Strategie terapeutiche innovative:

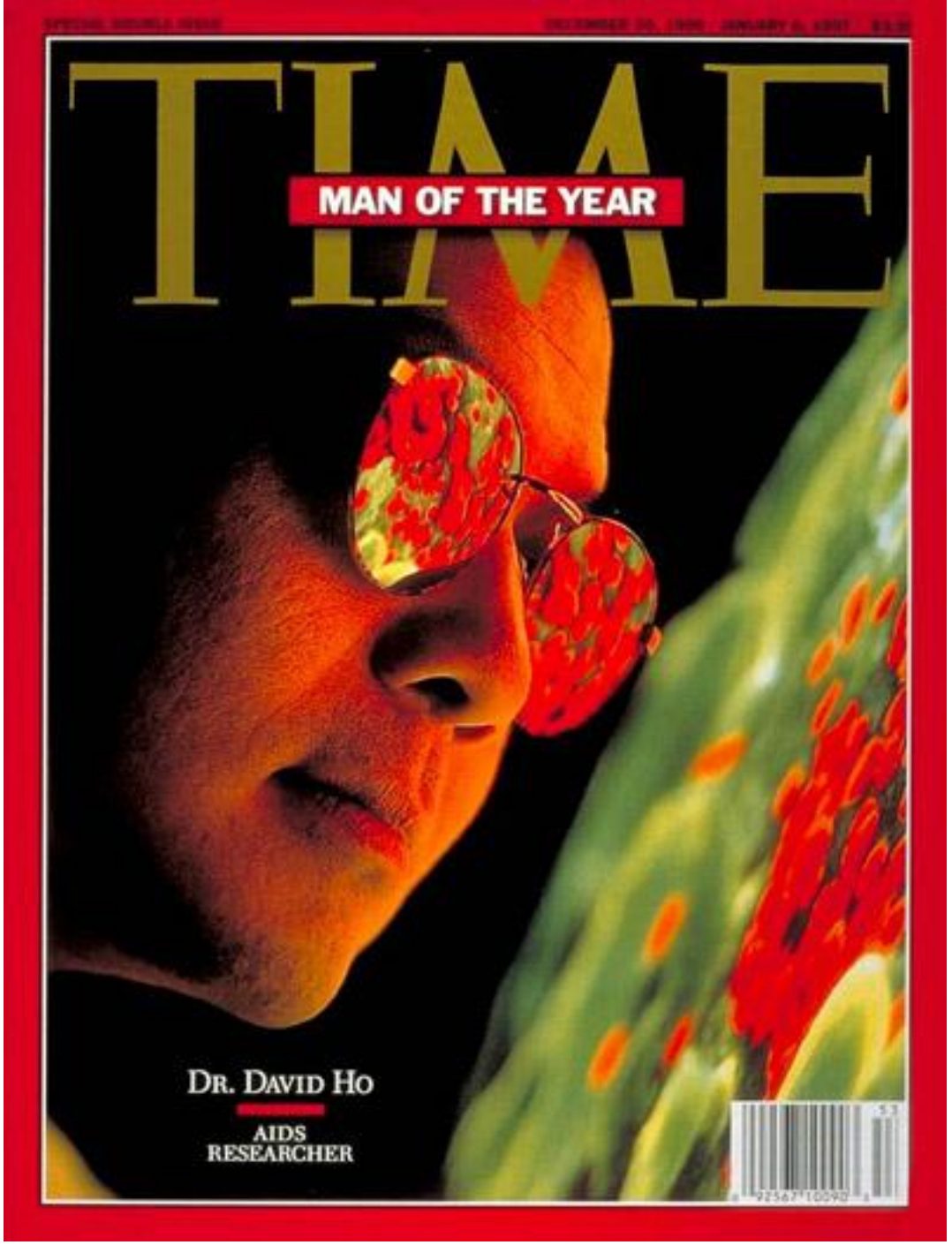
induzione e mantenimento

Induzione-mantenimento

a) Iniziare con 3 o più farmaci poi scendere a 0
b) Iniziare con più farmaci poi scendere a 3
c) Iniziare con 3 poi scendere a meno farmaci

Time to hit early and hard

1995 NEJM

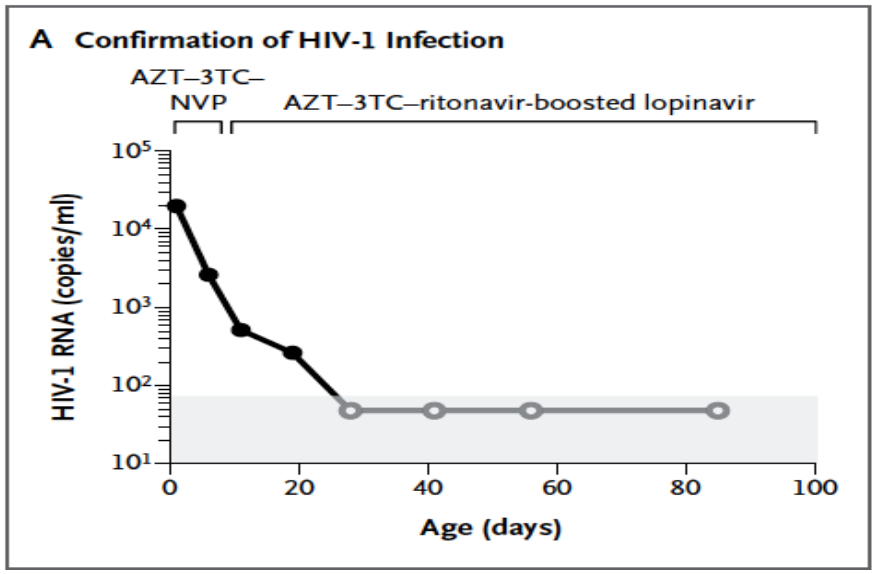


HIT EARLY

BRIEF REPORT

Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.



N Engl J Med 2013;369:1828-35.

Table 1. Laboratory Testing and Antiretroviral Therapy Received by Mother and Child.*

Test	Result	Antiretroviral Therapy
Mother		
Rapid HIV antibody, at delivery	Positive	None
HIV ELISA and confirmatory Western blot, at 24 hr	Positive	None
Viral load, at 24 hr	2423 copies/ml	None
CD4+ T-cell count, at 14 days	644 cells/mm^3	None
HIV-1 genotype and subtype, at 14 days	Wild-type, subtype B	None
CD4+ T-cell count, at 26 mo	513 cells/mm^3	None
HIV-1 viral load, at 26 mo	6763 copies/ml	None
HLA typing, at 26 mo	A3, A23, B7, B14, Cw7, and Cw8	None
Mutation status in *CCR5* delta32, at 26 mo	Nonmutated	None
Frequency of infected cells, at 28 mo	137 IUPM	None
Child		
HIV-1 DNA, at 30 hr	Positive	Zidovudine
HIV-1 RNA, at 31 hr	19,812 copies/ml	Zidovudine, lamivudine, and nevirapine
HIV-1 RNA, at 6 days	2617 copies/ml	Zidovudine, lamivudine, and nevirapine
HIV-1 RNA, at 11 days	516 copies/ml	Zidovudine, lamivudine, and ritonavir-boosted lopinavir
HIV-1 RNA, at 19 days	265 copies/ml	Zidovudine, lamivudine, and ritonavir-boosted lopinavir
HIV-1 RNA, at 29 days	<48 copies/ml	Zidovudine, lamivudine, and ritonavir-boosted lopinavir
CD4+ T-cell percentage, at 8 days	69%	Zidovudine, lamivudine, and ritonavir-boosted lopinavir
HLA typing, at 26 mo	A3, A68, B7, B39, and Cw7	None
Mutation status in *CCR5* delta32, at 26 mo	Nonmutated	None

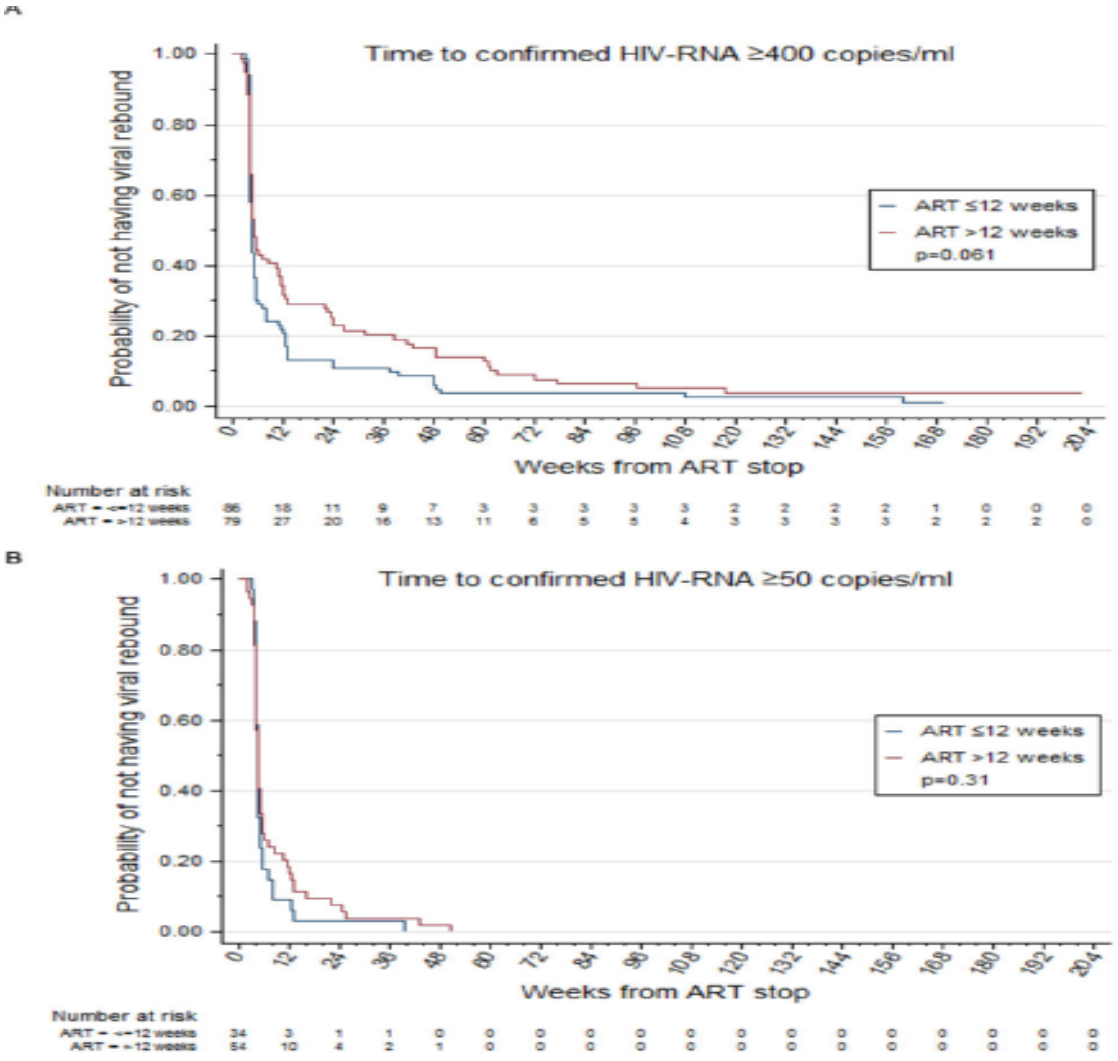
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 17, 2013 VOL. 368 NO. 3

Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*

Duration of HIV viral suppression on cessation of antiretroviral therapy correlates with time on therapy



PLOS ONE

October 2013 | Volume 8 | Issue 10 | e78287

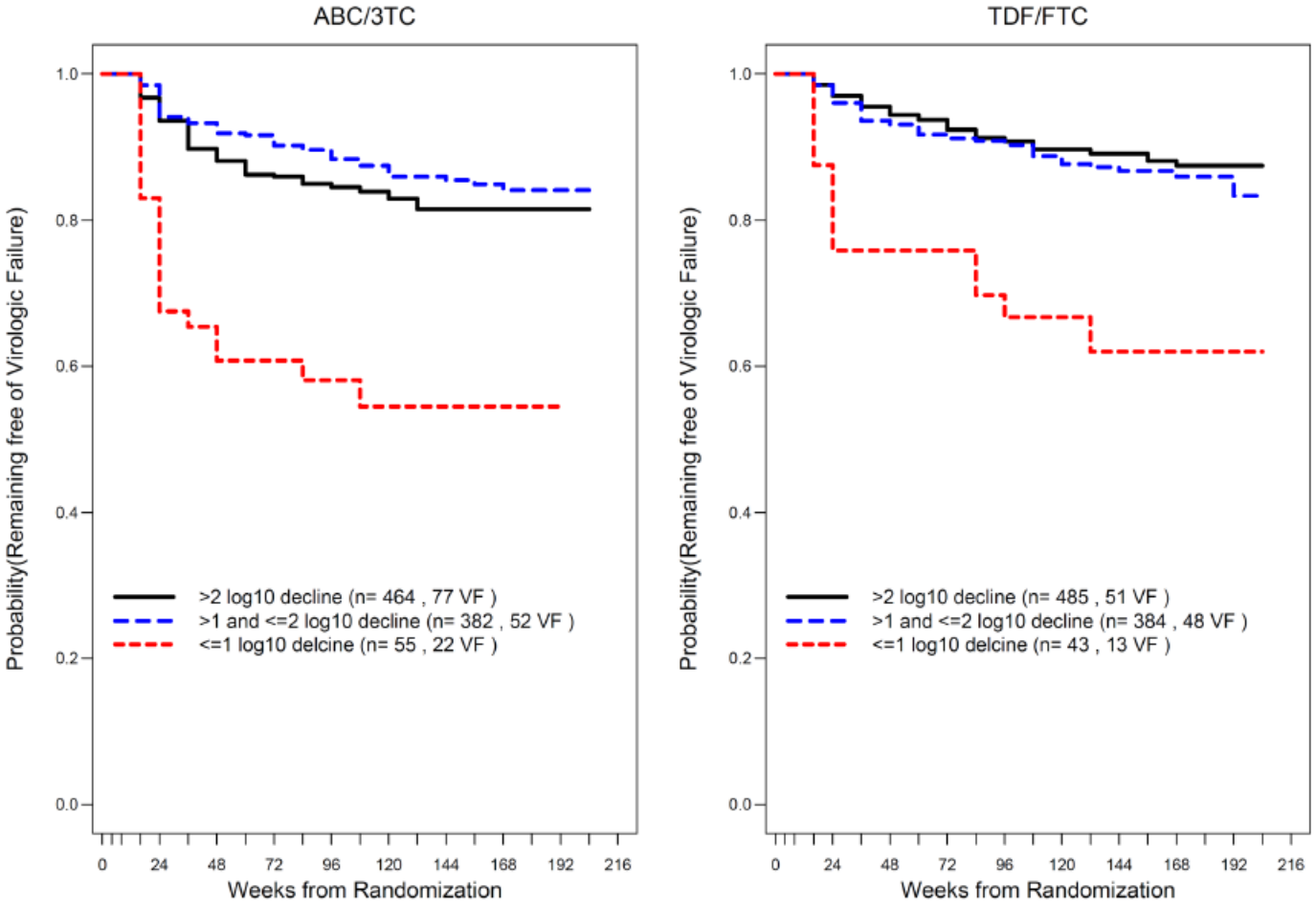
HIT EARLY AND HARD

Association of Baseline Viral Load, CD4 Count, and Week 4 Virologic Response (VR) with Virologic Failure (VF) in ACTG Study A5202

Philip Grant[1], Camlin Tierney[2], David Katzenstein[1], Paul Sax[3], Chakra Budhathoki[2], Katie Mollan[2], Ann Collier[4], Margaret Fischl[5], Andrew Zolopa[1], Eric Daar[6], and ACTG Study A5202

[1]Stanford University, Stanford, CA, [2]Harvard School of Public Health, Boston, MA [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]University of Washington, Seattle, WA, [5]University of Miami, Miami, FL, [6]UCLA, Los Angeles, CA.

Smaller Week 4 VL decline was associated with increased risk of VF



HR (95% CI) (per 1 log10copies/mL less decline)

ABC/3TC: Adjusted 1.90 (1.52, 2.38)

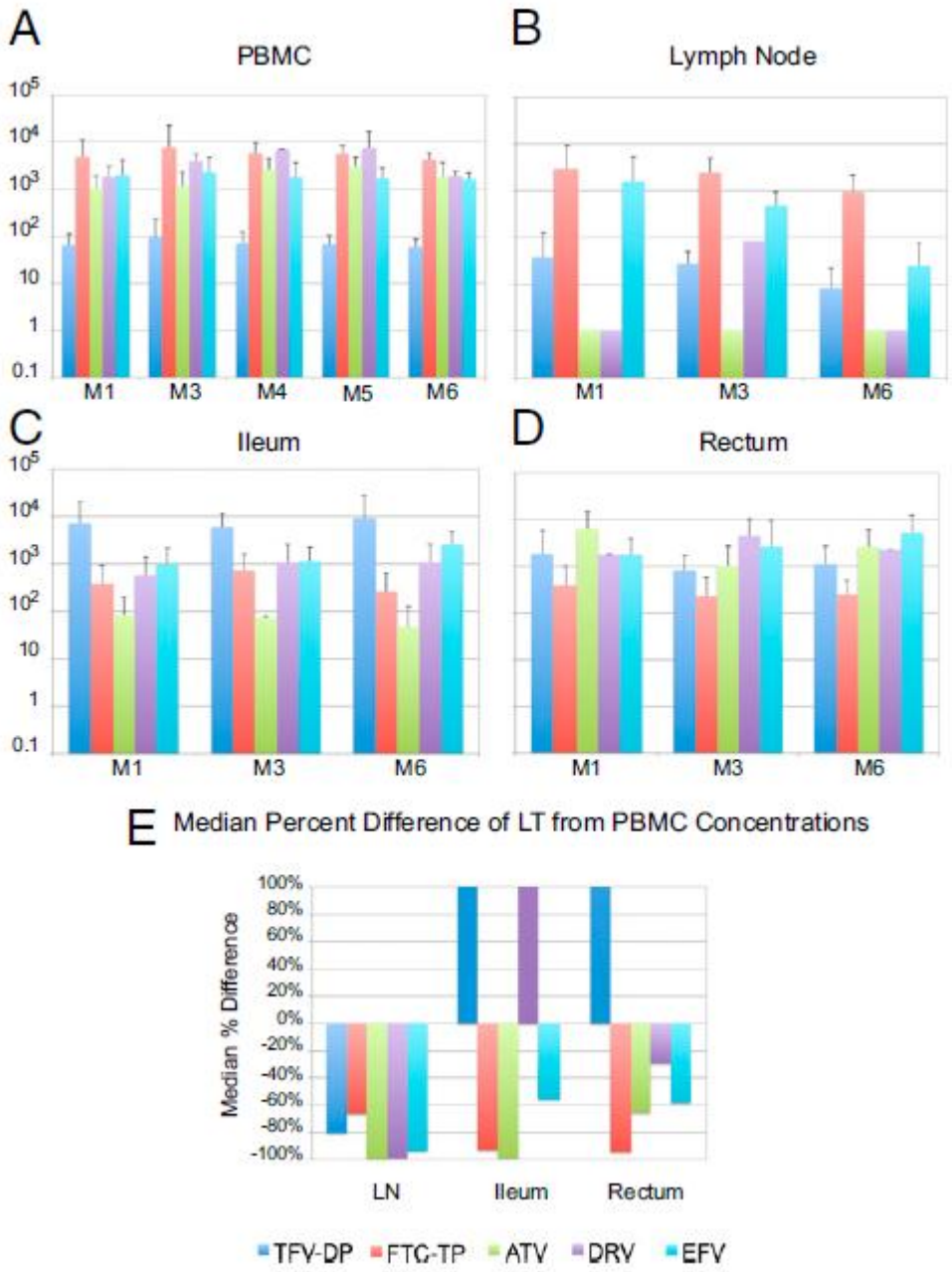
TDF/FTC: Adjusted 1.79 (1.38, 2.33)

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Courtney V. Fletcher[a], Kathryn Staskus[b,1], Stephen W. Wietgrefe[b], Meghan Rothenberger[c], Cavan Reilly[d], Jeffrey G. Chipman[e], Greg J. Beilman[e], Alexander Khoruts[c], Ann Thorkelson[c], Thomas E. Schmidt[c], Jodi Anderson[c], Katherine Perkey[b], Mario Stevenson[f], Alan S. Perelson[g], Daniel C. Douek[h], Ashley T. Haase[b], and Timothy W. Schacker[c,2]

Antiretroviral therapy can reduce HIV-1 to undetectable levels in peripheral blood, but the effectiveness of treatment in suppressing replication in lymphoid tissue reservoirs has not been determined. Here we show in lymph node samples obtained before and during 6 mo of treatment that the tissue concentrations of five of the most frequently used antiretroviral drugs are much lower than in peripheral blood. These lower concentrations correlated with continued virus replication measured by the slower decay or increases in the follicular dendritic cell network pool of virions and with detection of viral RNA in productively infected cells. The evidence of persistent replication associated with apparently suboptimal drug concentrations argues for development and evaluation of novel therapeutic strategies that will fully suppress viral replication in lymphatic tissues. These strategies could avert the long-term clinical consequences of chronic immune activation driven directly or indirectly by low-level viral replication to thereby improve immune reconstitution.

PNAS 2104



Compared with concentrations in PBMCs, the IC concentration of TFV-DB, FTC-TP, ATV, DRV and EFV was lower in the lymphatic tissue (LT) compartment, particularly in the lymph node.

Fig. 1. IC ARV concentrations by compartment and month of therapy. Mean (and SD error) IC concentrations (log scale) for TFV-DP, FTC-TP, ATV, DRV, and EFV are shown for PBMCs (*A*), LN MNCs (*B*), ileal MNCs (*C*), and rectal MNCs (*D*). For *B*, where values were below the limit of quantitation (BLQ), a value of 1 has been assigned for illustration purposes; for example, all LN samples for ATV had IC concentrations that were BLQ. (*E*) Overall median percent difference between the concentration in PBMCs and those in the LN, ileum, and rectum, respectively, for each of the five drugs from all samples obtained during the 6 mo of therapy in the individual subjects. The scale is truncated at +100%. Actual values >100% were as follows: TFV-DP, 2,229%, and DRV, 1,318% in the ileum; and TFV-DP, 599%, and DRV, 149% in the rectum. In the LN, concentrations were uniformly lower than PBMCs for all drugs: TFV-DP concentrations, –80%; FTC-TP, –66%; ATV, –100%; DRV, –99%; and EFV, –94% (all $P < 0.0001$). TFV-DP, TFV-diphosphate; FTC-TP, FTC-triphosphate.

714 determinations of ARV drug concentrations in plasma and 592 analyte determinations for IC drug concentrations in PBMCs and in mononuclear cells (MNCs) from the LN, ileum, and rectum were performed.

Fletcher et al., PNAS 2104

Initial viral decay to assess the relative antiretroviral potency of protease inhibitor-sparing, nonnucleoside reverse transcriptase inhibitor-sparing, and nucleoside reverse transcriptase inhibitor-sparing regimens for first-line therapy of HIV infection

Richard H. Haubrich[a], Sharon A. Riddler[b], Heather Ribaudo[c], Gregory DiRenzo[c,d], Karin L. Klingman[e], Kevin W. Garren[f], David L. Butcher[g], James F. Rooney[h], Diane V. Havlir[i], John W. Mellors[b], for the AIDS Clinical Trials Group (ACTG) A5160 and A5142 Study Teams

Objectives: To evaluate the effects of sex and initial antiretroviral regimen on decay of HIV-RNA and virologic outcome.

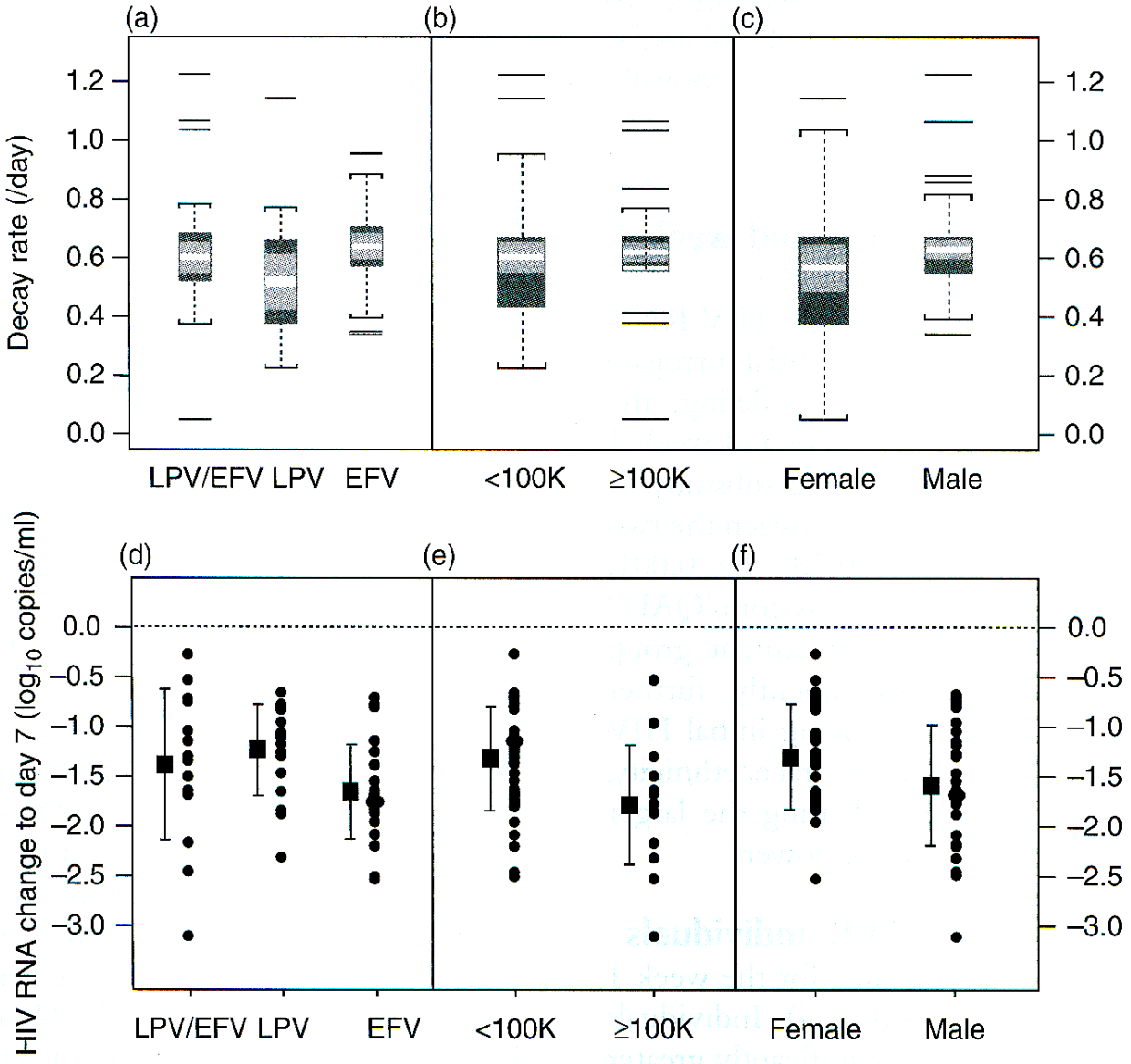
Methods: We conducted a viral dynamics substudy of A5142, a trial comparing lopinavir (LPV)/ritonavir with efavirenz (LPV/EFV) versus LPV and two nucleoside reverse transcriptase inhibitor (NRTI) (LPV) versus EFV and two NRTI (EFV) in antiretroviral (ARV)-naive individuals. HIV-RNA was measured at days 2, 10, and 14 in the substudy and at weeks 1, 4, and 8 in A5142 participants. Two-phase viral decay was estimated in the substudy with biexponential mixed-effects modeling and compared using Wilcoxon tests. Week 1 HIV-RNA change was assessed as a predictor of virologic failure (HIV-RNA above 50 or 200 copies/ml) at weeks 24–96 using logistic regression.

Results: Sixty-eight individuals were enrolled in the substudy (median HIV-RNA 4.9 $\log_{10}$ copies/ml). Median rates of phase 1 viral decay by treatment were 0.61(EFV/LPV), 0.53(LPV), and 0.63(EFV) per day. Phase 1 decay was significantly faster for EFV than LPV ($P = 0.023$); other comparisons were not significant ($P > 0.11$). Viral decay did not differ by sex ($P = 0.10$). Week 1 HIV-RNA change, calculated in 571 participants of A5142, was greater for the EFV (median -1.47 $\log_{10}$ copies/ml) than either the LPV/EFV or LPV groups (-1.21 and -1.16 $\log_{10}$ copies/ml, respectively; $P < 0.001$). Week 1 HIV-RNA change was associated with virologic failure above 50 copies/ml at weeks 24 and 48 ($P < 0.018$), but not above 200 copies/ml at these time points or for any value at week 96.

Conclusion: Phase 1 decay was faster for EFV than LPV or LPV/EFV. Week 1 HIV-RNA change predicted virologic outcome up to week 48, but not at week 96.

Phase 1 HIV-RNA decay (a-c) and week 1 change in HIV-RNA by regimen, baseline HIV-RNA and sex

Haubrich 2011



Haubrich 2011

- **Week 1 HIV-RNA change was associated with virological failure at week 24 and 48 (p<0.018)**
- **Baseline HIV-RNA correlated with virological failure at week 24, 48 and 96 (p<0.015)**

Table 2. Predictors of virologic failure after 24–96 weeks on study.

Predictors of virologic failure	Analysis sample size (number of events)	OR (95% confidence interval)	*P* value
At week 24			
HIV-RNA >50 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	530 (170)	0.22 (0.14–0.35)	<0.001
Baseline HIV-RNA (per 1 $\log_{10}$)	530 (170)	4.21 (2.95–6.14)	<0.001
HIV-RNA >200 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	530 (55)	0.68 (0.38–1.19)	0.18
Baseline HIV-RNA (per 1 $\log_{10}$)	530 (55)	1.92 (1.24–3.01)	0.004
At week 48			
HIV-RNA >50 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	535 (127)	0.61 (0.40–0.91)	0.018
Baseline HIV-RNA (per 1 $\log_{10}$)	535 (127)	2.05 (1.48–2.86)	<0.001
HIV-RNA >200 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	535 (60)	0.67 (0.39–1.15)	0.15
Baseline HIV-RNA (per 1 $\log_{10}$)	535 (60)	1.40 (0.92–2.14)	0.12
At week 96			
HIV-RNA >50 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	524 (136)	0.76 (0.51–1.13)	0.18
Baseline HIV-RNA (per 1 $\log_{10}$)	524 (136)	1.46 (1.08–2.00)	0.015
HIV-RNA >200 copies/ml			
Change to week 1 (per 1 $\log_{10}$ decrease)	524 (84)	0.89 (0.56–1.41)	0.62
Baseline HIV-RNA (per 1 $\log_{10}$)	524 (84)	1.04 (0.73–1.50)	0.81

A Randomized Open-Label Study of 3- Versus 5-Drug Combination Antiretroviral Therapy in Newly HIV-1–Infected Individuals

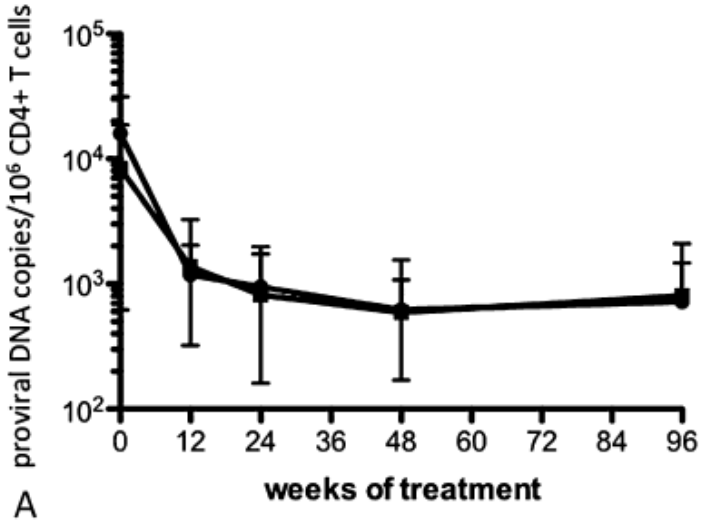
Martin Markowitz, MD, Teresa H. Evering, MD, MS,* Donald Garmon, NP,* Marina Caskey, MD,† Melissa La Mar, BA,* Kristina Rodriguez, MPH,* Vincent Sahi, MS,* Sarah Palmer, PhD,‡ Nicole Prada, PhD,* and Hiroshi Mohri, MD, PhD**

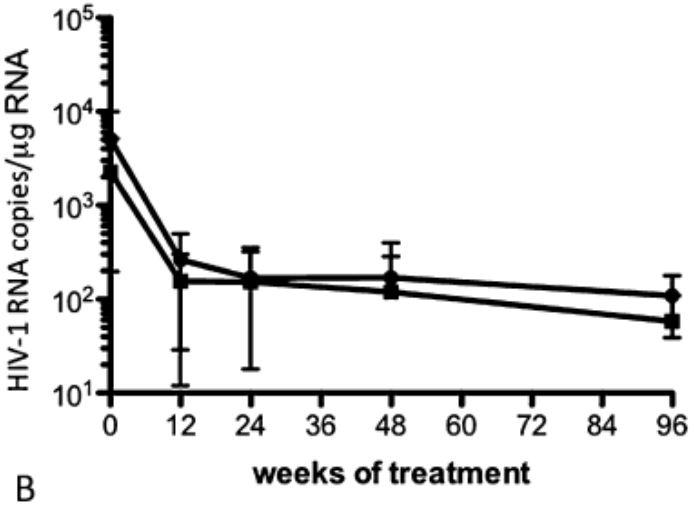
TABLE 1. Baseline Characteristics

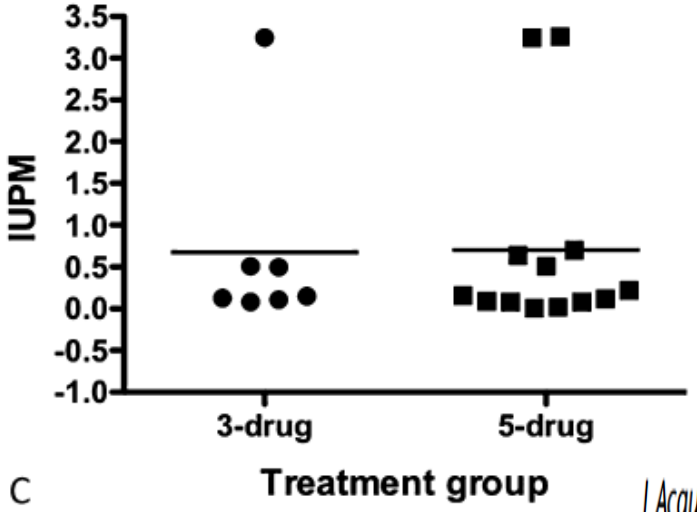
	3-Drug Therapy (N = 11)	5-Drug Therapy (N = 23)	*P*
% Male sex	100	100	NA
% Men who have sex with men	90.9	100	NA
Mean age (yrs, range)	41 (29–69)	37 (25–48)	NA
% Symptomatic	100	91.3	NA
Mean, duration of symptoms	4, 7 d	4, 4 d	NA
Mean est. duration of infection (days, range)	48 (27–77)	54 (19–155)	NA
Mean log baseline HIV-1 RNA (log copies/mL, range)	6.3 (4.8–7.0)	5.6 (3.1–6.4)	0.17
Mean $CD4^+$ T-cell count (cells/mm^3, range)	405 (305–524)	539 (230–1066)	0.15

NA, not applicable.

Effetti sul virus?

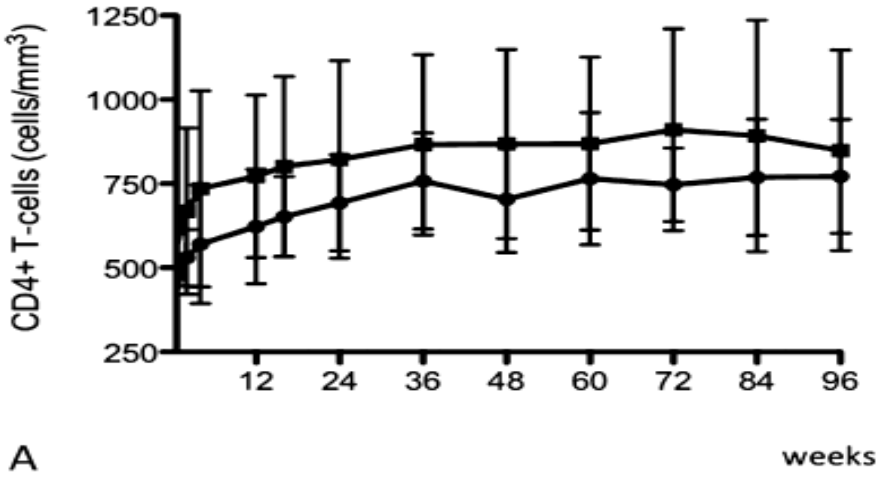


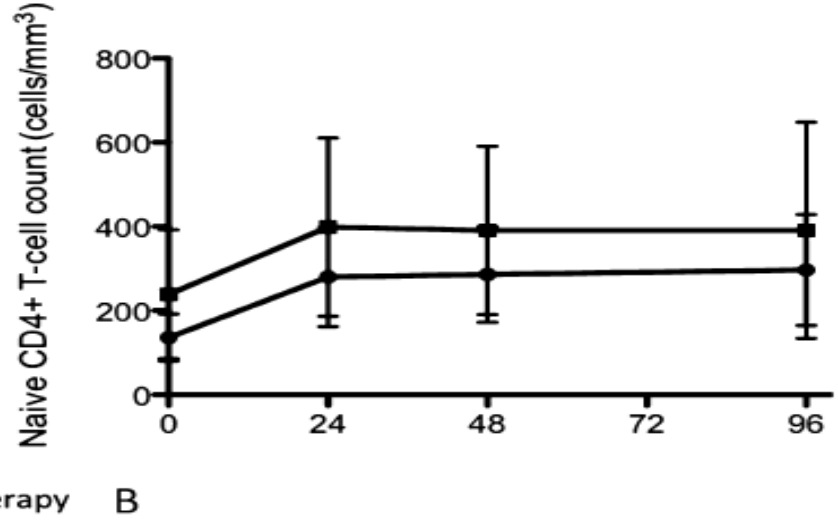


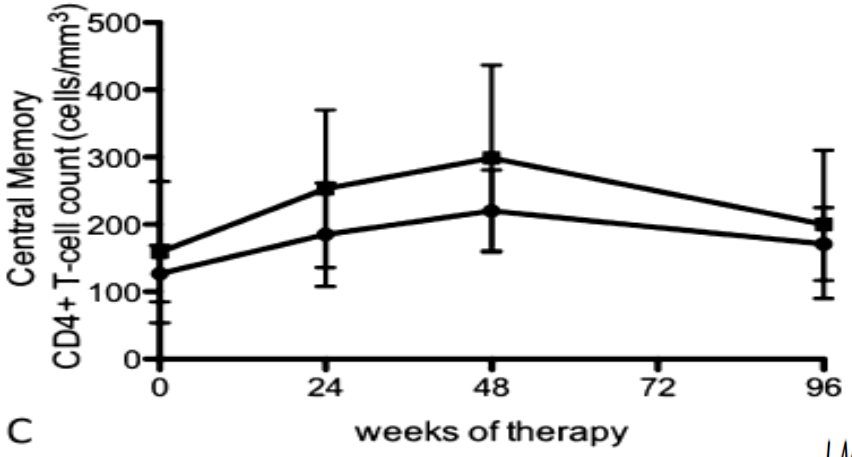


J Acquir Immune Defic Syndr • Volume 66, Number 2, June 1, 2014

….e sui linfociti CD4?







J Acquir Immune Defic Syndr • Volume 66, Number 2, June 1, 2014

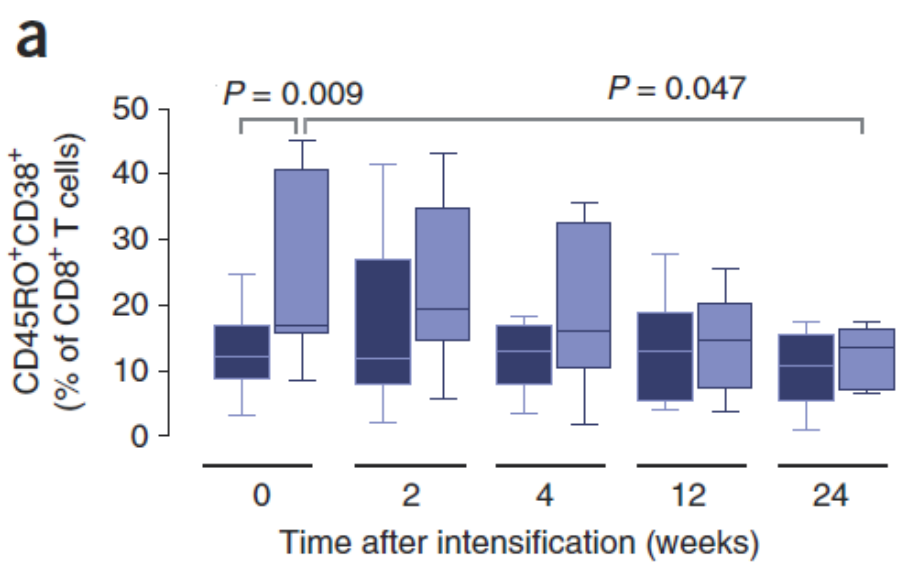
nature medicine

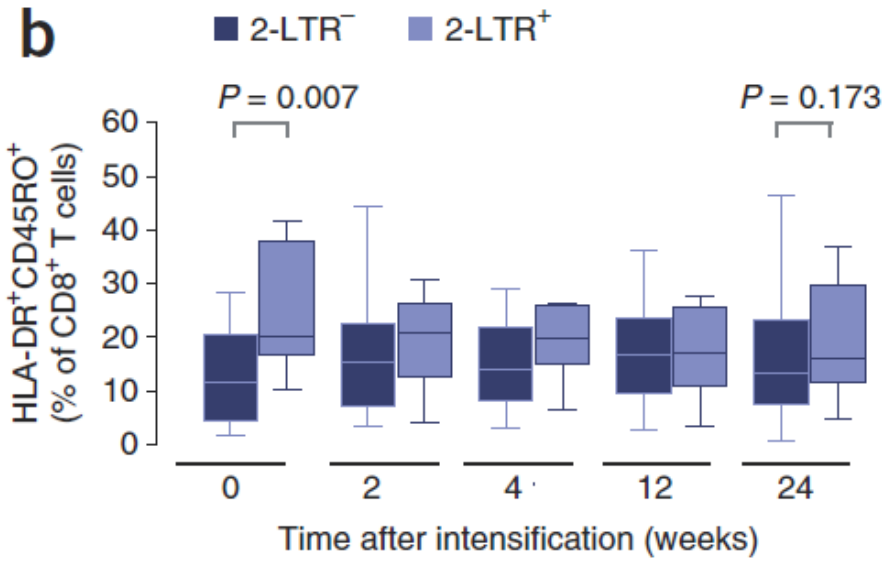
14 March 2010

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

Maria J Buzón[1,9], Marta Massanella[1,9], Josep M Llibre[2], Anna Esteve[3], Viktor Dahl[4], Maria C Puertas[1], Josep M Gatell[5], Pere Domingo[6], Roger Paredes[1,2], Mark Sharkey[7], Sarah Palmer[4], Mario Stevenson[7], Bonaventura Clotet[1,2], Julià Blanco[1] & Javier Martinez-Picado[1,8]

In subjects with increased episomal DNAs, immune activation was higher at baseline and was subsequently normalized after RAL intensification.

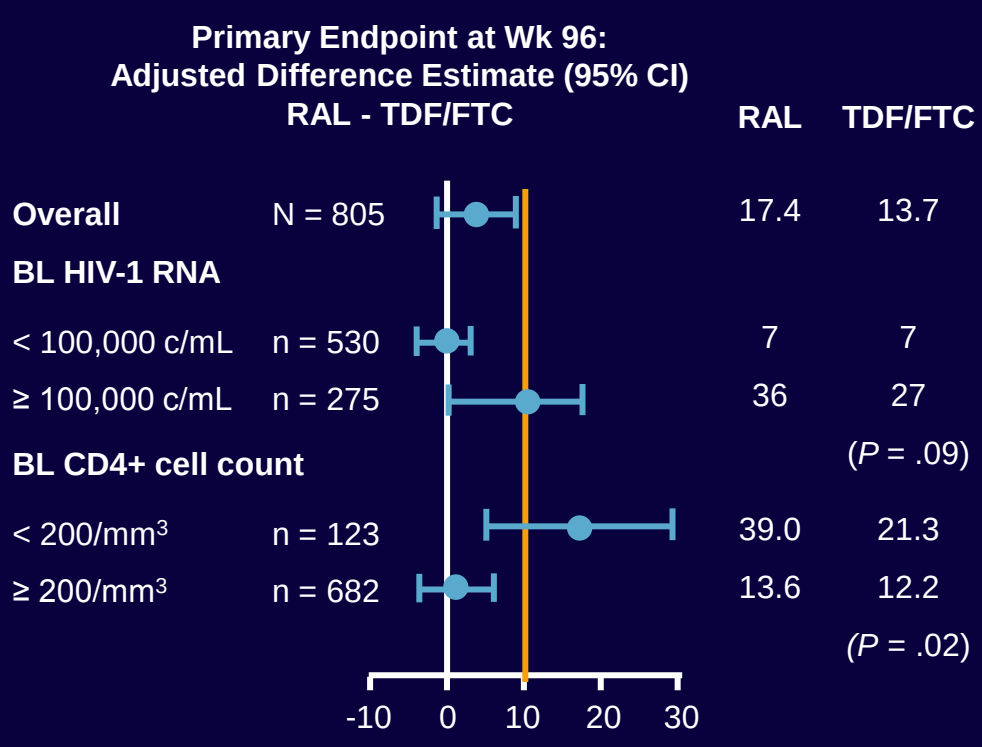




Why do we have to use less drugs?

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

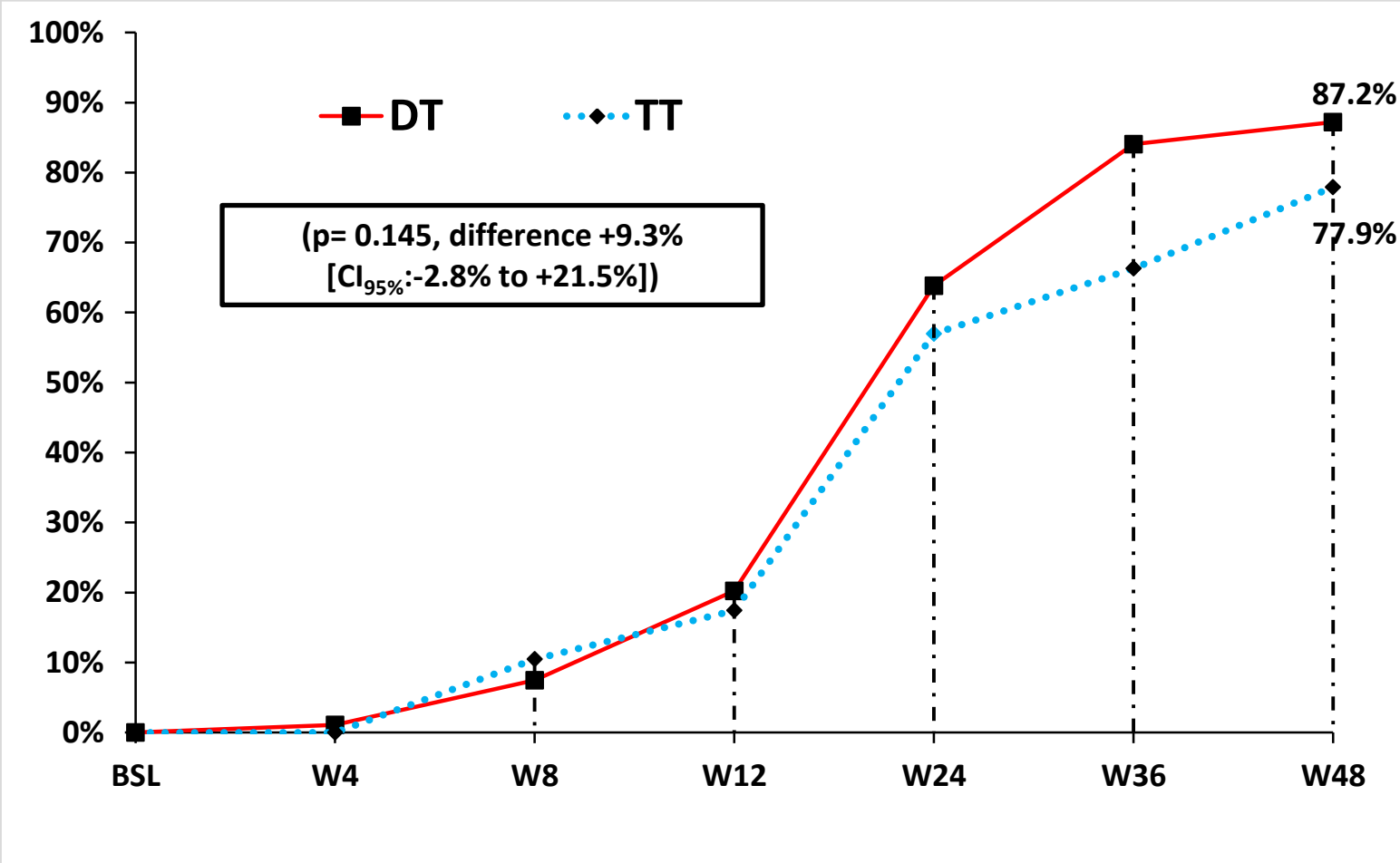
- Overall, regimens noninferior by % reaching composite primary endpoint of 6 virologic and clinical endpoints at Wk 96
  - RAL: 17.4%; TDF/FTC: 13.7%
  - Inferior response in pts with BL CD4 < 200 and a trend toward more primary endpoints in pts with BL VL ≥ 100K
- Similar numbers of pts with PDVF (RAL: 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.

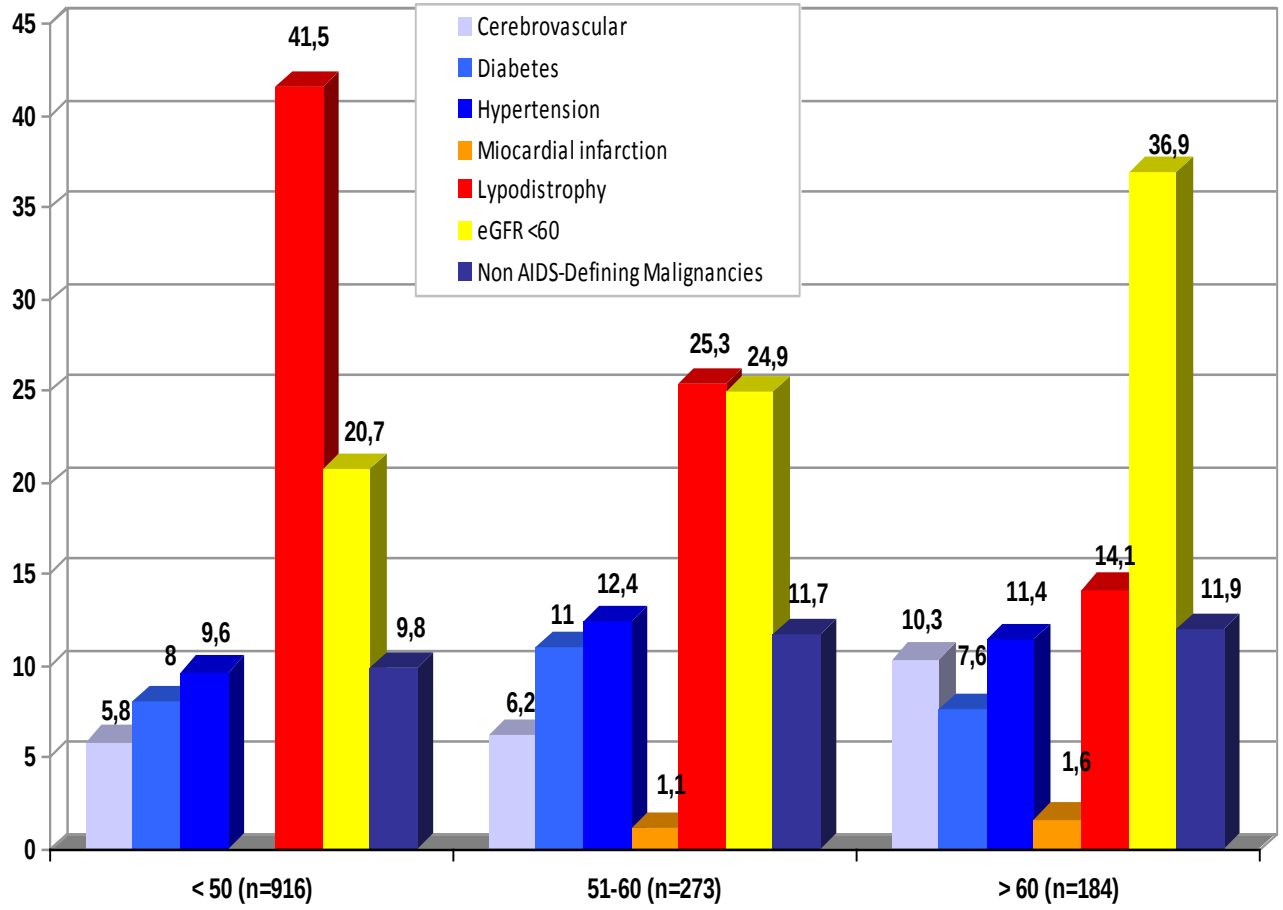
Viral load <50 copies/mL at week 48 (ITTe), baseline VL > 100.000 copies/mL



GARDEL

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

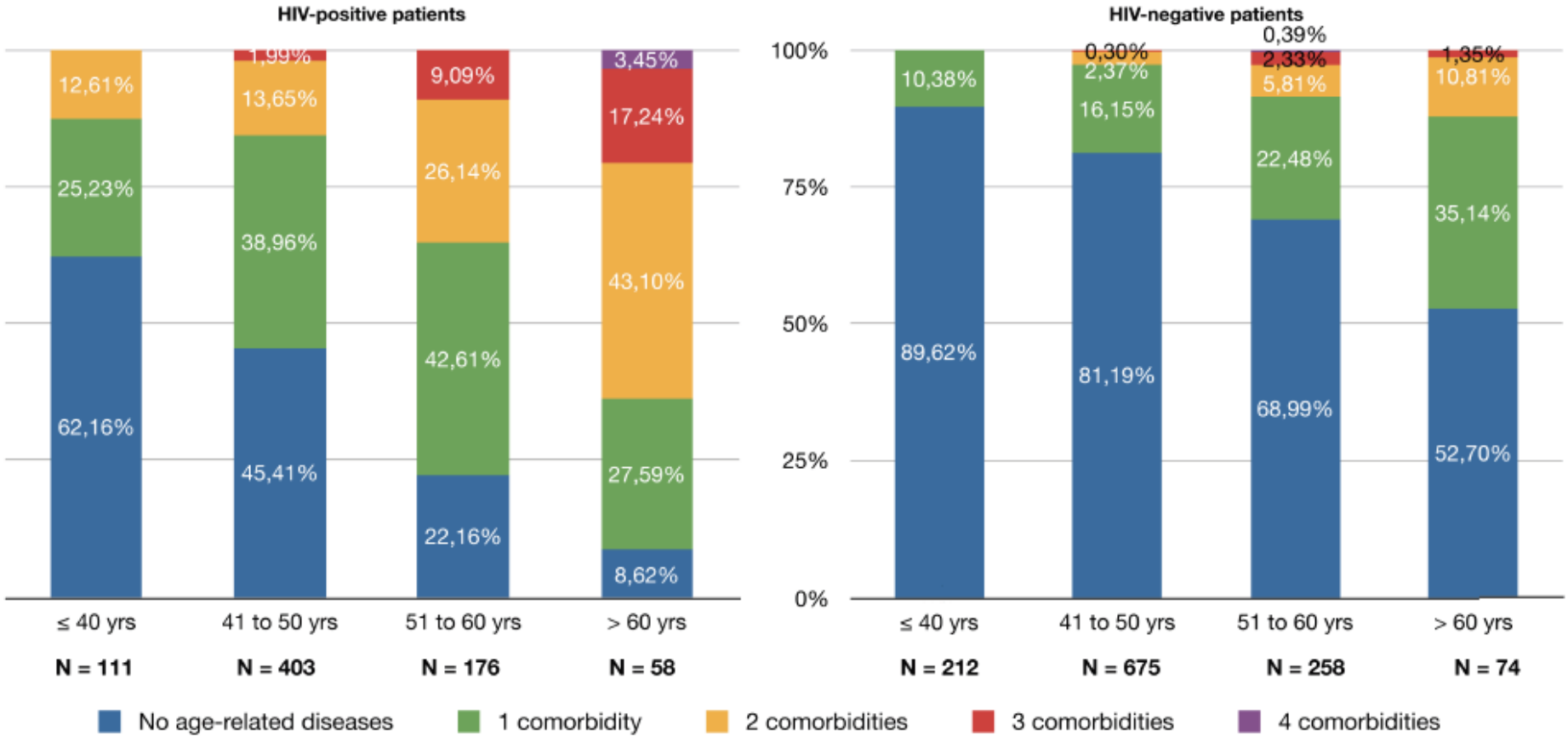
Icona: prevalence of different non-ADS related comorbidities according to age in **ART-treated patients**



ICONA Foundation. Internal data

Clinical Infectious Diseases

Prevalence of Poly-pathology is More Common in HIV Infected Patients than in HIV Negative Controls in Any Age Strata

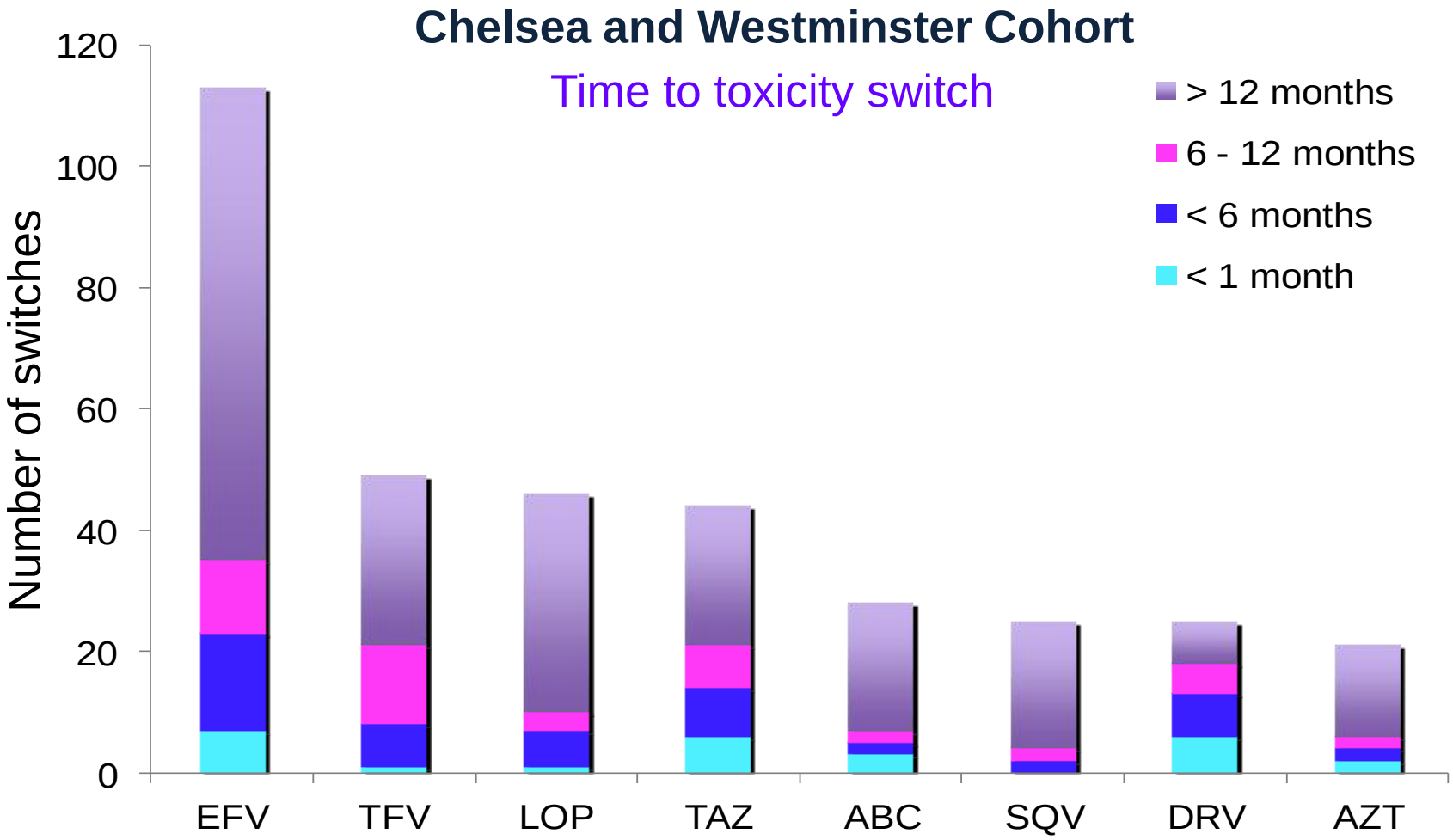


The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.

Pp prevalence was higher in cases than controls in all age strata (all p-values <0.001). Pp prevalence seen cases aged 41-50 was similar to that observed among controls aged >60 controls (p=0.282).

Guaraldi G. et al. CID 2011

Time to toxicity switch not neccesarily short



Boyle A et al. Why do patients switch therapy? 18th Annual Conference BHIVA, April 2012

ATLAS: ATV/r + 3TC in Suppressed Patients

- **Single-arm, Pilot Simplification Study (N=40)**
- **Inclusion criteria:**
  - Patients on ATV/r + 2 NRTIs ≥3 months (97.5% on TDF)
  - HIV-RNA <50 copies/mL ≥3 months
  - CD4 >200 cells/mm^3 ≥6 months
- **Exclusion criteria:**
  - History consistent with possible resistance to 3TC or atazanavir
  - Proton pump inhibitor use
  - HBsAg positive

Baseline Characteristics	
Age (median, years)	45
Male sex	57.5%
Injecting drug users	22.5%
HCV co-infection	20%
Time (median, years) from starting last cART regimen	2.6
CD4 cells count (median, cells/mm^3)	598

De Luca A, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB207.

Table 2. Changes in CD4 cell count, blood lipids, bilirubin and renal function after 48 weeks (on-treatment analysis)

	Baseline	Week 48	Mean change after 48 weeks	*P* value
Immunological parameters				
CD4 cell count, cells/mm^3	630 (190)	669 (232)	+36 (159)	0.179
Lipid parameters				
total cholesterol, mg/dL	188 (37)	204 (47)	+17 (27)	**0.001**
HDL cholesterol, mg/dL	45 (11)	50 (12)	+6 (8)	**<0.001**
LDL cholesterol, mg/dL	109 (25)	116 (36)	+8 (24)	0.052
total cholesterol/ HDL cholesterol	4.4 (1.3)	4.3 (1.4)	−0.16 (0.9)	0.287
HDL cholesterol/ LDL cholesterol	0.4 (0.2)	0.5 (0.2)	+0.04 (0.1)	0.086
triglycerides, mg/dL	185 (137)	196 (131)	+8 (116)	0.668
Bilirubin				
total bilirubin, mg/dL	2.6 (0.9)	2.8 (1.4)	+0.1 (1.4)	0.657
unconjugated bilirubin, mg/dL	2.2 (0.8)	2.4 (1.3)	+0.18 (1,3)	0.402
Renal function				
estimated GFR, mL/min/1.73 m^2	70 (13)	77 (17)	+7.3 (11.6)	**<0.001**

Risk factors for HIV RNA > 50 copies/ml at week 96

MONOI study: Patients randomized in the monotherapy arm

	Univariate analysis OR (95%CI), p value	**Multivariate analysis** OR (95%CI), p value
Difficulty in adherence (<100% vs 100%)	2.36 (0.94 – 5.92) p= 0.07	**3.84** (1.29 – 12.49) p= 0.02
Duration of prior HAART (per 5 years decrease)	2.38 (1.30 – 4.38) p= 0.003	**2.93** (1.43 – 6.66) p= 0.006
Baseline US HIV-1 RNA (< 1 copy/mL vs others)	0.41 (0.16 – 1.05) p= 0.06	
HIV-1 DNA at D0 (per 1 Log copy/10^6 cells increase)	2.45 (1.07 – 5.61) p= 0.03	**2.66** (1.11 – 7.48) p= 0.04
HIV-1 RNA at D0 (blips vs < 50 copies/mL)	4.05 (0.76 – 21.5) p= 0.11	

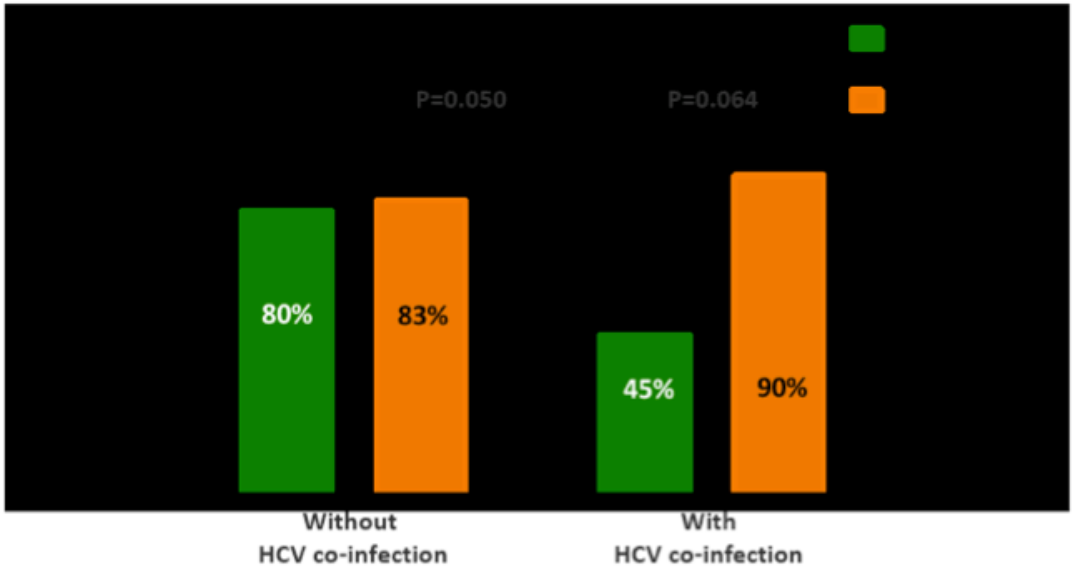
Odds ratio (95% confidence intervals) for treatment failure

Lambert-Niclot S et al. JID 2011;204:1211-16.

MODAt Characteristics of patients with CVR

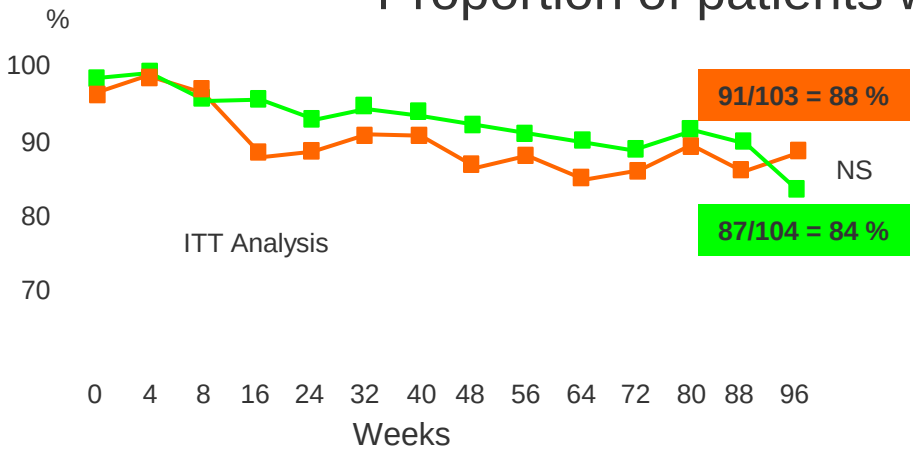
Arm	Patient ID	HCV	1st HIV-RNA (cp/mL)	2nd HIV-RNA (cp/mL)	Adherence	Mutations at CVR	HIV-1 RNA > 12 weeks (cp/mL)
ATV/r	T020	Neg	376	515	88%	None	<50
	T033	Neg	1704	505	95%	None	<50
	T046	Neg	121	164	100%	None	<50
	T055	Neg	260	211	91%	Not amplifiable	<50
	T061	Neg	72	146	90%	None	<50
	T026	Pos	150	182	95%	None	<50
	T038	Pos	50	279	99%	None	<50
	T050	Pos	1397	250000	72%	None	<50
	T053	Pos	6695	3897	88%	None	<50
	T003	Pos	57	98	96%	Not amplifiable	<50
	T002	Pos	93	52	95%	Not amplifiable	<50
ATV/r + 2NRTIs	T065	Neg	254	92	93%	None	NA
	T025	Neg	138	9602	89%	L10I, V179D	NA

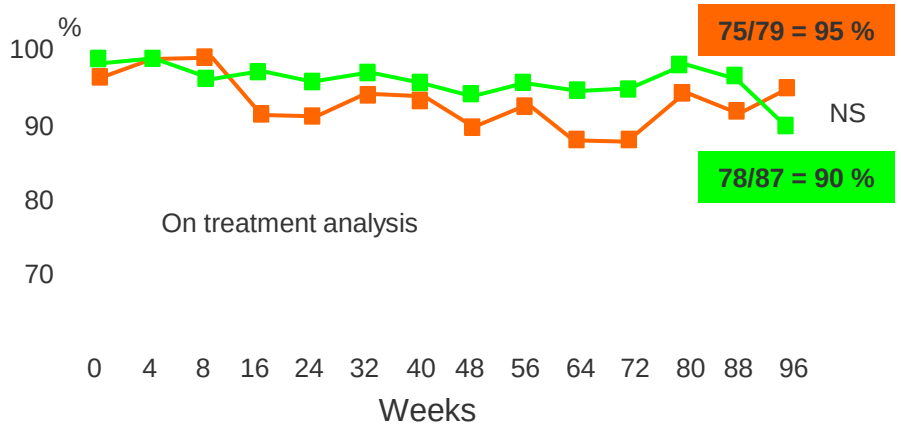
MODAt Virological efficacy according to HCV co-infection



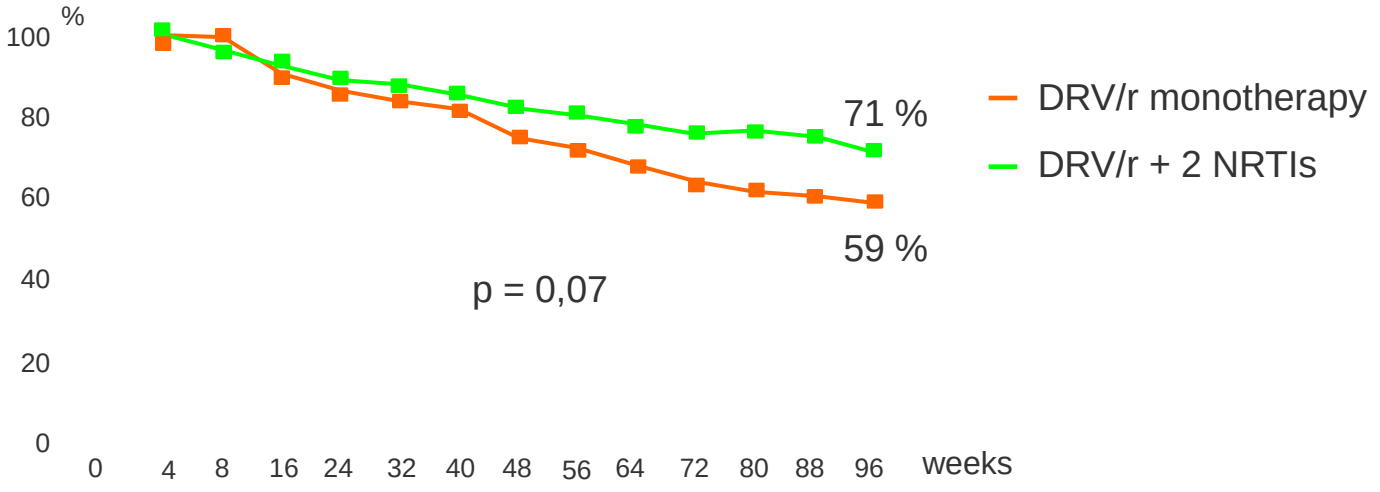
MONOI Study : W96 results

Proportion of patients with VL < 50 c/ml





Proportion of patients with VL < 50 c/ml at all visits between D0 and W96

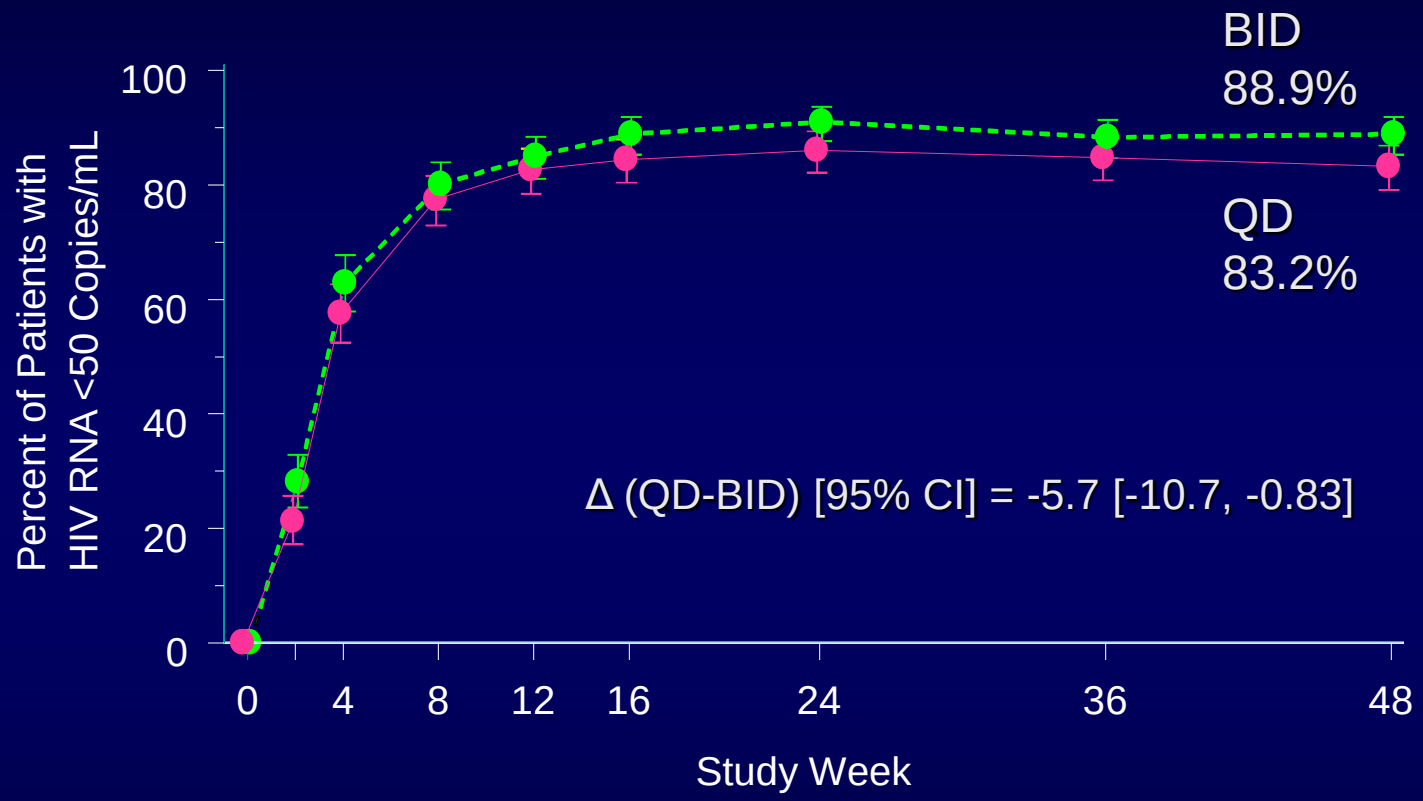


Valantin MA, J Antimicrob Chemother 2012

Do patients with suppressed viral load need less drug?

QDMRK

% of Patients with HIV RNA < 50 copies/mL (NC=F†)



Number of Contributing Patients

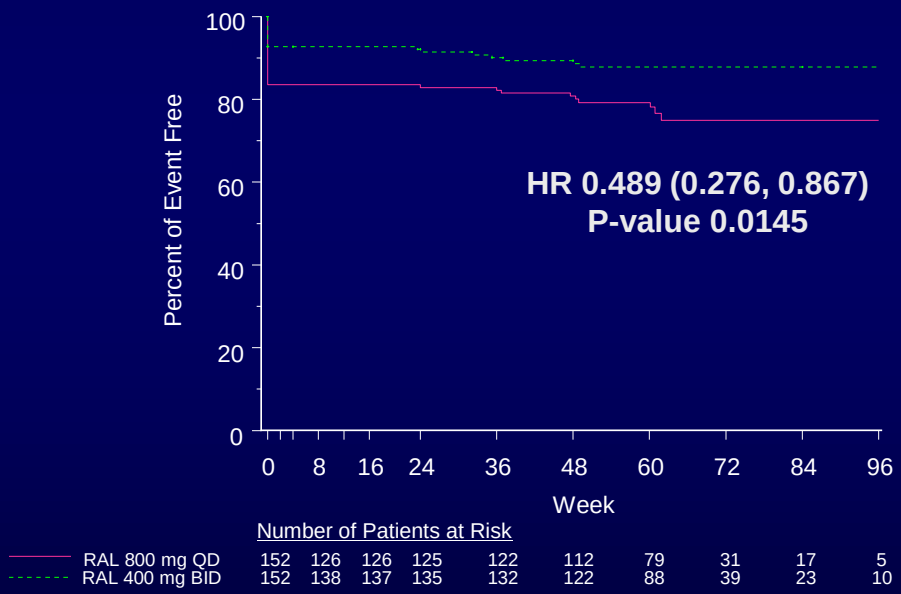
RAL 800 mg QD	382	382	377	381	379	380	381	382
RAL 400 mg BID	388	388	386	387	386	387	386	386

*All patients received TDF/FTC FDC

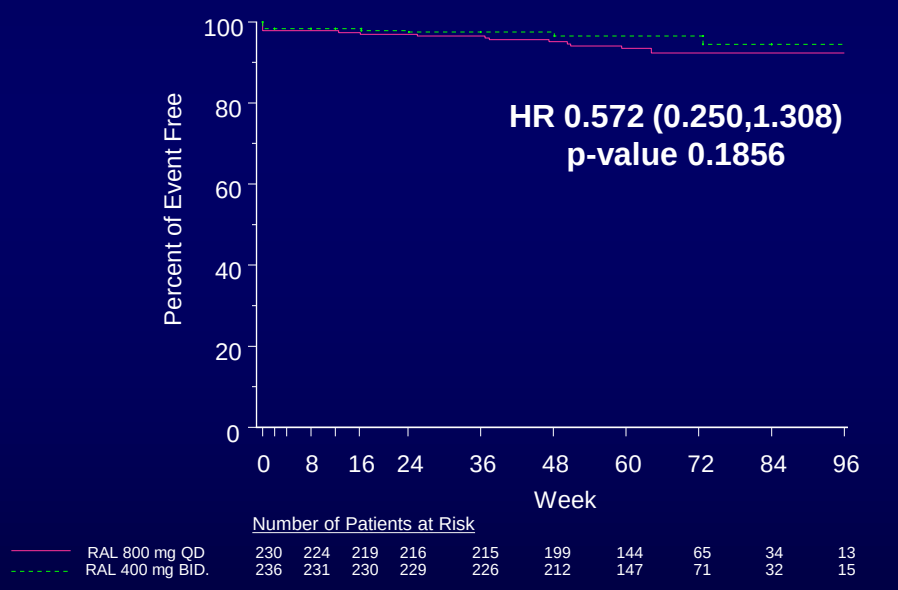
† Non-completer equals failure (NC=F) approach treats all discontinuations as failures

QDMRK
Time to Loss of Virologic Response (TLOVR)

TLOVR (OF)
Patients With BL vRNA >100,000 cp/mL



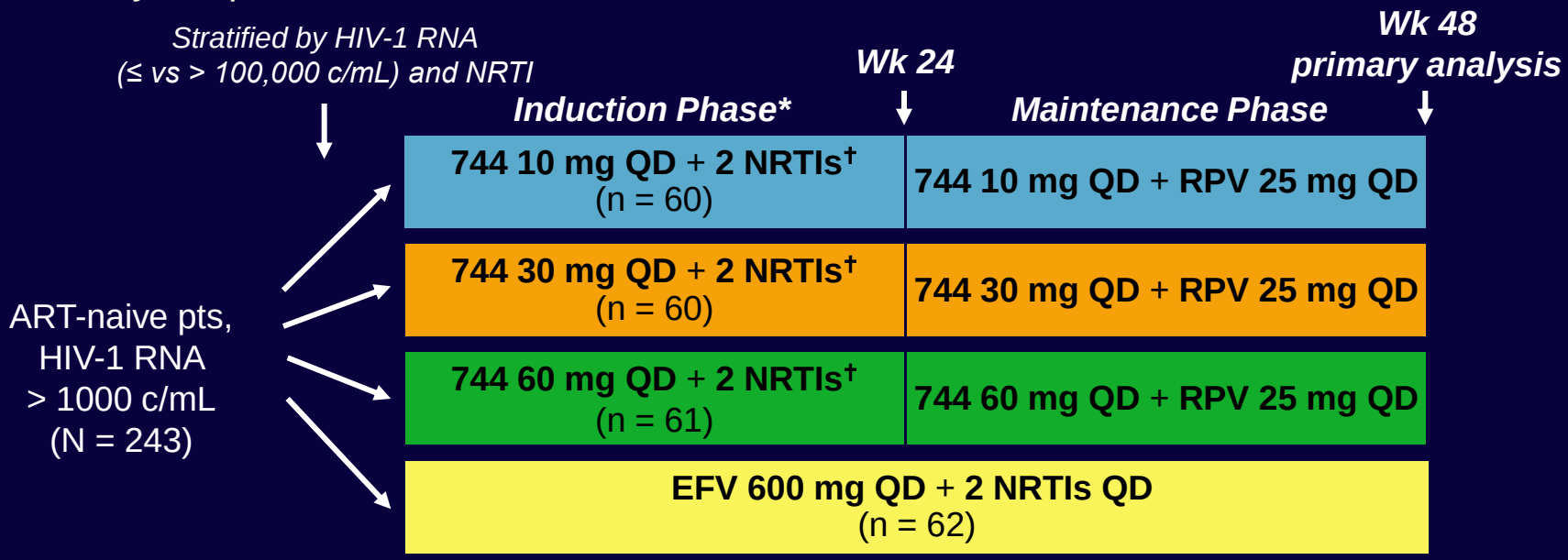
TLOVR (OF)
Patients With BL vRNA <=100,000 cp/mL



…… and the future?

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

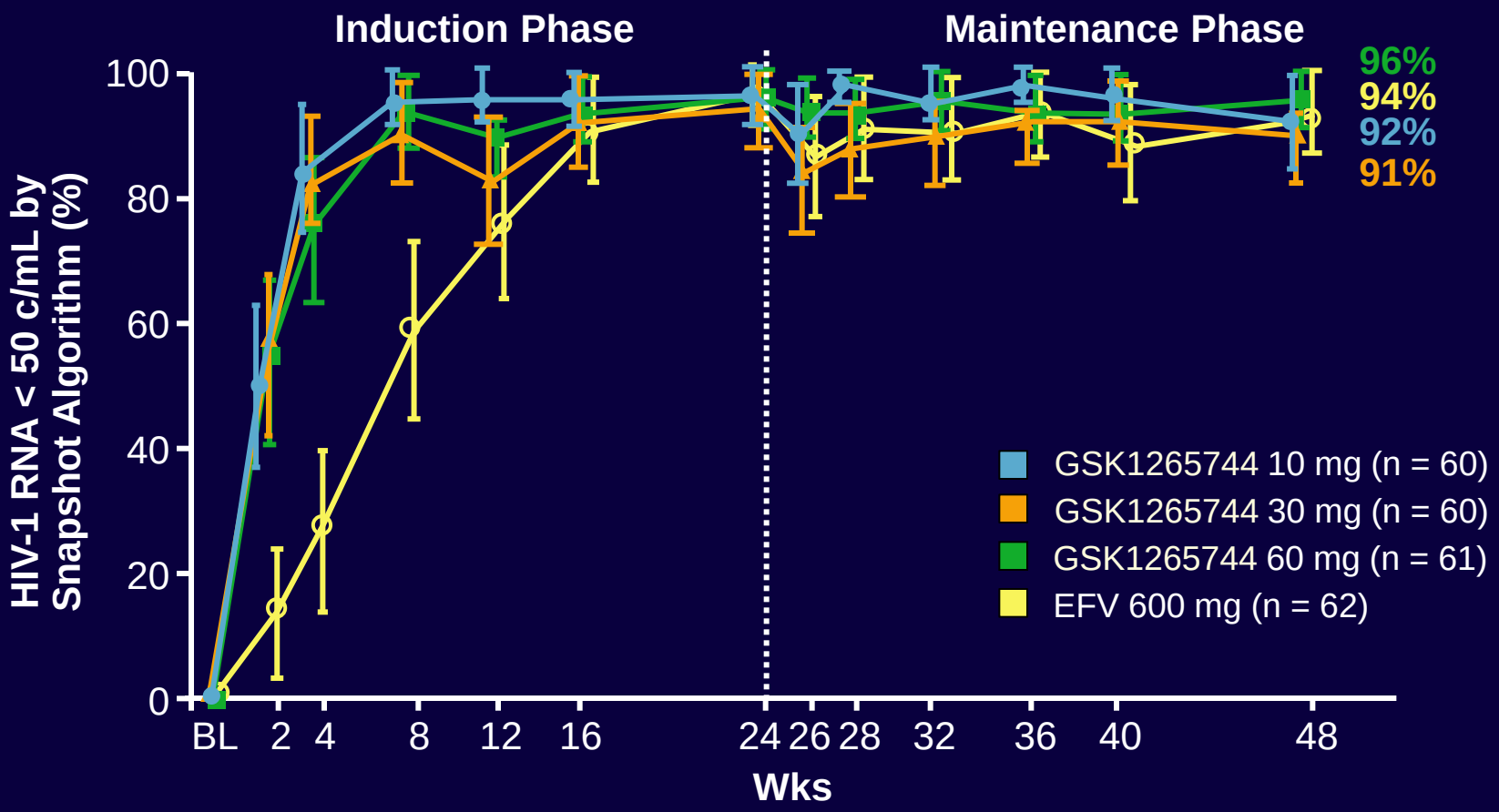
- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*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

Conclusions

Induction maintenance therapy could be prescribed in order to decrease the number of drugs, but not all strategies have obtained good results.

Clinical cure is a not so easy to be achieved

Treating with more drugs as an induction does not seems to work as a general strategy

Decreasing the number of drugs after starting with 3 is possible in selected populations, but carefully.