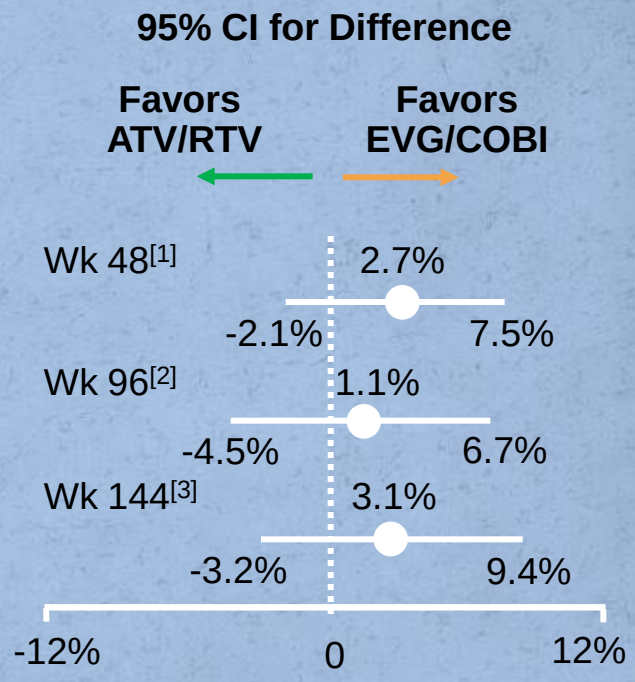
Increasing evidence for integrase inhibitors in ART-naive patients



1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

EVG/COBI/TDF/FTC Noninferior to EFV/TDF/FTC and to ATV/RTV + TDF/FTC in Treatment-Naive Pts





1. Sax PE, et al. Lancet. 2012;379:2439-2448. 2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 3. Wohl D, et al. ICAAC 2013. Abstract H-672a.

EVG/COBI/TDF/FTC Resistance Summary

EVG/COBI vs EFV Through Wk 144[1-3]

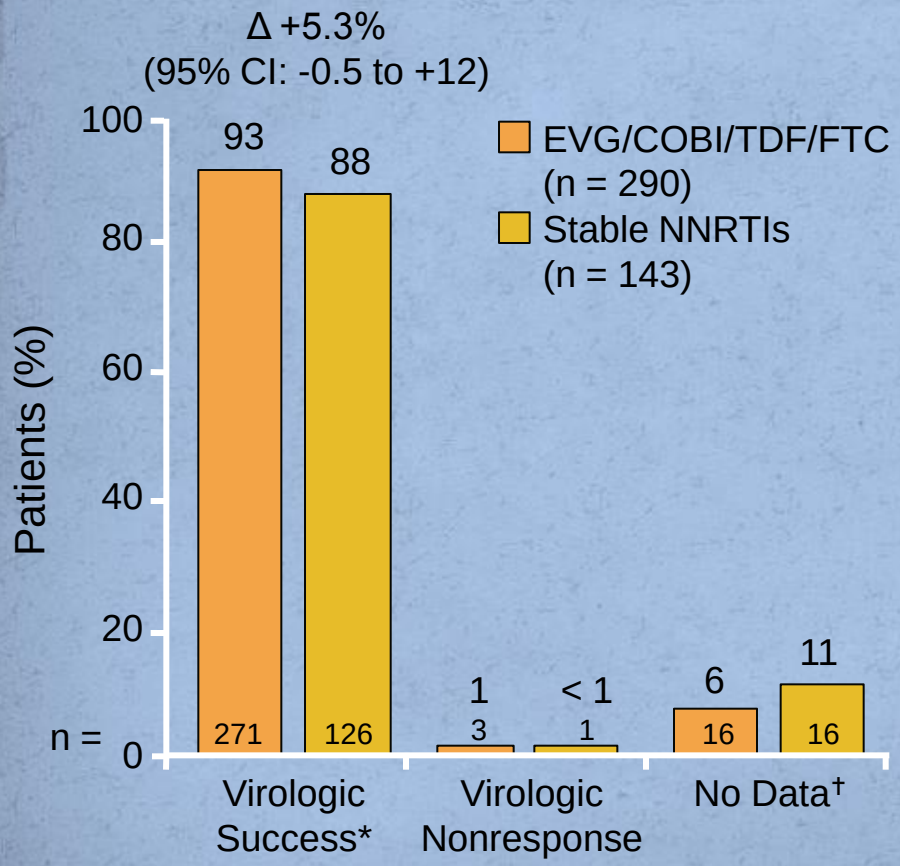
	EVG/COBI (n = 348)			EFV (n = 352)		
Wk	**48**	**96**	**144**	**48**	**96**	**144**
Resistance at VF, n	8	+2	+0	8	+2	+4
INSTI mutations, n	7	+2	+0			
NNRTI mutations, n				8	+2	+4
NRTI mutations, n	8	+2	+0	2	+1	+1

EVG/COBI vs ATV/RTV through Wk 144[4-6]

	EVG/COBI (n = 353)			ATV/RTV (n = 355)		
Wk	**48**	**96**	**144**	**48**	**96**	**144**
Resistance at VF, n	5	+1	+2	0	0	+2
INSTI mutations, n	4	0	+1			
PI mutations, n				0	0	
NRTI mutations, n	3	+1	+2	0	0	+2

1. Sax PE, et al. Lancet. 2012;379:2439-2448. 2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 3. Wohl D, et al. ICAAC 2013. Abstract H-672a. 4. DeJesus E, et al. Lancet. 2012;379:2429-2438. 5. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486.
6. Clumeck N, et al. EACS 2013. Abstract LBPS7/2.

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

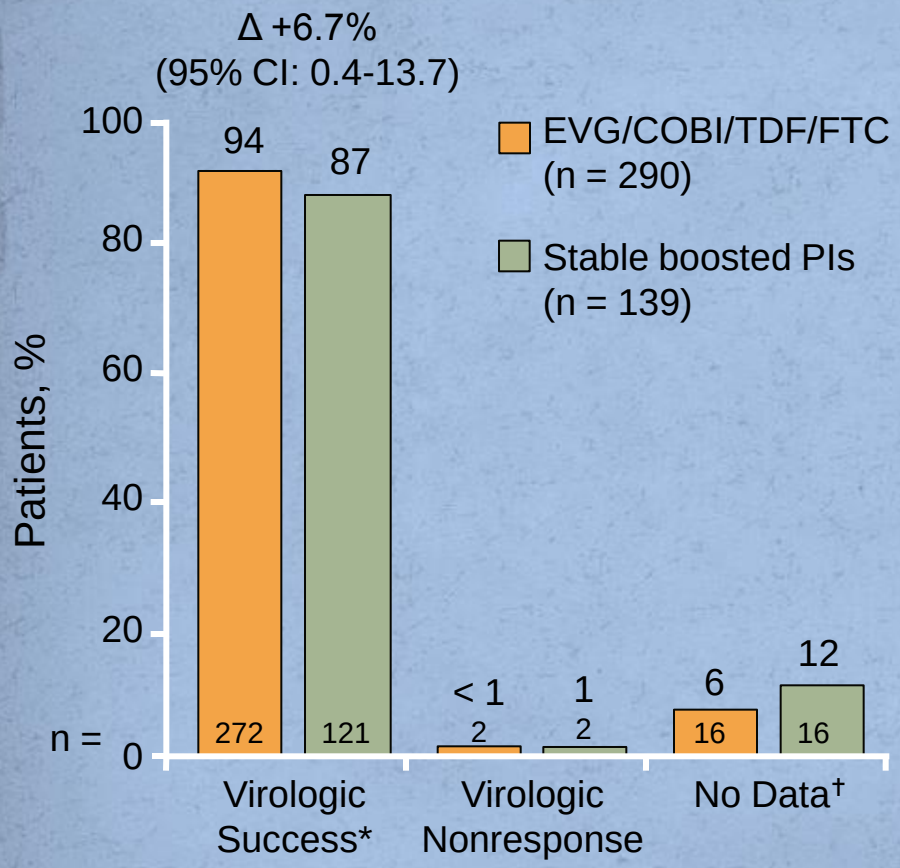


- Regimens: EFV, 78%; NVP, 17%; RPV, 4%; ETR, < 1%; 74% on EFV/TDF/FTC; 91% on first regimen
- Results similar across all baseline virologic and demographic subgroups
- 3 pts with VF in EVG/COBI arm and 1 in NNRTI arm
  - No pts with resistance in either arm
- 5 in the switch arm and 1 in the NNRTI arm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

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

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

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

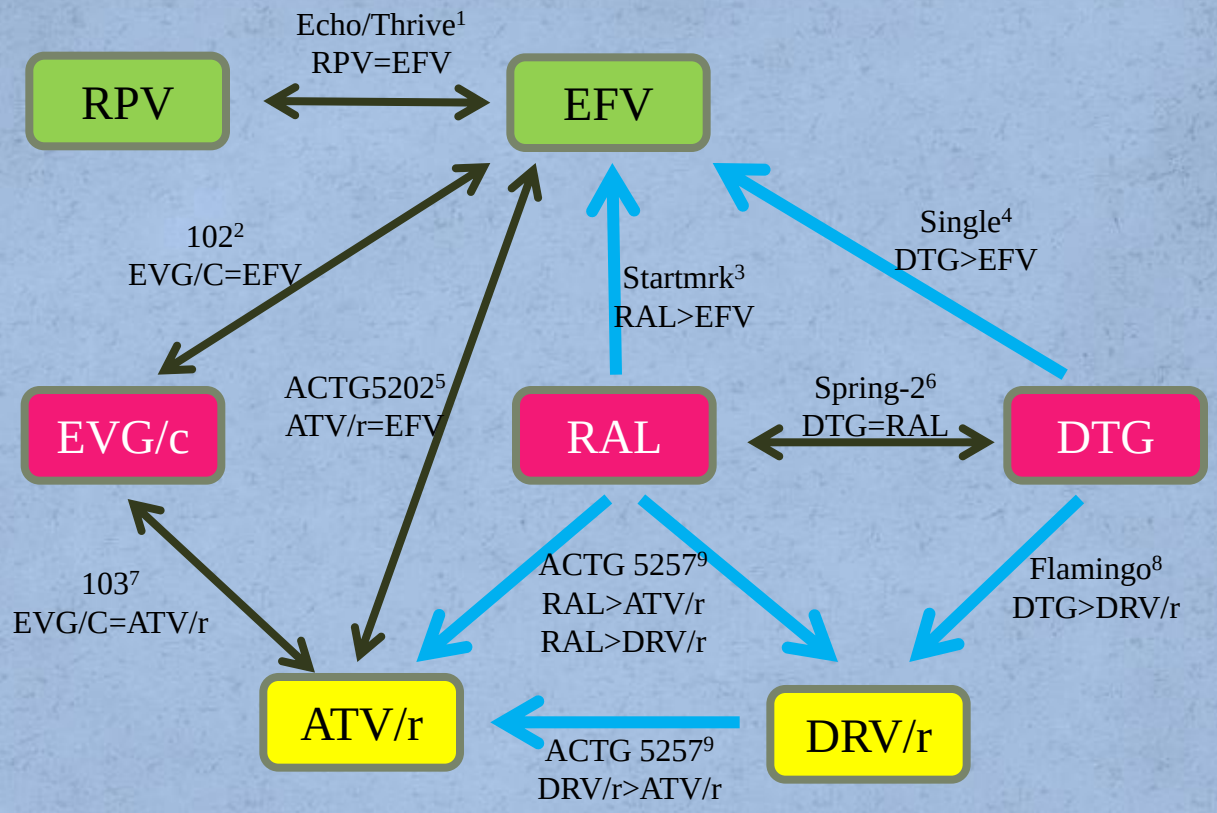


*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

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

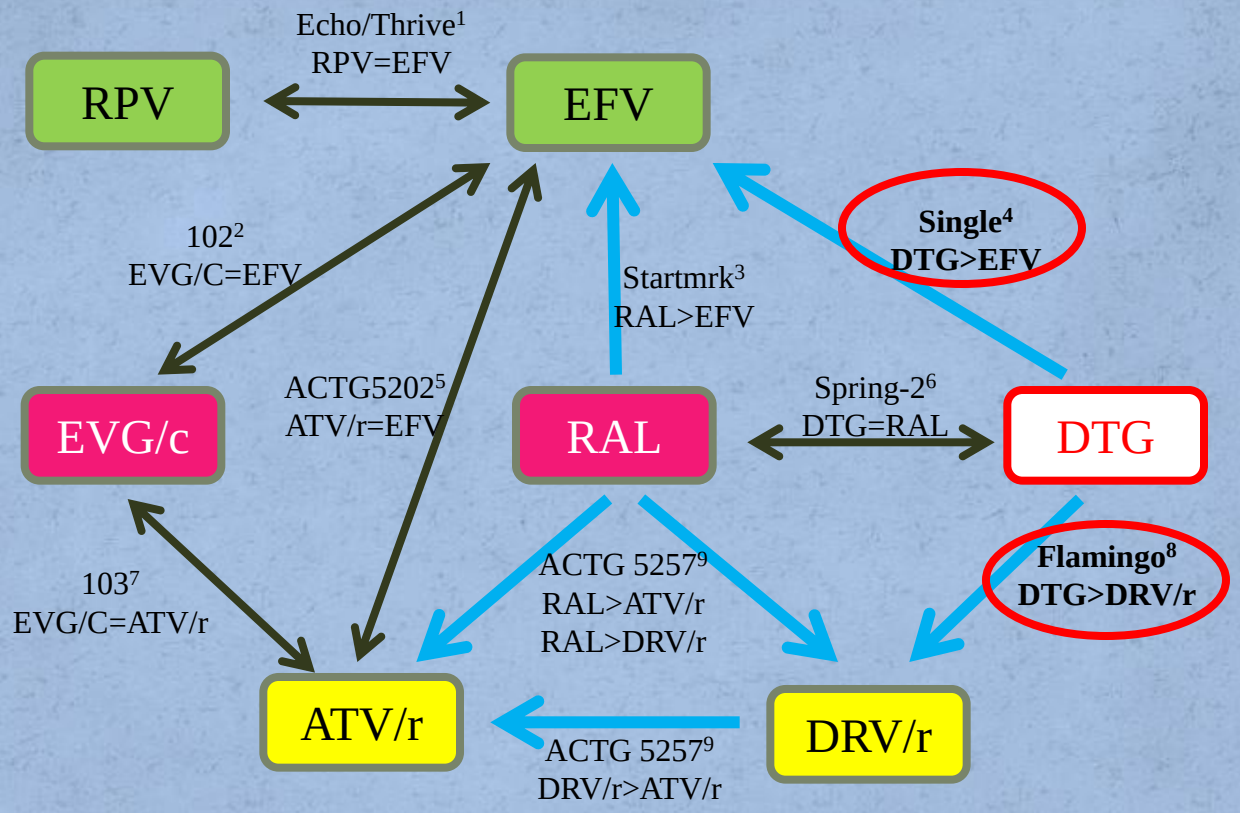
- Regimens: ATV, 40%; DRV, 40%; LPV, 17%; FPV, 3%; SQV, < 1%; 79% on first regimen
- Results similar across all baseline virologic and demographic subgroups
- 2 pts with VF in each arm but no pts with resistance in either arm
- 5 in the switch arm and 2 in the boosted PI arm discontinued due to adverse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

Increasing evidence for integrase inhibitors in ART-naive patients



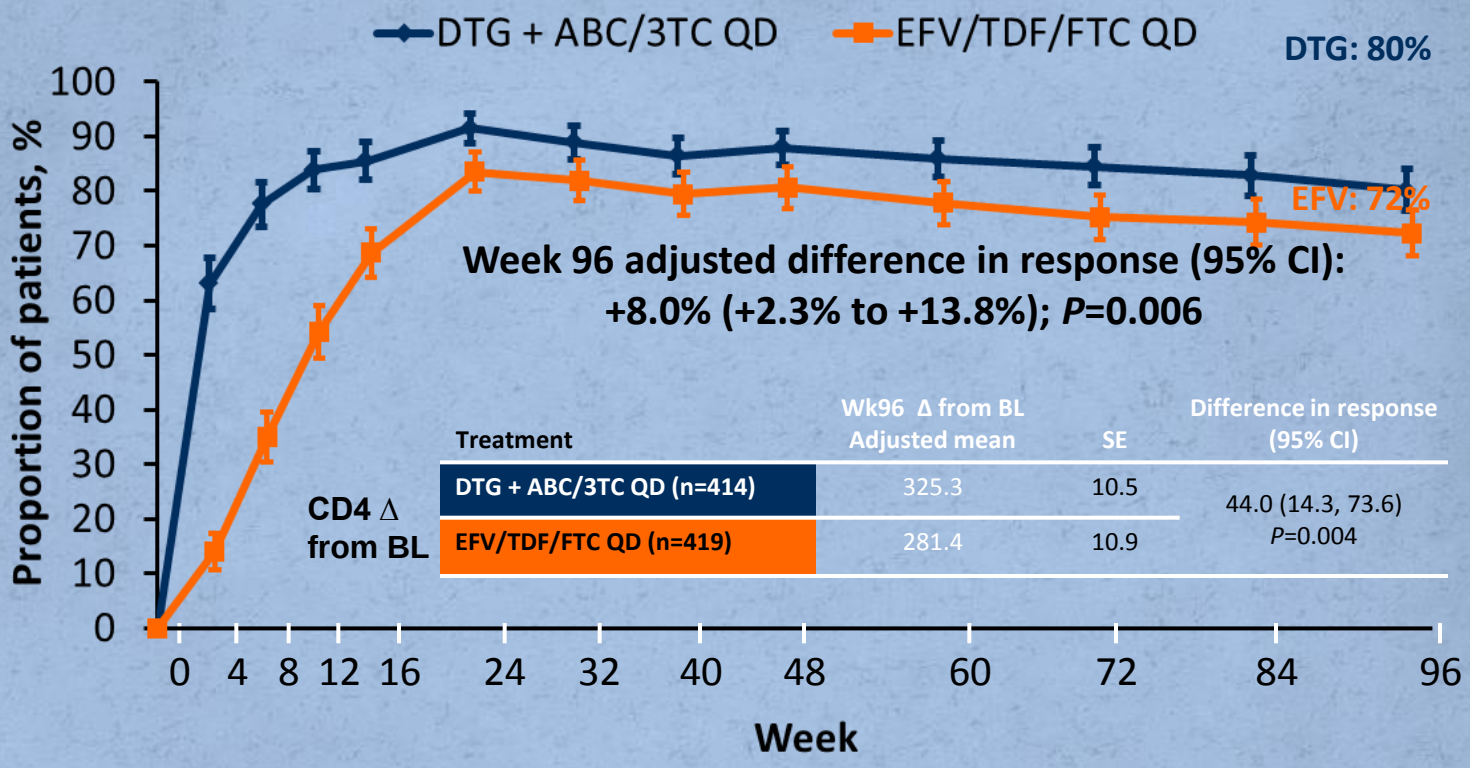
1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

Increasing evidence for integrase inhibitors in ART-naive patients



1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

SINGLE: Virologic Suppression (HIV-1 RNA <50 c/mL; FDA Snapshot)



- Overall, the statistically higher responses on DTG + ABC/3TC vs EFV/TDF/FTC were driven by **withdrawals due to AEs (3% vs 11%, respectively), irrespective of viral load strata.**
- Differences in **time to viral suppression favored DTG + ABC/3TC** (28 vs 84 days, *P*<0.0001).

Walmsley et al. CROI 2014; Boston, MA. Poster 337.

Resistance Mutations

Mutation	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
NRTI TE major mutations	0	1 (K65R)
NNRTI TE major mutations	0	6 (K101E, K103N, G190A)*
INI-r TE major substitution	0**	0

TE = treatment emergent
*n=1 with K101E, n=1 with K103N, n=2 with K103K/N, n=1 with G190A and n=1 with K103N + G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Discontinuations

Parameter	DTG + ABC/3TC QD (n=414)	EFV/TDF/FTC QD (n=419)
Body system (at least 2% in either arm)		
Psychiatric disorders	4 (<1%)	23 (5%)
Nervous system disorders	1 (<1%)	17 (4%)
Skin and subcutaneous tissue disorders	2 (<1%)	9 (2%)
General disorders and administration site conditions	0	10 (2%)
Gastrointestinal disorders	0	8 (2%)

Laboratory Analyses: Change from Baseline in Renal Parameters

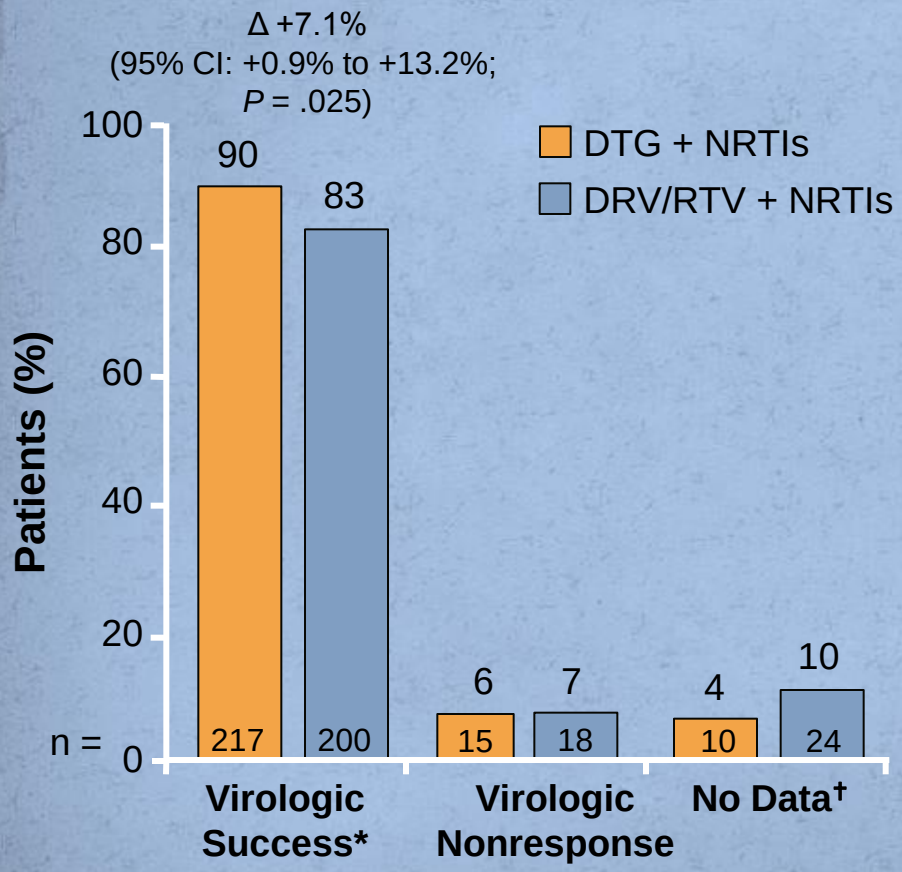
Parameter	DTG + ABC/3TC QD		EFV/TDF/FTC QD	
	Week 48	Week 96	Week 48	Week 96
Urine albumin/ creatinine ratio (mg/mmoL) Median change (IQR)	0 (-0.3, 0.3)	0 (-0.3, 0.2)	0.05 (-0.2, 0.3)	0.05 (-0.2, 0.3)
Serum creatinine (mg/dL) Median change (IQR)	0.11 (0.05, 0.18)	0.14 (0.07, 0.20)	-0.01 (-0.06, 0.04)	0.02 (-0.04, 0.07)

- Small, non-progressive changes in serum creatinine were observed in the DTG + ABC/3TC arm, due to **known inhibition of tubular creatinine secretion by DTG**.[1]
- Grade 2 or higher ALT elevations were observed more commonly in the EFV/TDF/FTC arm (24/419; 6%) than in the DTG + ABC/3TC arm (12/414; 3%).

1. Koteff J, Borland J, Chen S, et al. *Br J Clin Pharmacol.* 2013;75:990-996.

Walmsley et al. CROI 2014; Boston, MA. Poster 337.

FLAMINGO: DTG Superior to DRV/RTV + 2 NRTIs in Tx-Naive Patients at Wk 48



- Treatment-related study d/c:
  - 1% in DTG arm vs 4% in DRV/RTV arm
- More diarrhea with DRV; more headache with DTG
- 2 pts (< 1%) in each arm met criteria for VF
  - No pts with resistance in either arm
- Similar increase in CD4+ cell count at Wk 48:
  - +210 cells/mm^3 in each arm

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

Feinberg J, et al. ICAAC 2013. Abstract H-1464a.

Novel boosting agents: cobicistat

Cobicistat: A New Boosting Agent

- Small molecule with **no HIV activity** (no concern of drug resistance in pts with suboptimal virologic response)

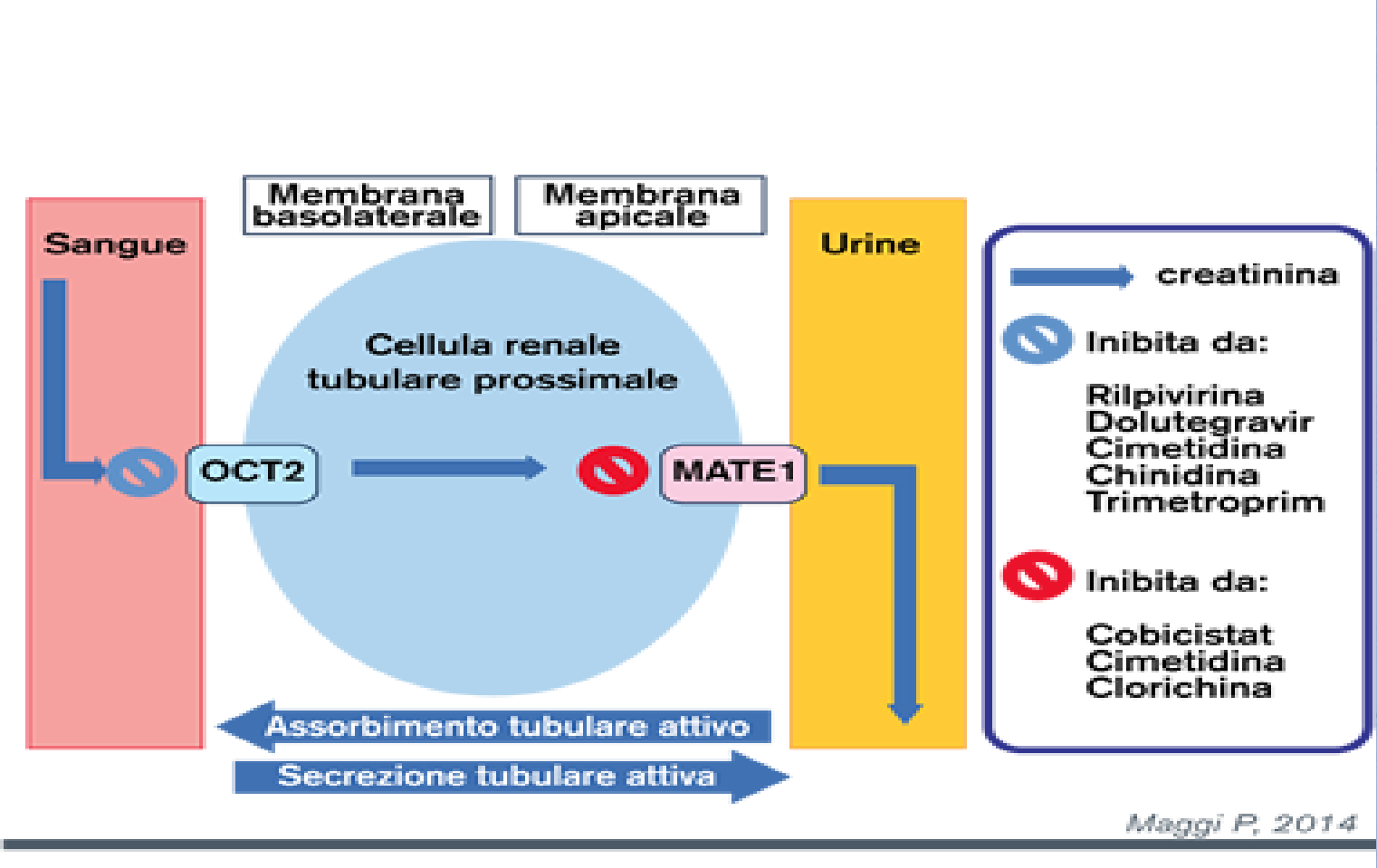
- Similar ↑ from BL in fasting TC and TGs compared with RTV when boosting same agent[1]
- **Inhibitor of CYP3A4**; many drug–drug interactions[2,3]

- 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]

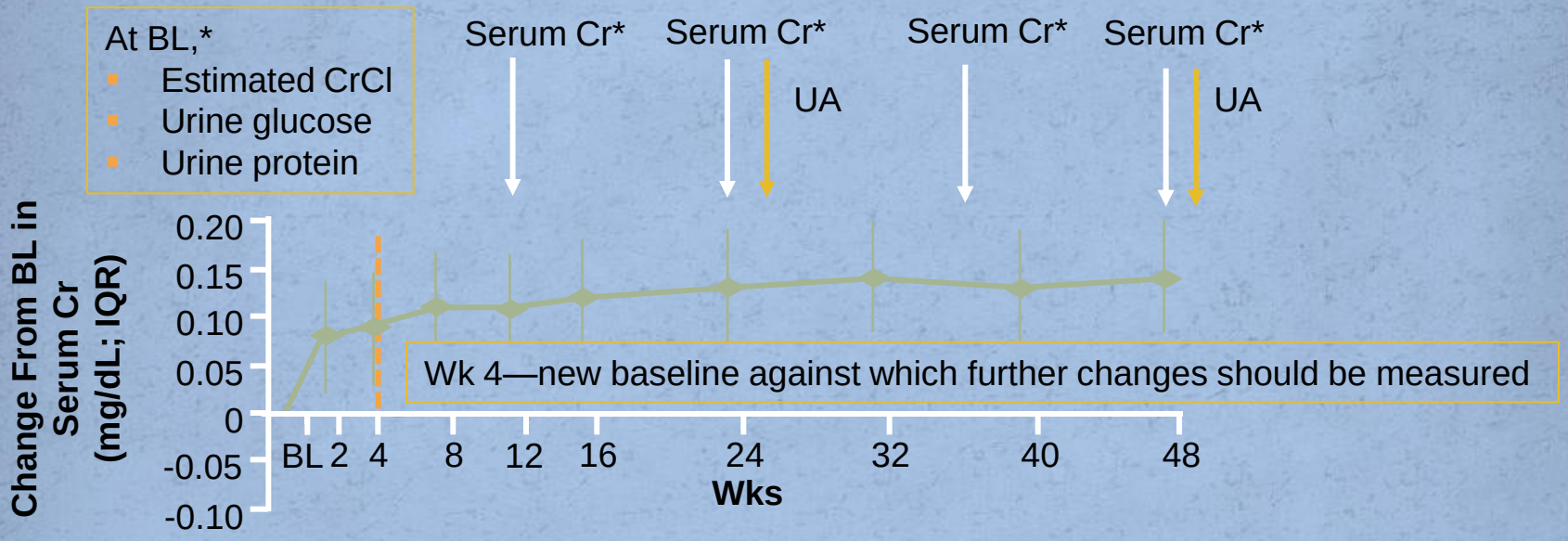
- Availability of cobicistat has allowed for development of new coformulated agents and regimens

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].

Cobicistat: inhibition of MATE1



Renal Monitoring With Cobicistat



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

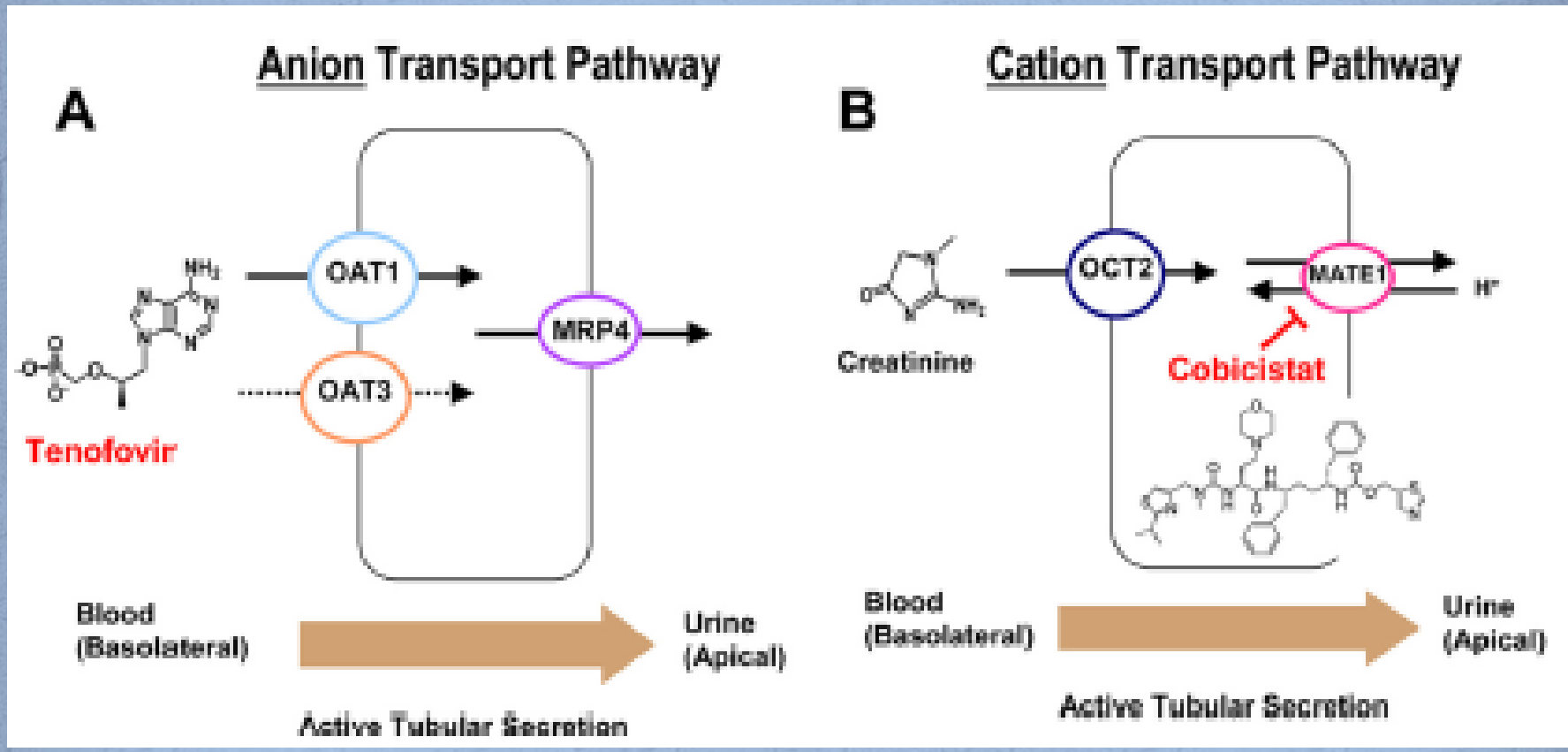
Coformulated drugs containing COBI should not be initiated in pts with estimated CrCl < 70 mL/min (Studies ongoing in pts with CrCl < 70

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.

Cobicistat: inhibition of MATE1

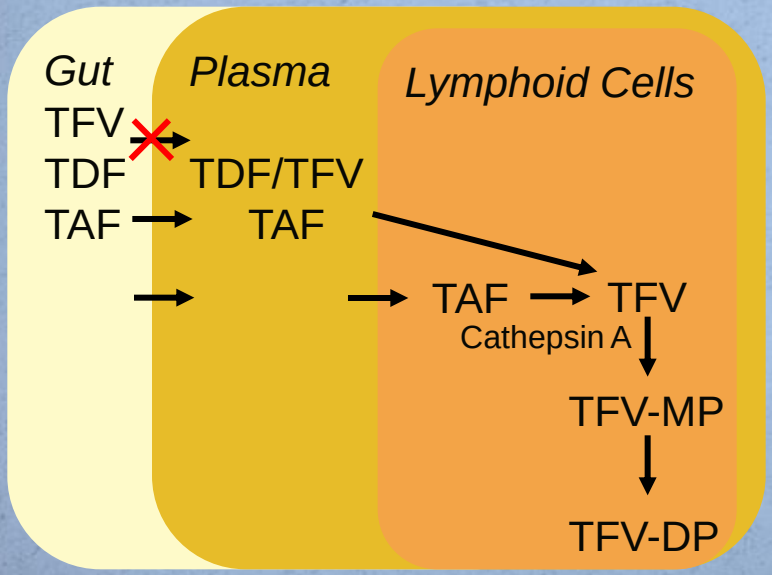


From TDF to TAF

Tenofovir Alafenamide vs Tenofovir DF in ART-Naive Patients

TAF (GS-7340), investigational prodrug of tenofovir with lower plasma concentrations, increased delivery to hepatocytes, lymphoid cells

- Randomized, placebo-controlled phase II trial in ART-naive patients



HIV-infected, ART-naive patients, with CD4+ cell count > 50 cells/mm^3 and eGFR ≥ 70 mL/min (N = 170)

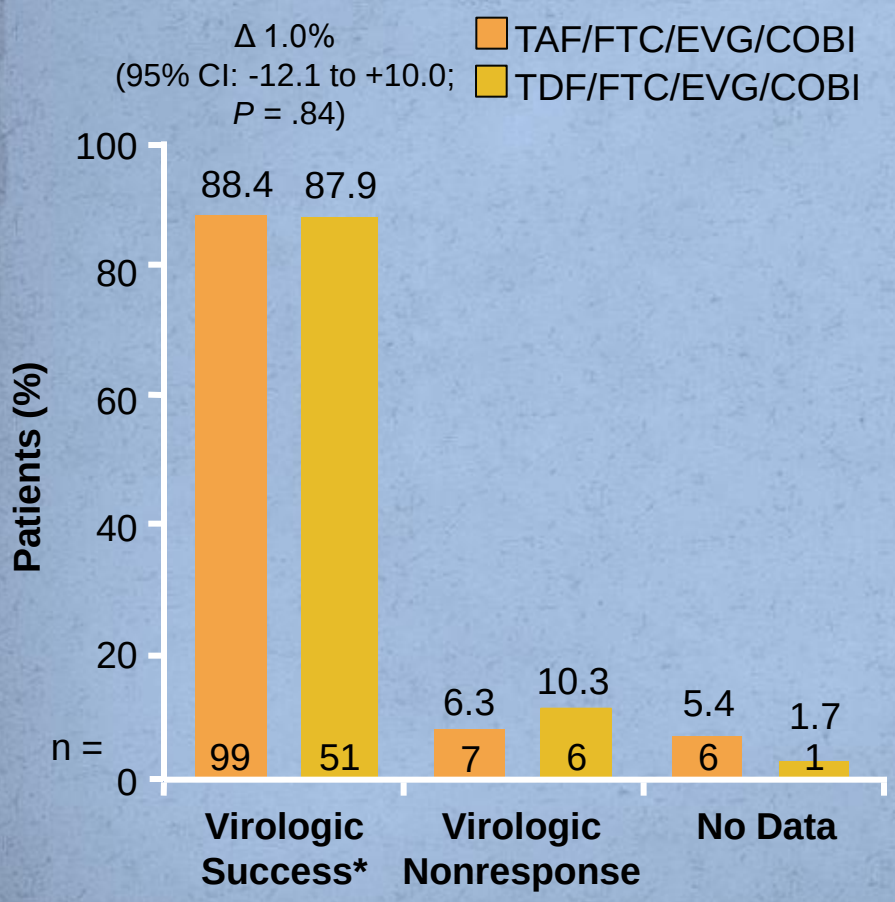
Wk 24 *Wk 48*

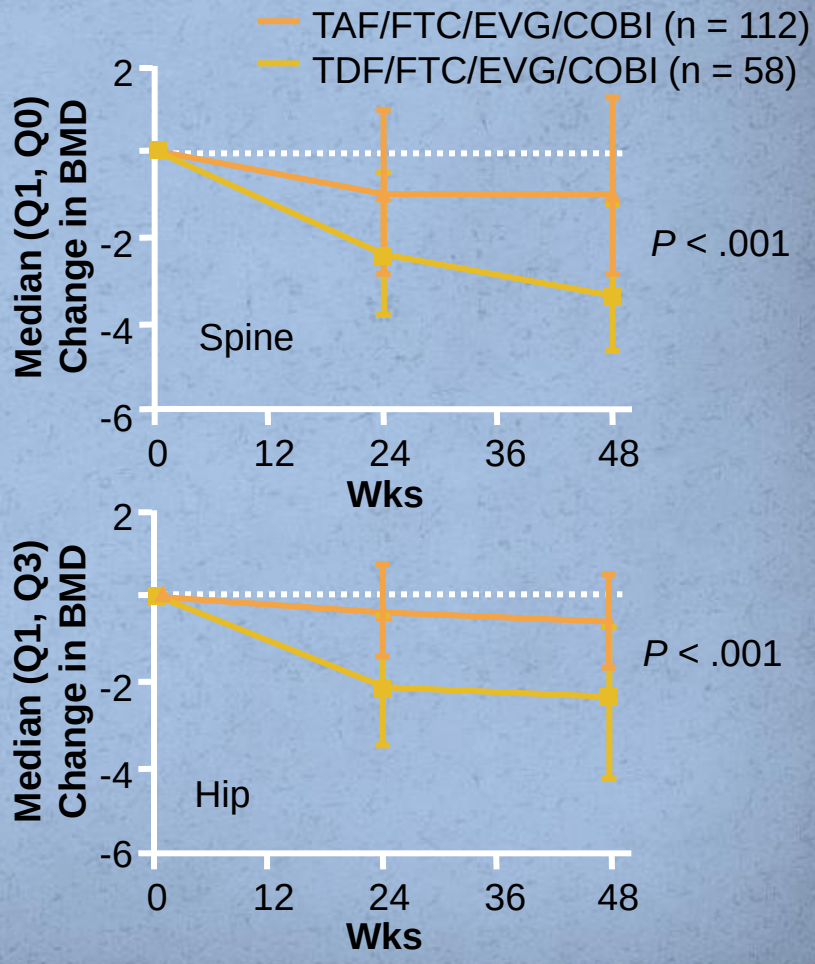
TAF/FTC/EVG/ COBI (n = 112)

TDF/FTC/EVG/ COBI (n = 58)

38. Zolopa A, et al. CROI 2013. Abstract 99LB. 39. Sax P, et al. ICAAC 2013. Abstract H-1464d.

TAF/FTC/EVG/COBI Noninferior to TDF/FTC/EVG/COBI Through Wk 48





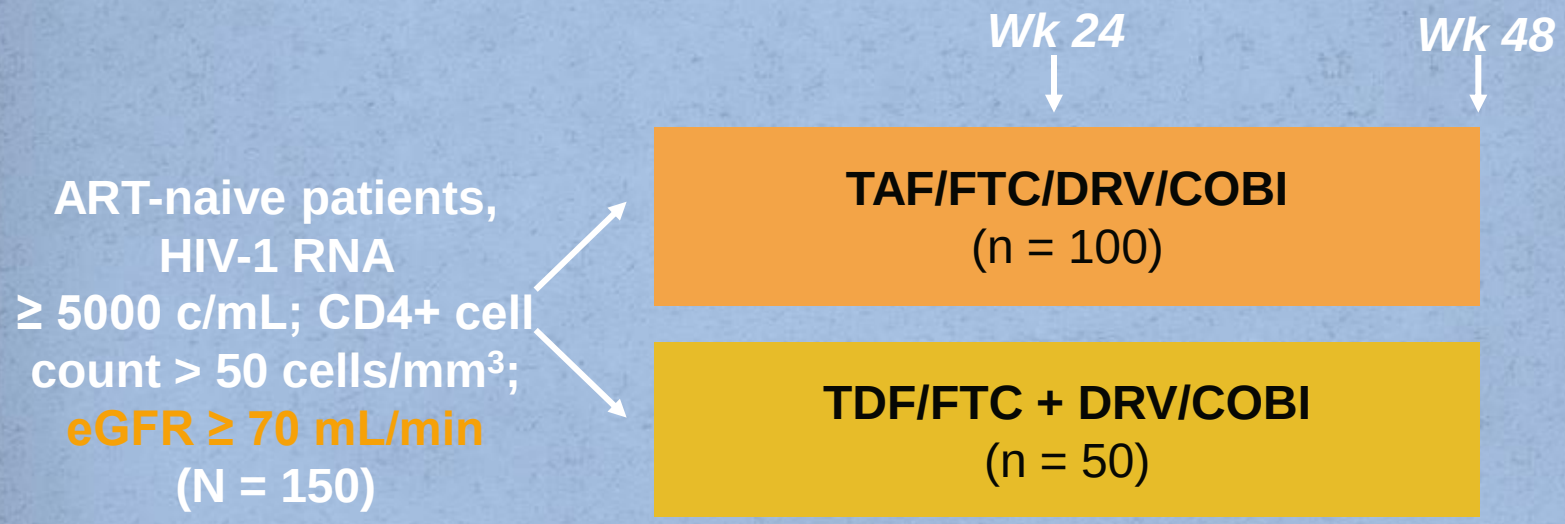
*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm.

40. Sax P, et al. ICAAC 2013. Abstract H-1464d.

Ongoing: TAF/FTC/DRV/COBI vs TDF/FTC + DRV/COBI in ART-Naive Patients

Ongoing, randomized, placebo-controlled phase II trial

Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24



41. ClinicalTrials.gov. NCT01565850.

Novel NNRTIs

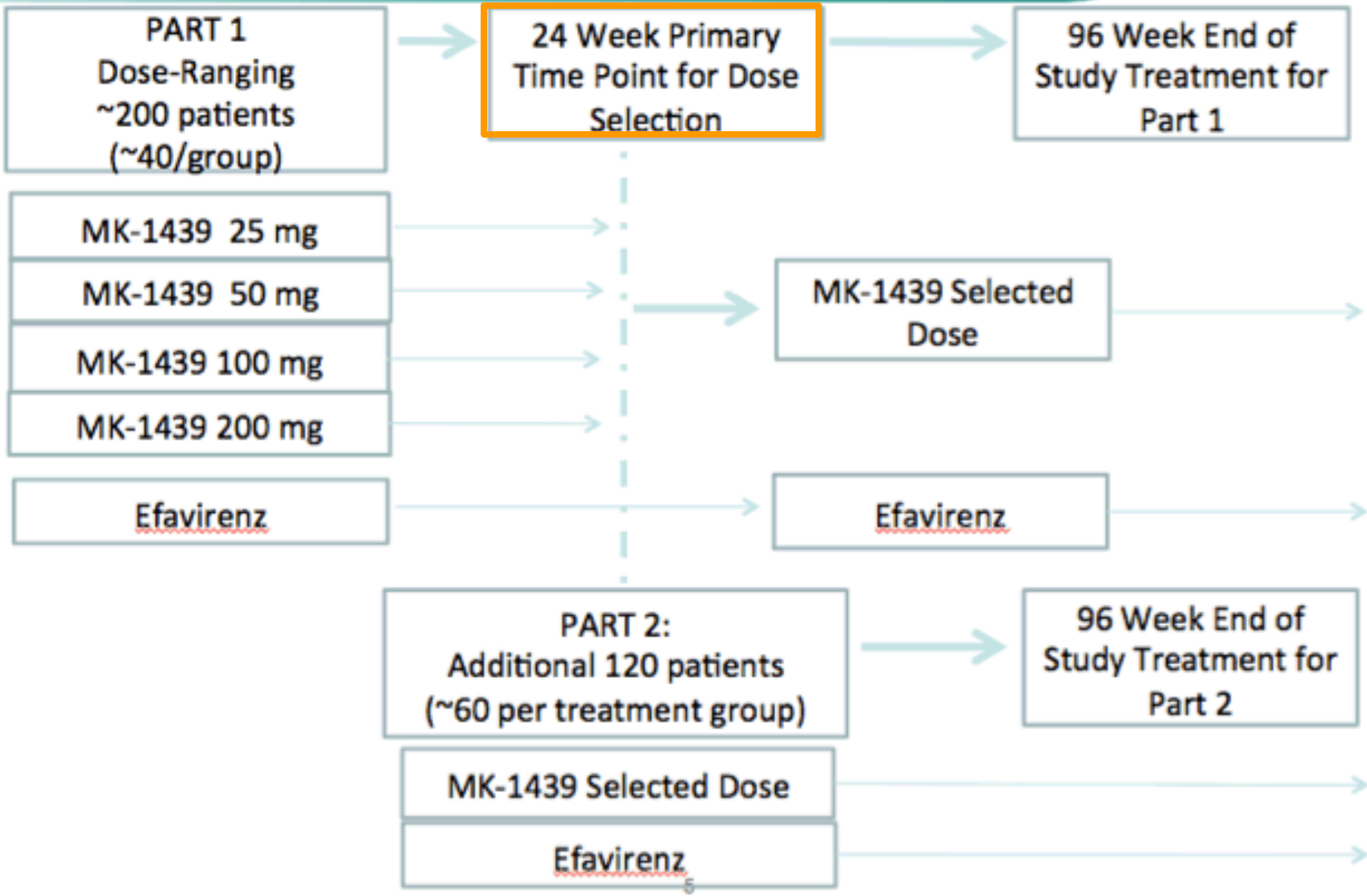
DORAVIRINE

Doravirine (MK-1439): Background

- **Commonly used NNRTIs are associated with suboptimal efficacy and/or safety profiles**
  - Efavirenz is frequently associated with CNS adverse experiences [1]
  - Rilpivirine is indicated in treatment naïve patients with RNA ≤100,000 copies/mL [2]
- **Doravirine (MK-1439) is a next generation NNRTI with the potential for improved efficacy and safety profiles**
  - High *in vitro* potency against a broad panel of isolates of different HIV subtypes[3]
    - <3-fold potency shift *vs.* common NNRTI-resistance mutants K103N, Y181C, G190A, E138K[4]
    - Distinct mutations selected *in vitro*: V106A, F227L, and L234I
      - V106A, F227L do not confer cross resistance to rilpivirine or etravirine
  - Low potential for CNS effects, drug-drug interactions; lower protein-binding *vs.* other NNRTIs
  - In Phase 1 studies:
    - Single doses up to 1200 mg and multiple doses up to 750 mg were generally well tolerated[5]
    - Minimal food effect observed (after 50-mg single dose)
    - Primary metabolism by CYP3A4, but is not an inducer or an inhibitor[6]
    - In a 7-day monotherapy study in treatment-naïve HIV-1 patients, ~1.3 log HIV RNA decline at 25 and 200 mg po QD[7]

CROI 2014, abst 92LB

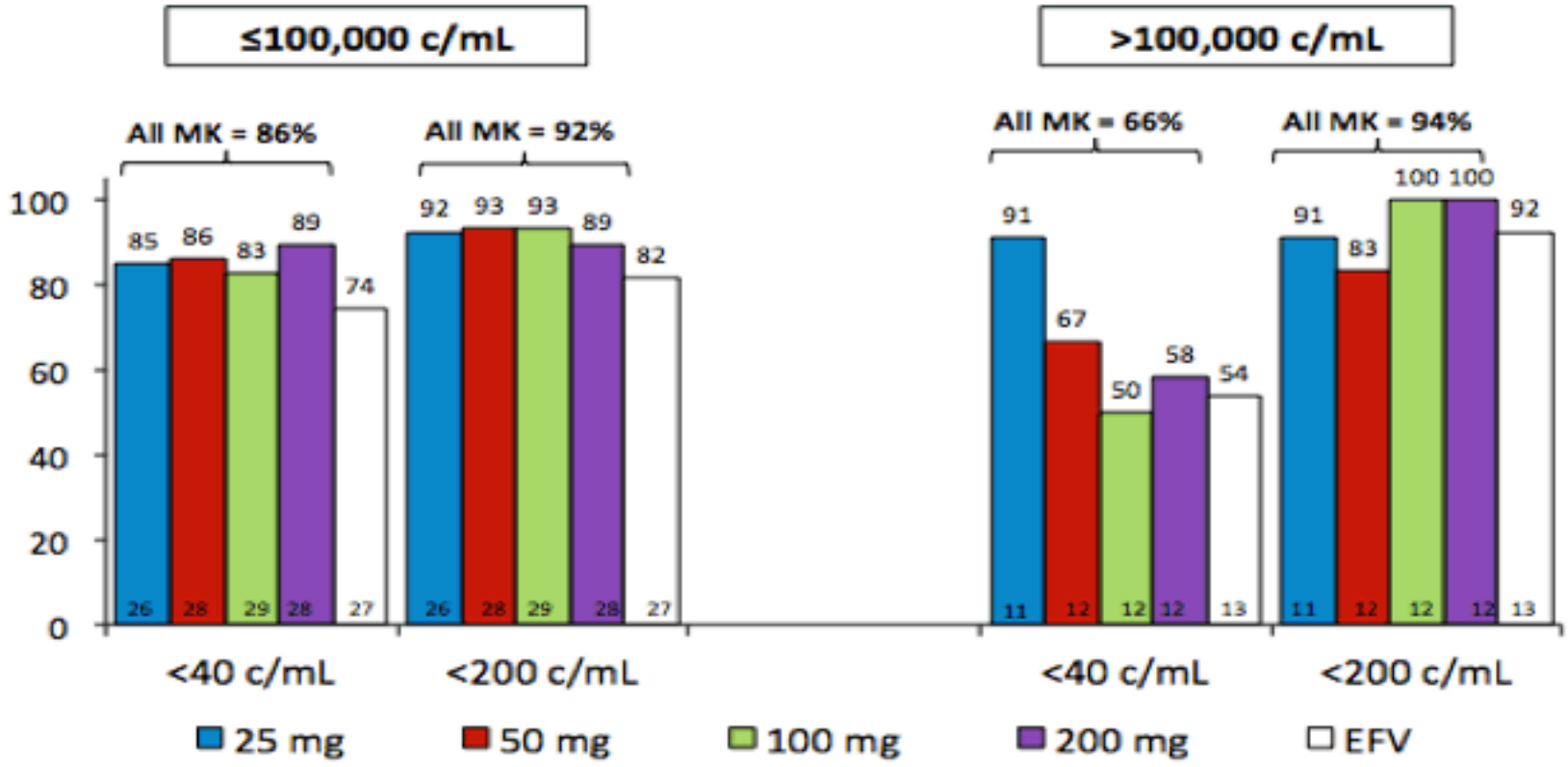
PN007: Phase 2b Study of Doravirine vs. Efavirenz in Treatment Naïve HIV-1 Infection



PN007: Phase 2b Study of Doravirine vs. Efavirenz in Treatment Naïve HIV-1 Infection

Virologic Response by Screening RNA

Ad hoc analysis (Week 24), Observed Failure



New STRATEGIES…

GSK-12657 **744** (**integrase inhibitor**) and **Rilpivirine** As Two Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results

Long Acting anTiretroviral Treatment Enabling study (LATTE)

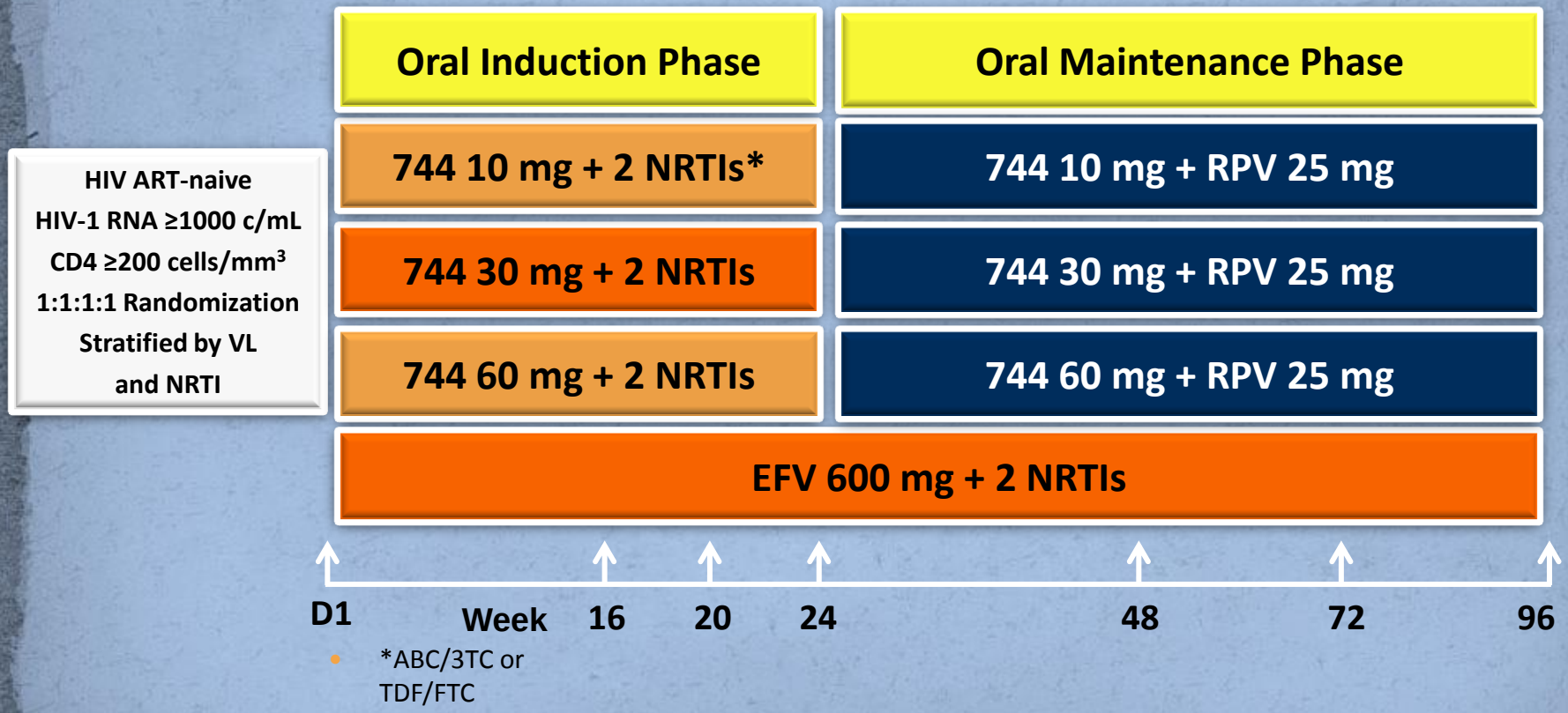
David A. Margolis[1], Cynthia C. Brinson[2], Joseph J. Eron[3], Gary J. Richmond[4], Roger P LeBlanc[5], Sandy K. Griffith[1], Marty H. St. Clair[1], Marita C. Stevens[6], Peter E. Williams[6], William R. Spreen[1]

[1]GlaxoSmithKline, Research Triangle Park, NC; [2]Central Texas Research Institute, Austin, TX; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Ft Lauderdale, FL; [5]Clinique OPUS Medical Director Montreal Qc Canada; [6]Janssen Research and Development, Beerse, Belgium

21st Conference on Retroviruses and Opportunistic Infections
March 3-6, 2014; Boston, MA

LATTE Study Design

Phase IIb, randomized, multicenter, partially blind, dose-ranging study
744 + NRTI subjects with a W20 HIV-1 RNA <50 c/mL simplified to 744 + RPV at W24

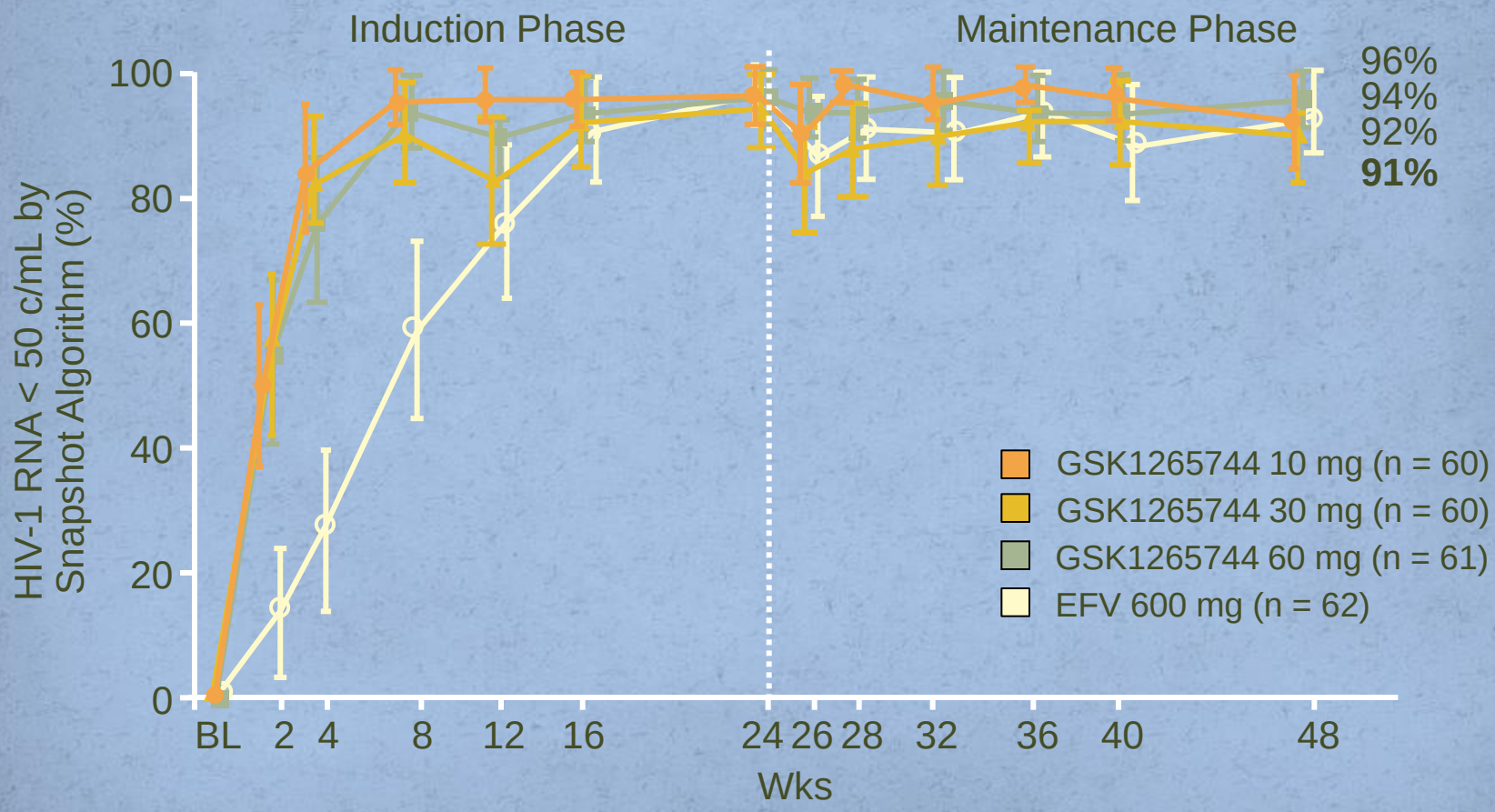


Primary endpoint: % HIV-1 RNA <50 c/mL at 48 weeks (FDA "Snapshot")

Intent-to-treat exposed (ITT-E) – received at least one dose of Investigational Product (IP)

Intent-to-treat maintenance exposed (ITT-ME) – received at least one maintenance dose

LATTE: Virologic Success During Induction and Maintenance Phases



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

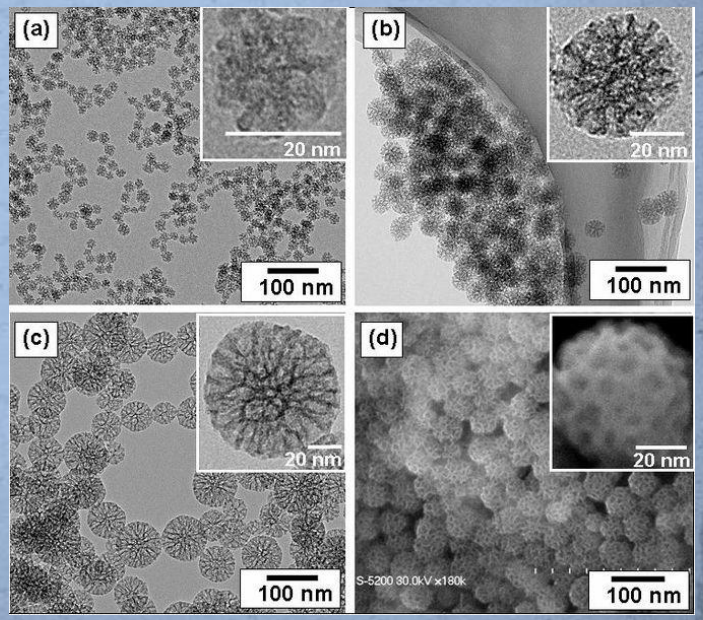
Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB

LATTE Study – Week 48 Analysis Conclusions

- **Following induction therapy, oral 744+RPV maintained virologic suppression at a rate similar to EFV+NRTIs**
  - ✓ Primary Endpoint: **82%** of 744+RPV and 71% of EFV+NRTIs subjects had HIV-1 RNA <50 copies/mL
  - ✓ Secondary Endpoint (ITT-ME): 93% of 744+RPV and 94% of EFV+NRTIs subjects had HIV-1 RNA <50 copies/mL
  - ✓ Similar response rate across 744 10mg, 30mg, and 60mg arms
    - One subject, with persistently low 744 and RPV drug concentrations, developed treatment emergent INI and NNRTI mutations
- **744+RPV** was **well tolerated,** with **few drug related AEs** leading to withdrawal
- Long-term data needed, however, these regimen POC **results support evaluation of long-acting injectable regimen of 744 LA + TMC278 LA as maintenance therapy**

Nanoparticles

- optimisation of long-active release
- better penetration into reservoirs



Optimisation of Intramuscular Sustained Release Nano-Formulations Using In Silico Modelling

Rajith Kumar Reddy Rajoli[1], David Back[1], Steve Rannard[2], Andrew Owen[1], Marco Siccardi[1]
[1]Department of Clinical & Molecular Pharmacology, University of Liverpool, Liverpool, United Kingdom, [2]Department of Chemistry, University of Liverpool, Liverpool, United Kingdom

Drug	IM Dose (mg)	Release rate (h^{-1})	Weekly/Monthly	AUC ($\mu g\ h\ mL^{-1}$) (Mean ± SD)	C_{max} ($ng\ mL^{-1}$) (Mean ± SD)	C_{trough} ($ng\ mL^{-1}$) (Mean ± SD)	Cut-off limit ($ng\ mL^{-1}$)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Emtricitabine	600	0.0015	**Monthly**	21.0 ± 10.9	45.8 ± 22.7	17.3 ± 10.7	14 (IC_{95})
	125	0.01	Weekly	7.2 ± 10.7	68.2 ± 79.4	14.5 ± 9.0	
Tenofovir	1500	0.001	**Monthly**	25.5 ± 17.8	56.6 ± 38.9	20.0 ± 14.0	18 (IC_{95})
	350	0.008	Weekly	6.7 ± 5.3	67.2 ± 49.1	18.7 ±13.8	
Non-Nucleoside Reverse Transcriptase Inhibitors (NRTIs)							
Efavirenz	1000	0.002	**Monthly**	190.6 ± 101.3	377.5 ± 165.6	154.0 ± 130.8	126 ($PBIC_{95}$)
	200	0.015	Weekly	34.0 ± 9.1	268.5 ± 60.9	138.1 ± 81.3	
Etravirine	225	0.011	Weekly	11.7 ± 1.8	88.6 ± 12.7	59.8 ± 16.0	52 (MEC)
Rilpivirine*	250	0.002	**Monthly**	40.2 ± 19.7	76.9 ± 33.6	35.0 ± 20.0	20.3 ($PBIC_{95}$)
	60	0.02	Weekly	8.0 ± 2.5	71.8 ± 16.4	20.7 ± 14.0	
Integrase Inhibitors (IIs)							
Dolutegravir	105	0.002	**Monthly**	91.2 ± 9.4	192.3 ± 16.6	64.3 ± 8.1	64 ($PBIC_{95}$)
	20	0.006	Weekly	12.3 ± 1.3	89.6 ± 9.5	65.5 ± 7.6	
Raltegravir	1000	0.002	**Monthly**	89.1 ± 17.9	62.8 ± 9.7	15.4 ± 2.5	15 ($PBIC_{95}$)
	225	0.007	Weekly	17.8 ± 3.4	46.8 ± 7.2	15.8 ± 2.5	
Protease Inhibitors (PIs)							
Atazanavir	600	0.009	Weekly	124.5 ± 4.1	192.1 ± 10.7	60.6 ± 2.3	60 ($PBIC_{95}$)

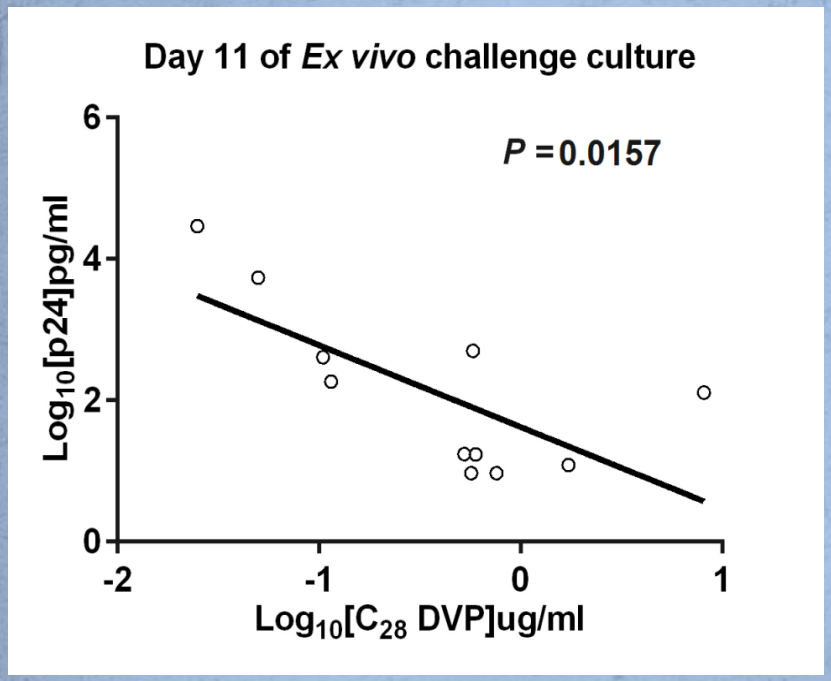
* Note that this dose does not apply to the existing RPV formulation. Rather, as for other listed drugs, the data represent a prediction for optimal performance of a reformulation.

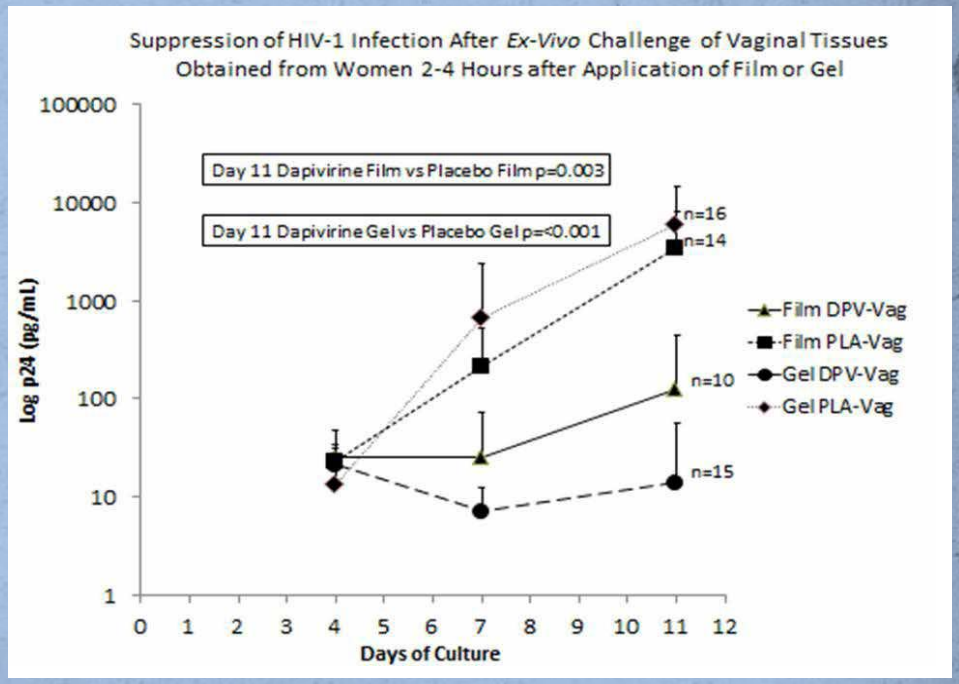
CROI 2014, abst 518

DAPIVIRINE (NNRTI): vaginal rings, gel and films

Safety and Pharmacokinetics/Pharmacodynamics of Dapivirine and Maraviroc Vaginal Rings

Beatrice A. Chen[1], Lori Panther[2], Craig Hoesley[3], Craig Hendrix[4], Ariane van der Straten[5], Marla Husnik[6], Lydia E. Soto-Torres[7], Annalene Nel[8], Sherri Johnson[9], Charlene S. Dezzutti[10]





CROI 2014, abst 41

CROI 2014, abst 42

Pre-clinical studies of novel ART approaches

Pre-clinical studies of novel ART approaches

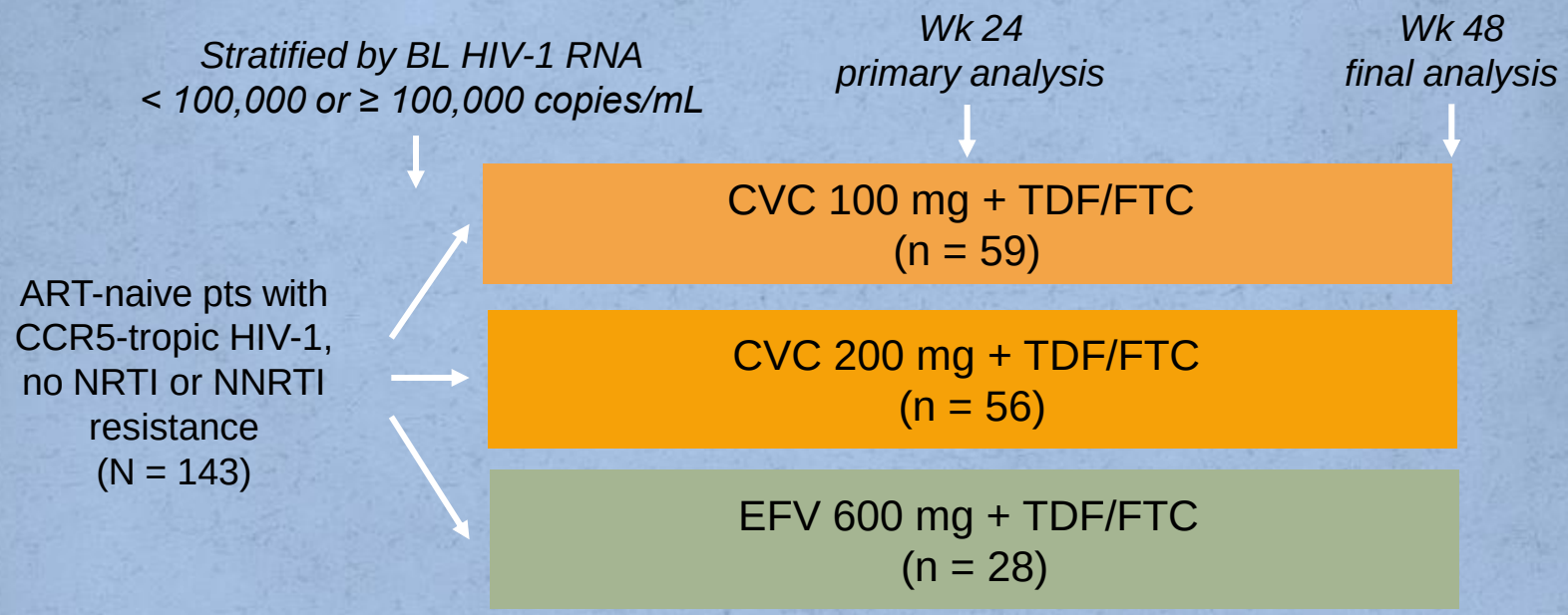
- Entry:
  - cenicriviroc (CCR5 and CCR2 inhibitor)

- Post - entry:
  - Vif inhibitors (enhancement of APOBEC)
  - CA inihibitors (maturation inhibitors)

Bevirimat

Cenicriviroc: Investigational QD Oral CCR5/CCR2 Receptor Antagonist

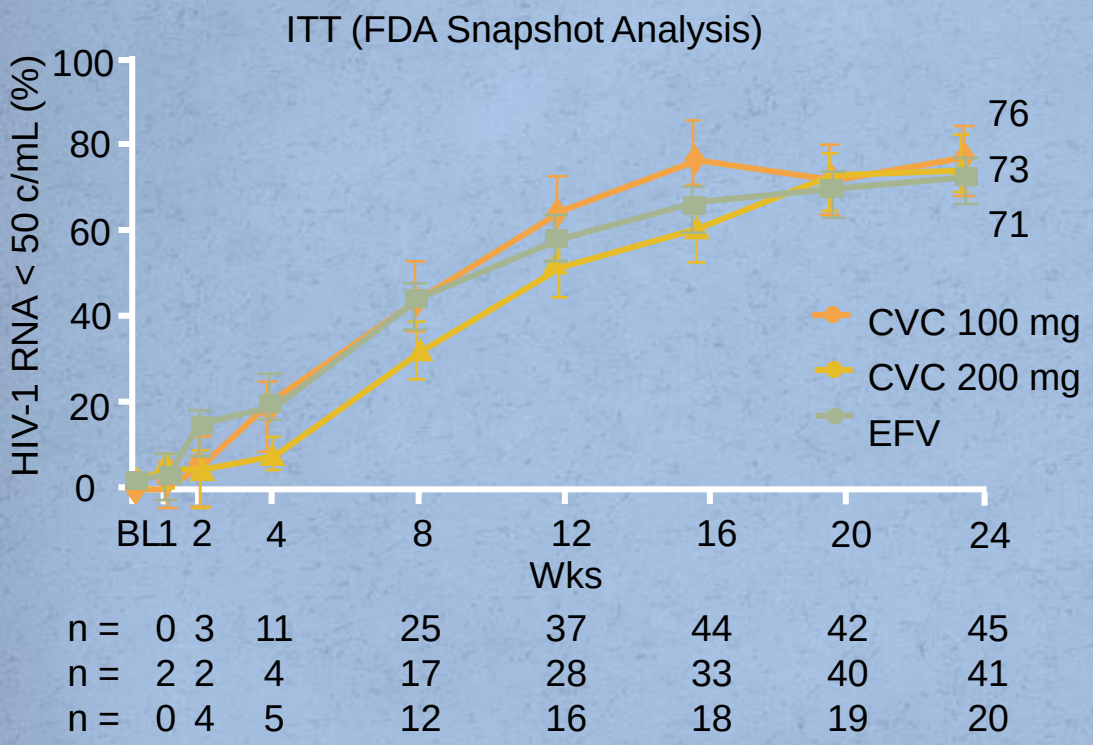
Randomized, double-blind, double-dummy, dose-finding **phase IIb** trial



Complex dosing: 4 pills with breakfast (4 CVC or 4 CVC placebo or 2 of each); 1 pill on empty stomach at bedtime (EFV or EFV placebo); 1 pill taken anytime (open-label TDF/FTC)

Gathe J, et al. CROI 2013. Abstract 106LB.

24-Wk Efficacy and Safety of Cenicriviroc + TDF/FTC vs EFV/TDF/FTC



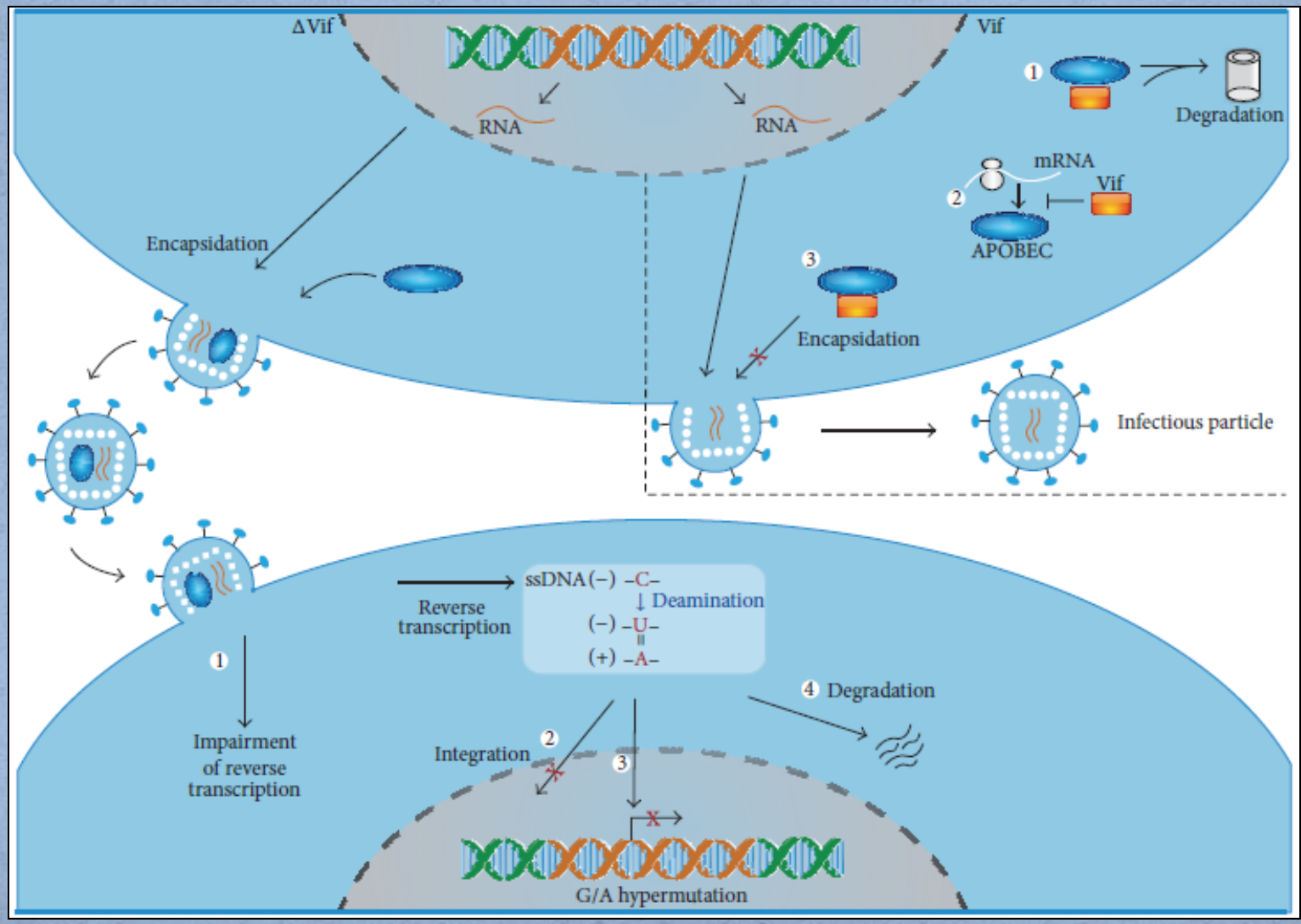
Virologic NR, %	DC Other Than AE, %	DC Due to AE, %
12	10	0
14	11	2
4	7	18

CVC generally **well tolerated** with no safety signals

Soluble CD14 decreased with CVC and increased with EFV

Gathe J, et al. CROI 2013. Abstract 106LB. Graphic used with permission.

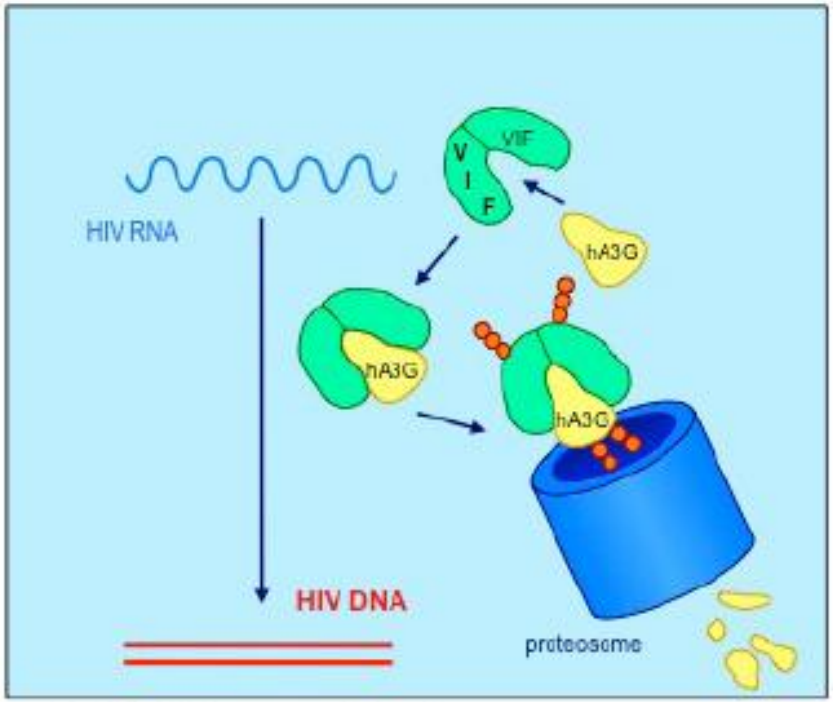
APOBEC and Vif inhibitors



Drugging HIV Vif as a Rational Approach To Eradication

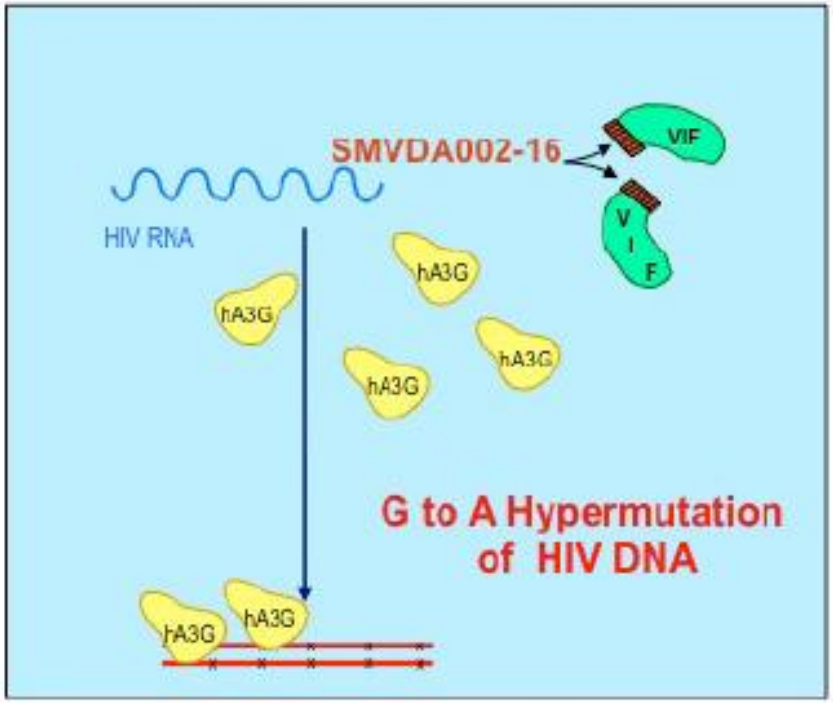
Harold C. Smith, **Ryan P. Bennett**
OyaGen, Inc, Rochester, NY, United States

With Vif dimer



HIV life cycle is not interrupted

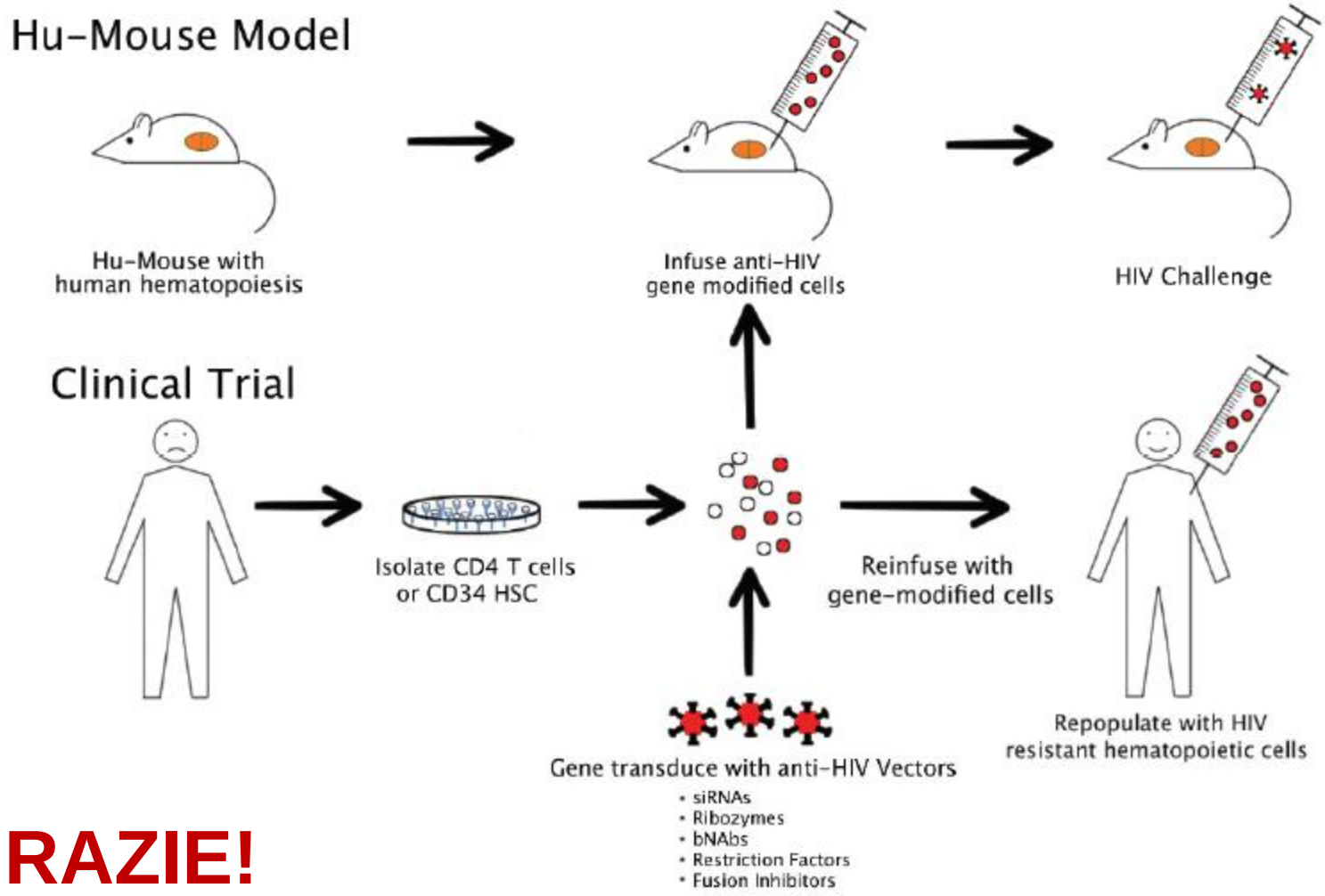
Without Vif dimer



HIV DNA functionality destroyed

CROI 2014, abst 532

Modeling HIV gene therapy in humanized mice and clinical application



GRAZIE!

Bennett and Akkina, Viruses, 2013