Chi potrebbe giovarne di più? Focus sulle popolazioni speciali

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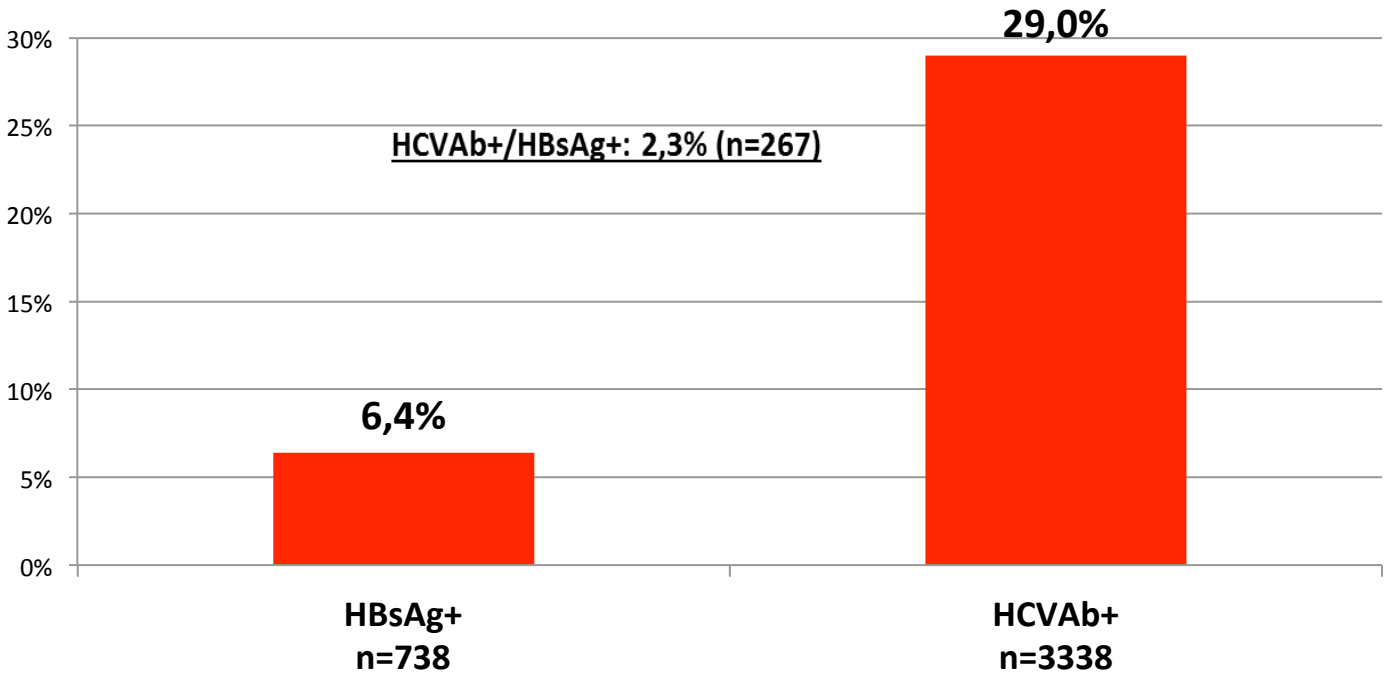
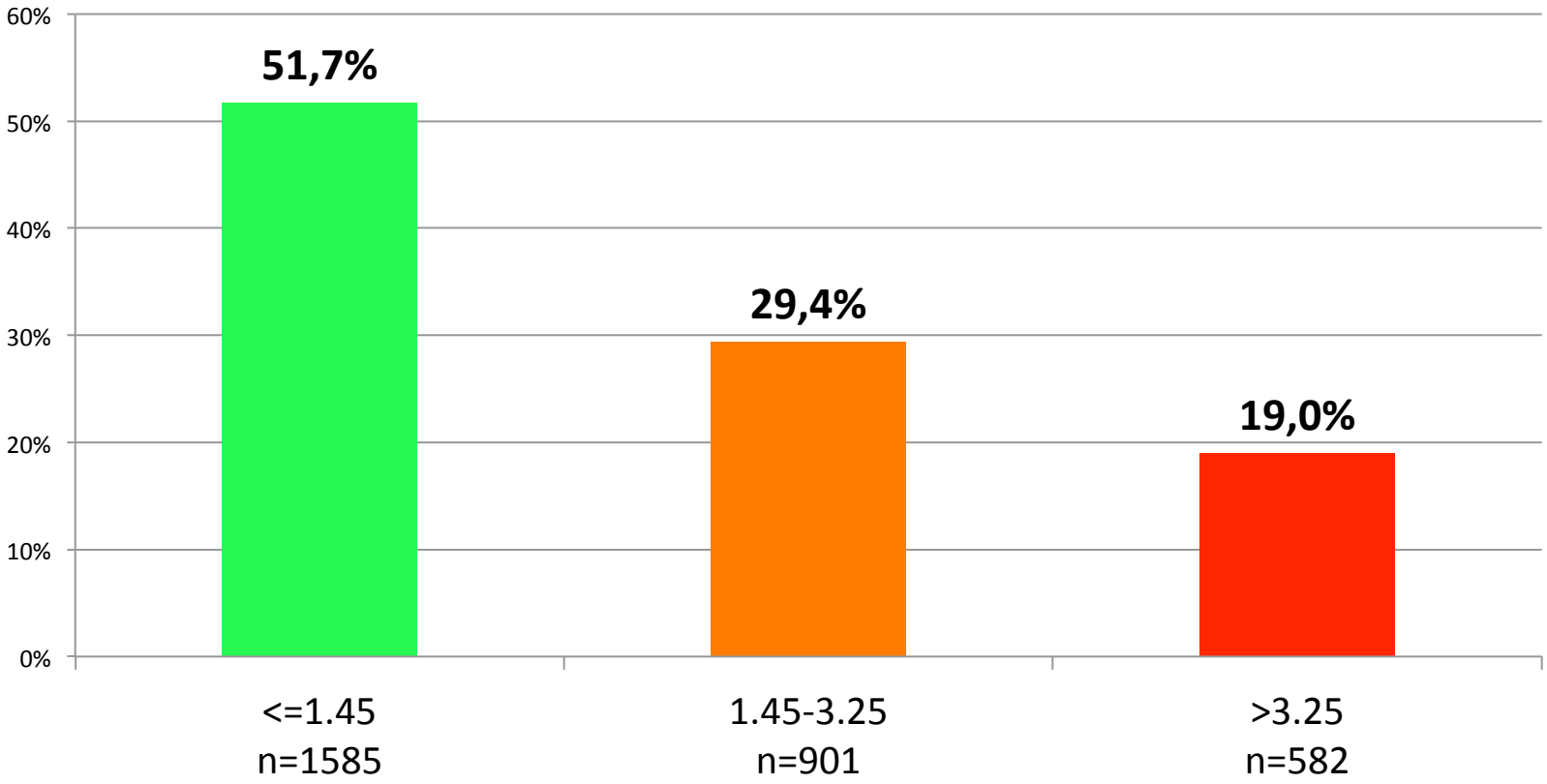
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

HBsAg and HCVAb positivity in 11,511 patients enrolled in ICONA



Dec 2014 Report

Last Fib4 values for HCVAb positive patients in ICONA, naive or failed at any anti-HCV therapy



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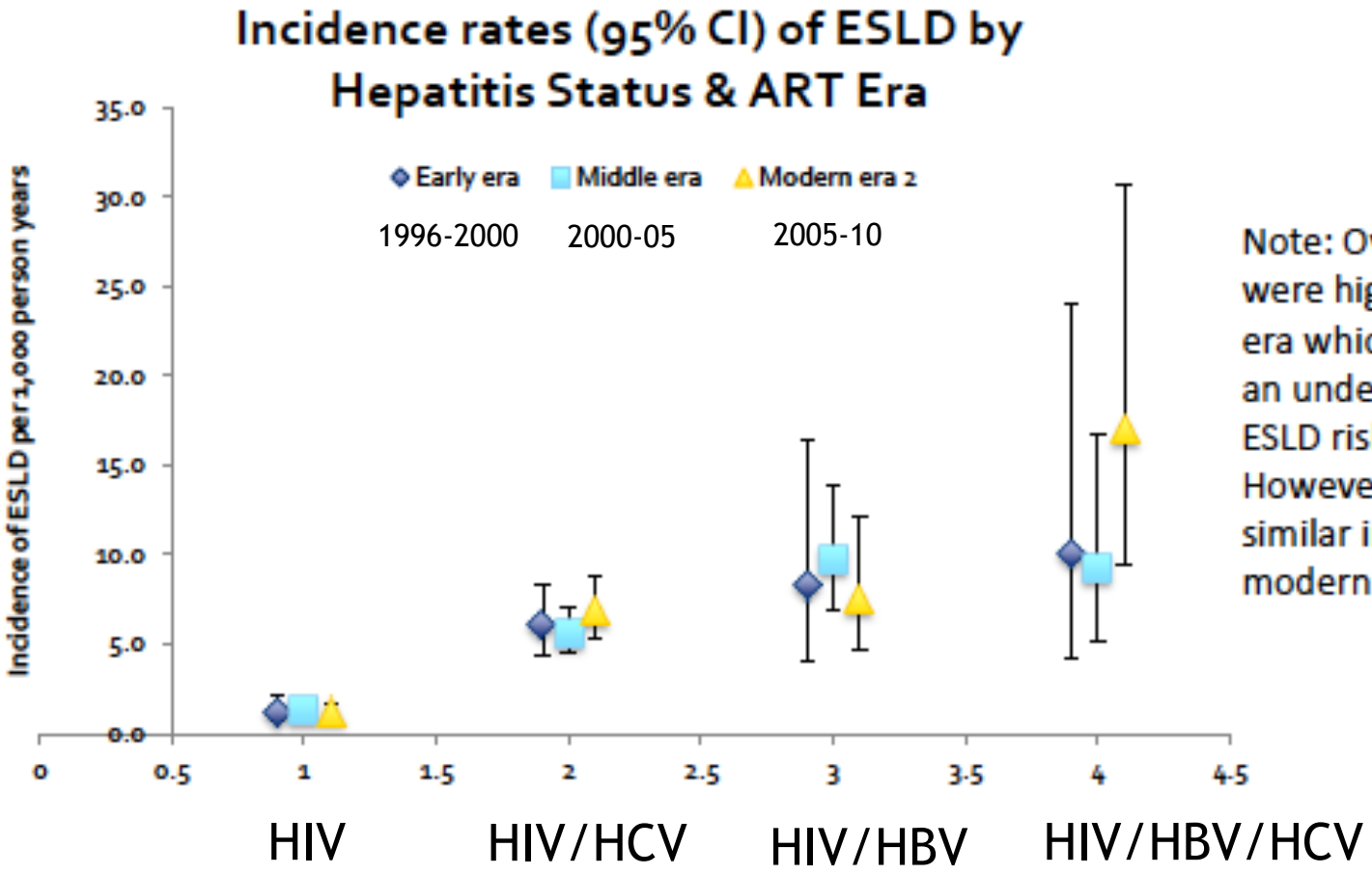
Impact of HCV Exposure/ Coinfection on HIV disease

Issue	HCV exposure (HCVAb+ vs HCVAb-)	HCV active replication (HCVAb+ HCVRNA+ vs HCVAb+ HCVRNA-)
Faster HIV disease progression	Yes[1]	
Impaired CD4 recovery on cART	Yes[2]	Yes[3]
Impaired HIVRNA suppression on cART	Yes [4]	
Worsened renal function	Yes[5]	Yes[6]
Higher incidence of osteopor. fractures	Yes[7]	
Higher incidence of Cardiovascular related events	Yes [8]	
Higher incidence of Diabetes	Yes [9]	
Higher non AIDS non liver related mortality	Yes[10]	Yes[11]

1. *Greub, Lancet, 2000, Piroth, J Viral Hepat, 2000 De Luca et al, Arch Intern Med, 2002), Herrero Martinez E JID 2002, Dorrucci AIDS 2004; Braitsein JID 2006;*
2. *Lincoln, HIV Med, 2003*
3. *Potter M AIDS 2010*
4. *Pulido AIDS Review 2012; Hua L AIDS 2013*
5. *Izzedine AIDS 2009; Lucas JID 2013*
6. *Peters AIDS 2012; Mocroft A PLOS One 2012; Lucas jiD 2013*
7. *Lo Re Hepatology 2012; Maalouf J Bon Min Res 2013, Casado Osteopos Int 2014*
8. *Erqou S CROI 2014*
9. *Howard AA JAIDS 2014; Butt AA AIDS 2009; Jain MK HIV Med 2007; Butt AA Hepatology 2004*
10. *Mallet V CROI 2014*
11. *Grint D CROI 2014*

Has Modern ART Reduced End stage Liver Disease Risk in HIV-Hepatitis Coinfection? (data from 34119 HIV + 380 with ESLD)



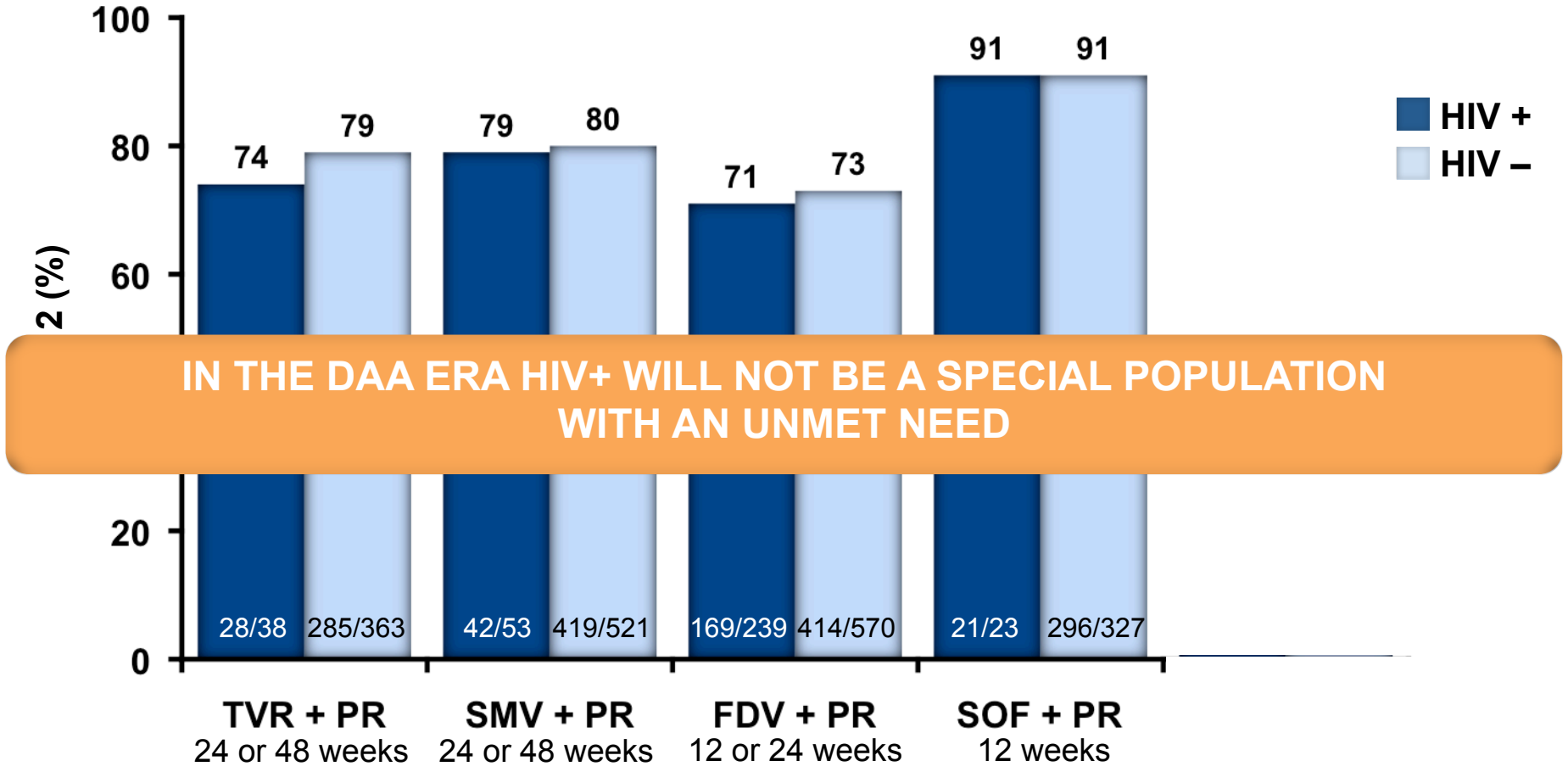
Note: Overall death rates were high in the early ART era which may have led to an underestimation of ESLD risk in this period. However, death rates were similar in the middle and modern eras.

Klein M et al CROI 2015; Abstract #638

WHOM TO TREAT:EASL AND AASLD-IDSA RECOMMENDATIONS
Individual health related issues

Clinical setting			
Cryoglobulinemia with vasculitis	Treatment should be prioritized regardless of fibrosis stage (A1)	Highest priority (IB)	
Extrahepatic disease		Highest priority (IIaB)	
Solid Organ Transplant Recipients (pre& post)		Highest priority (IB)	**> F1**
HIV coinfection		High priority based on available resources(IB)	
HBV			
NASH & Diabetes			
Debilitating fatigue			

SVR12 after treatment with PR + TVR, SMV, FDV and SOF in HCV G1 treatment-naïve patients: HIV + vs HIV –



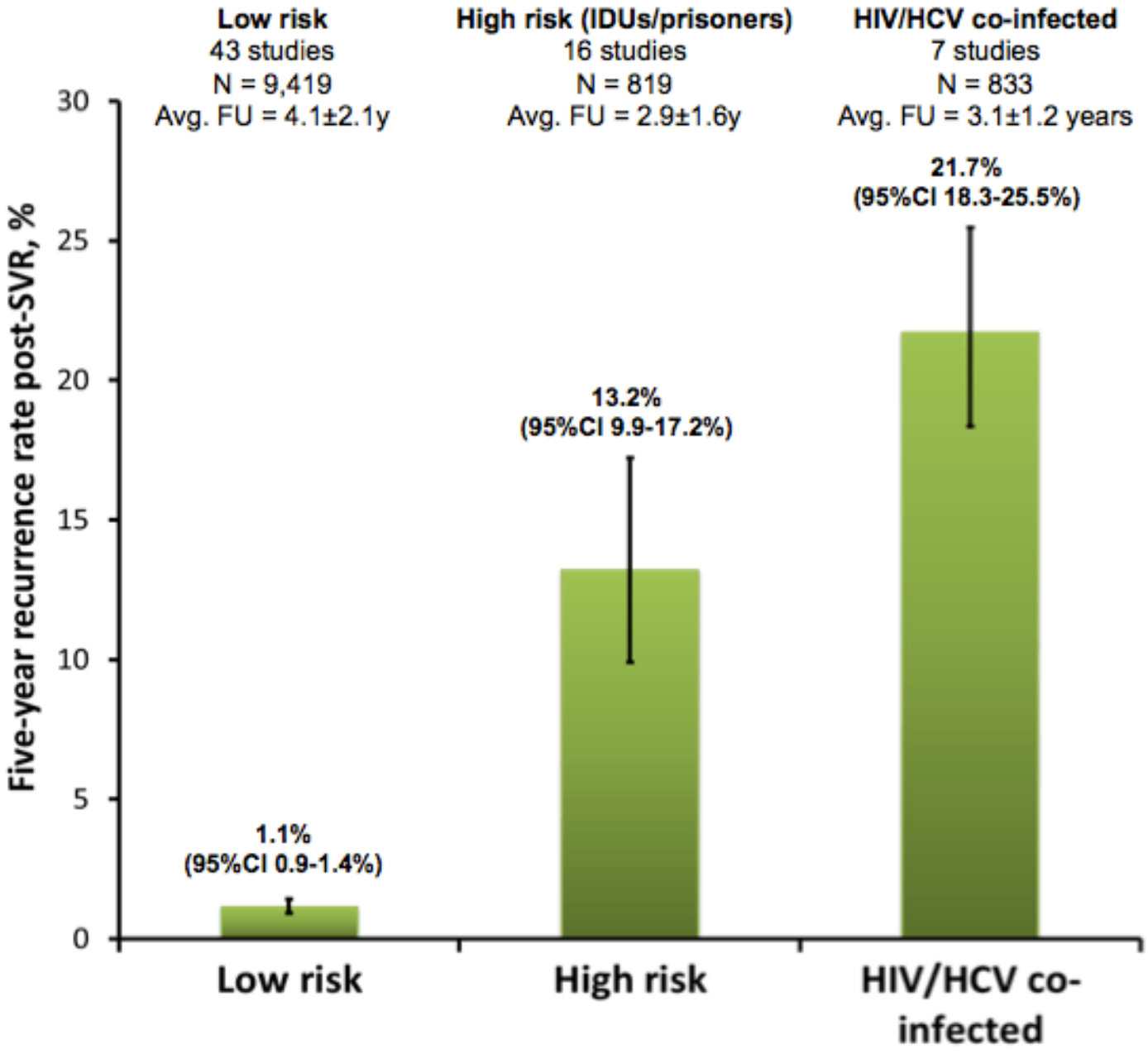
Cirrhosis	**10%**	**13%**	**11%**	**Excluded**

Drug-drug interactions between HCV DAAs and HIV antiretrovirals

		SIM	DCV	SOF	LDV/SOF	3D
NRTIs	Abacavir	◆	◆	◆	◆	◆
	Didanosine	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆
	Stavudine	◆	◆	◆	◆	◆
	Tenofovir	◆	◆	◆	■	◆
	Zidovudine	◆	◆	◆	◆	◆
NNRTIs	Efavirenz	●	◆ 90 mg	◆	■*	●
	Etravirine	●	◆ 90 mg	◆	◆	●
	Nevirapine	●	◆90 mg	◆	◆	●
	Rilpivirine	◆	◆	◆	◆*	■
Protease inhinitors	Atazanavir; Atazanavir/Ritonavir	●	◆30 mg	◆	◆*	■ no RTV
	Darunavir/Ritonavir; Darunavir/Cobicistat	●	◆	◆	◆*	■ no RTV low Dar Cthrough
	Fosamprenavir	●	◆ 30 mg	◆	◆*	■ no RTV
	Lopinavir	●	◆	◆	◆*	●
	Saquinavir	●	◆ 30 mg	◆	◆*	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆
	Elvitegravir/Cobicistat	●	◆30 mg	◆	■*	●
	Maraviroc	◆	◆	◆	■	■ 150 mg MVC
	Raltegravir	◆	◆	◆	◆	◆

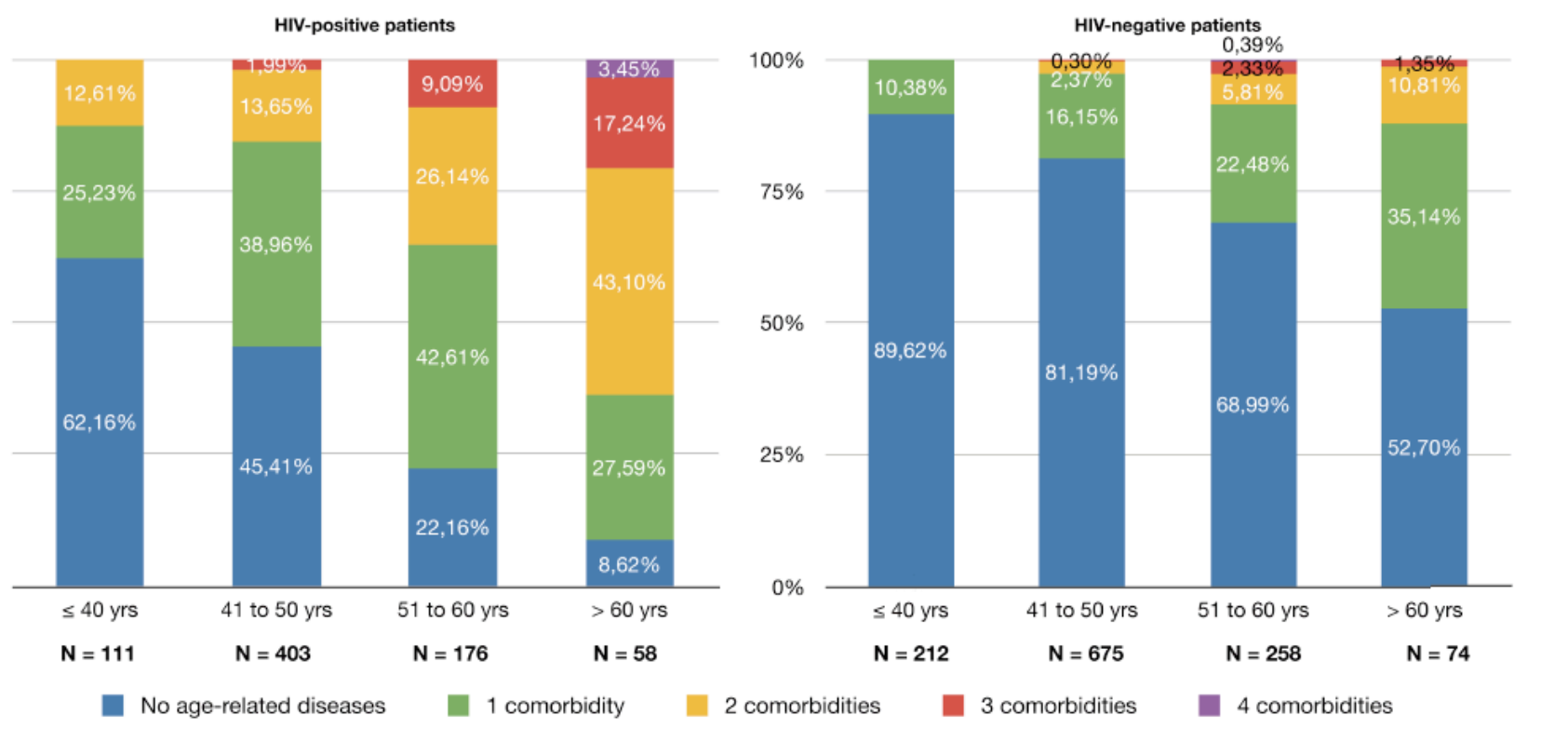
* Ledipasvir increases Tenofovir concentration with an additional increase in the presence of ritonavir or cobicistat boosting

Figure 1. Five-year rate (95%CI) of recurrence post-SVR, by risk group



Prevalenza di Poli-pathologie è più comune nei soggetti HIV positivi che nei controlli HIV negativi per ogni strato d'età

Poly-patology prevalence in cases and controls, stratified by age categories.



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

ACTG 5257: Tolerability Failure at Wk 96

Toxicity-Associated d/c of Randomized ART*	ATV/RTV (n = 605)	RAL (n = 603)	DRV/RTV (n = 601)
Any, n (%)	95 (15.7)	8 (1.3)	32 (5.3)
Gastrointestinal, n	25	2	14
Hyperbilirubinemia, n	47	0	0
Other hepatic, n	4	1	5
Skin, n	7	2	5
Metabolic, n	6	0	2
Renal, n	4	0	0
Abnormal chemistry/hematology findings (excluding LFTs), n	0	0	2
Other, n	2	3	4

*Participants allowed to switch therapy for intolerable toxicity.

Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

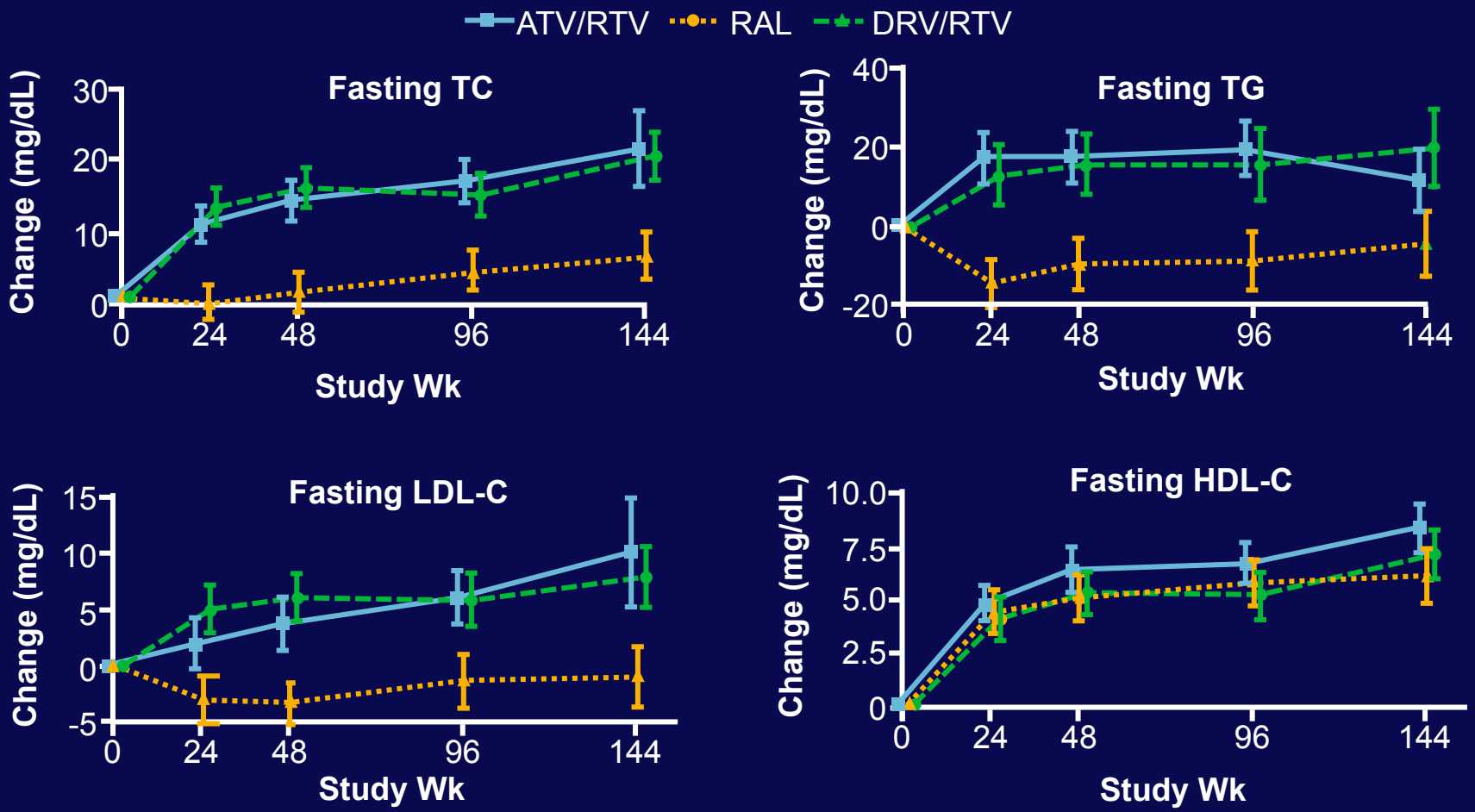
Study 103 (EVG/COBI/FTC/TDF vs ATV+RTV+FTC/TDF) at Week 144
AEs Leading to Study Drug Discontinuation

AE Leading to Study Drug Discontinuation (DC)*	EVG/COBI/FTC/TDF (n=353)			ATV+RTV+FTC/TDF (n=355)		
	W48[1,3]	W96[2,3]	W144[4,5]	W48[1,3]	W96[2,3]	W144[4,5]
Overall DC due to AE	13 (3.7%)	+2(+0.6%)	+6 (+1.7%)	18 (5.1%)	+3 (+0.8%)	+9 (2.5%)
Renal events	1 (0.3%)†	+2 (+0.6%)	+2 (+0.6%)	1 (0.3%)†	+1 (+0.3%)	+6 (+1.7%)
Diarrhoea	2 (0.6%)	0	0	1 (0.3%)	0	0
Pyrexia	2 (0.6%)	0	0	0	0	+1(+0.3%)
Nausea	1 (0.3%)	0	0	4 (1.1%)	0	0
Vomiting	1 (0.3%)	0	0	2 (0.6%)	0	0
Fatigue	1 (0.3%)	0	0	2 (0.6%)	0	0
Ocular icterus	0	0	0	4 (1.1%)	0	0
Jaundice	0	0	0	2 (0.6%)	0	0
Dizziness	0	0	0	2 (0.6%)	0	0
Drug eruption	0	0	0	2 (0.6%)	0	0

*>1 subject in either treatment group cumulatively at Week 144

1. DeJesus E, *et al. Lancet* 2012;379:2429–2438; 2. Rockstroh JK, *et al. JAIDS* 2013;62:483–486 ; 3. Rockstroh JK, *et al*. HIV-11 2012. Glasgow, UK. #O424B; 4. Clumeck N, *et al. JAIDS* 2014;65(3):e121–124; 5. Clumeck N, *et al.* EACS 2013. Brussels, Belgium. #LBPS7/2

ACTG 5257: Mean Change From BL in Fasting Lipids



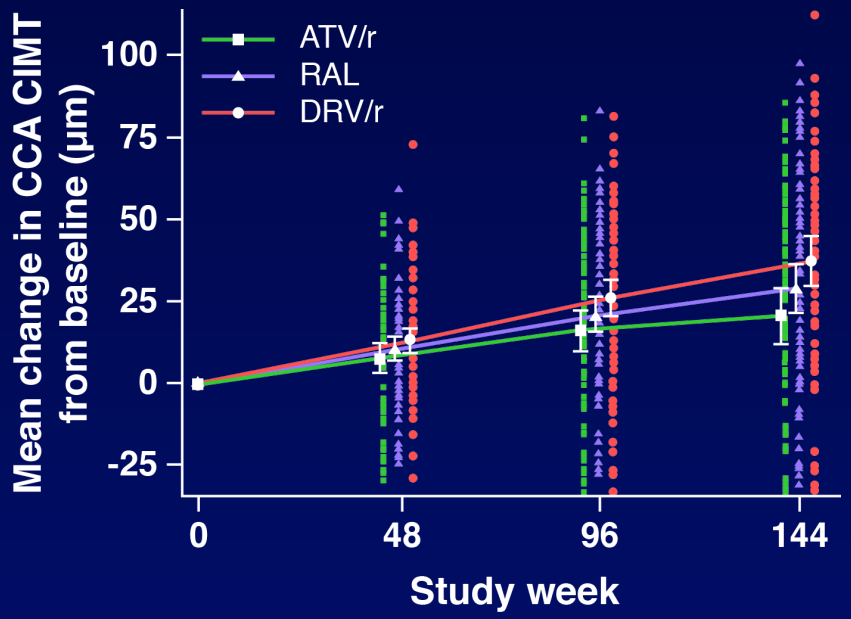
Ofotokun I, et al. CROI 2014. Abstract 746.

A5260s: Mean Change (95% CI) From Baseline in CCA CIMT (ITT)

ACC 2014

Stein JH, et al

Poster 147



- ATV/r progressed more slowly than DRV/r (p = 0.013)
- Intermediate progression for RAL (p = 0.15 versus ATV/r; p = 0.31 versus DRV/r)

	CCA CIMT (µm/year)		
Treatment group	Estimated rate of change	95% CI	p
ATV/r	8.2	5.6–10.8	< 0.001
DRV/r	12.9	10.3–15.5	< 0.001
RAL	10.7	9.2–12.2	< 0.001
Treatment group dfiference[1]	Estimated difference	97.5% CI	p
ATV/r versus DRV/r	-4.7	-8.9 to -0.4	0.013
ATV/r versus RAL	-2.8	-7.0 to 1.5	0.15
DRV/r versus RAL	1.9	-2.4 to 6.2	0.31

Analyses adjusted for time and two stratification factors of HIV-1 RNA level and10-year FRS.

[1]Estimated treatment group difference was defined as the difference in annual rate of CIMT change (treatment A - treatment B).

FRS, 10-year Framingham risk score.

A5260s: Mean Change (95% CI) From Baseline in Carotid Bifurcation IMT (ITT)

ACC 2014

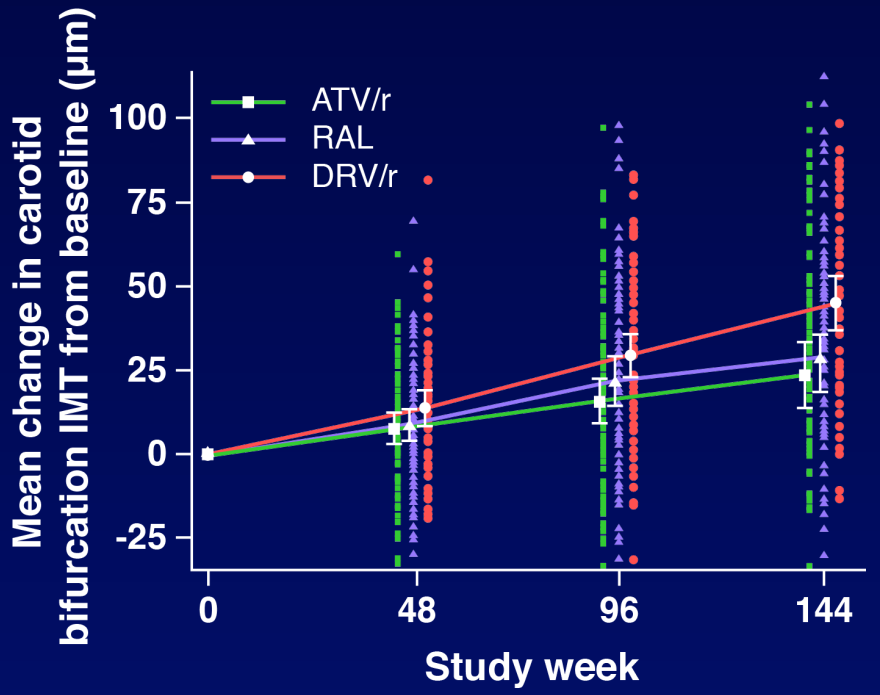
Stein JH, et al

Poster 147

	BIF CIMT (µm/year)		
Treatment group	Estimated rate of change	95% CI	p
ATV/r	8.7	5.6–11.8	< 0.001
DRV/r	14.7	11.6–17.8	< 0.001
RAL	11.5	9.7–13.3	< 0.001
Treatment group difference[1]	Estimated difference	97.5% CI	p
ATV/r versus DRV/r	-6.0	-11.0 to -1.0	0.007
ATV/r versus RAL	-2.3	-7.4 to 2.7	0.30
DRV/r versus RAL	3.7	-1.4 to 8.7	0.11

Analyses adjusted for time and two stratification factors of HIV-1 RNA level and 10-year FRS.

[1]Estimated treatment group difference was defined as the difference in annual rate of CIMT change (treatment A - treatment B).



- ATV/r progressed more slowly than DRV/r (p = 0.007)
- Intermediate progression for RAL (p = 0.30 versus ATV/r; p = 0.11 versus DRV/r)

BIF, bifurcation.

A5260s: Independent Predictors of Longitudinal CCA CIMT Progression (As-Treated Analysis)

	Rate of change (µm/year)		
Covariates	Estimated rate of change	95% CI	p
Age (per 10 years)	0.9	-1.0 to 2.7	0.35
Week 24 non-HDL-C (per 30 mg/dL)	2.2	0.4–3.9	0.016
Baseline hs-CRP (per $\log_{10}$ µg/mL)	3.7	0.0–7.4	0.050
Bilirubin ≥ 2.6 × ULN before week 48	7.1	0.3–13.9	0.041
Adjusted treatment effect			
ATV/r	-5.6	-14.5 to 3.3	0.22
DRV/r	3.7	-5.8 to 13.1	0.44
RAL	0.1	-8.6 to 8.8	0.98
Adjusted treatment group difference[1]	Estimated difference	97.5% CI	p
ATV/r versus DRV/r	-9.3	-14.5 to -4.1	< 0.001
ATV/r versus RAL	-7.8	-12.9 to -2.6	< 0.001
DRV/r versus RAL	1.5	-3.0 to 6.1	0.45

Analysis adjusted for time, two stratification factors of HIV-1 RNA level and 10-year FRS and baseline CCA CIMT in addition to covariates listed above.

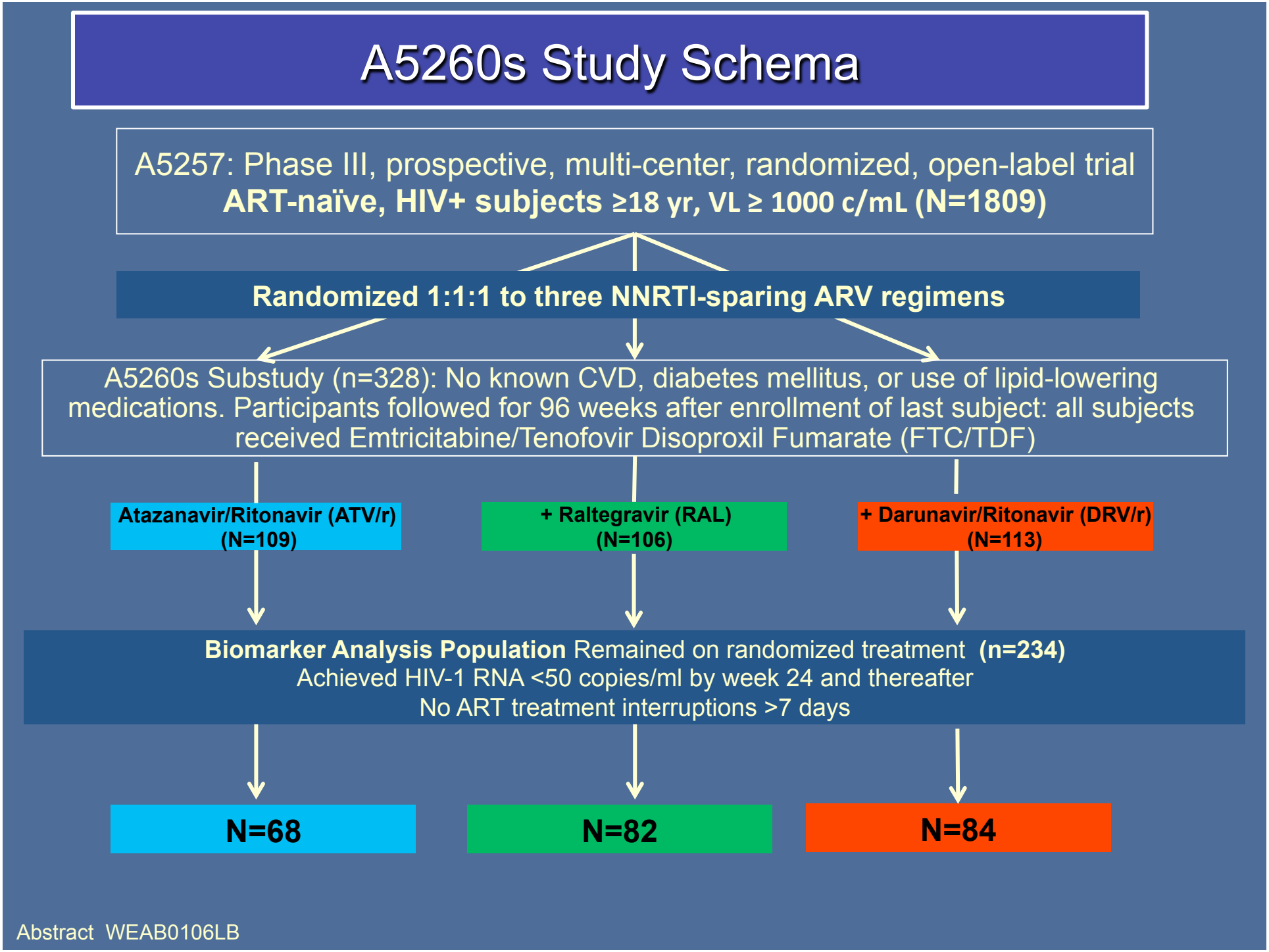
[1]Adjusted estimate of treatment group difference was defined as the difference in annual rate of CCA CIMT change (treatment A - treatment B).

HLD-C, high-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; ULN, upper limit of the normal range.

What does a 4-5 um difference in CIMT progression mean?

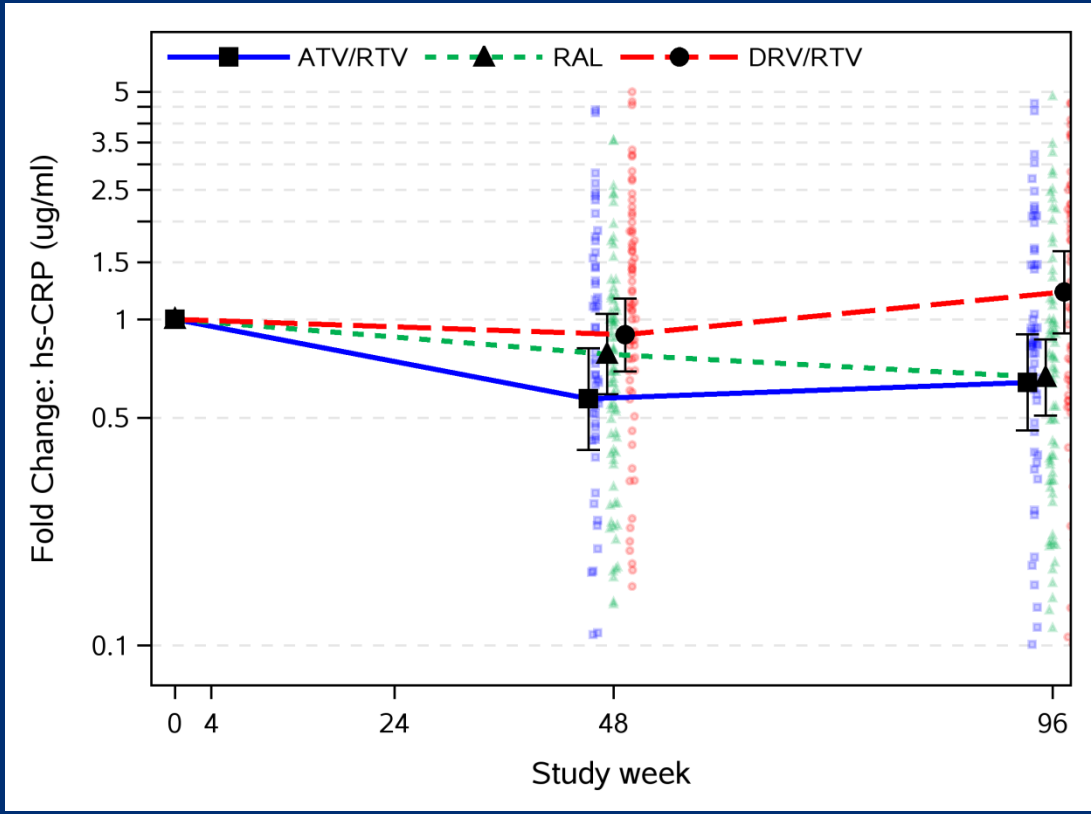
- Meta-analysis of CIMT studies
  - each 10 µm/year slower rate of carotid IMT, there was an 18% lower odds for myocardial infarction (Goldberger *Am Heart J* **2010**; 160:701-714)..
- Statin therapy has been associated with a 12 um/ year lower rate of carotid IMT progression and a 52% reduction in CVD events
  - 4 um difference is ~ 1/3 of the effect of statins (Espeland, *Curr Control Trials Cardiovasc Med* **2005**; 6:3).

A5260s Study Schema



Abstract WEAB0106LB

Results: Hs-CRP declined with ATV/r and RAL

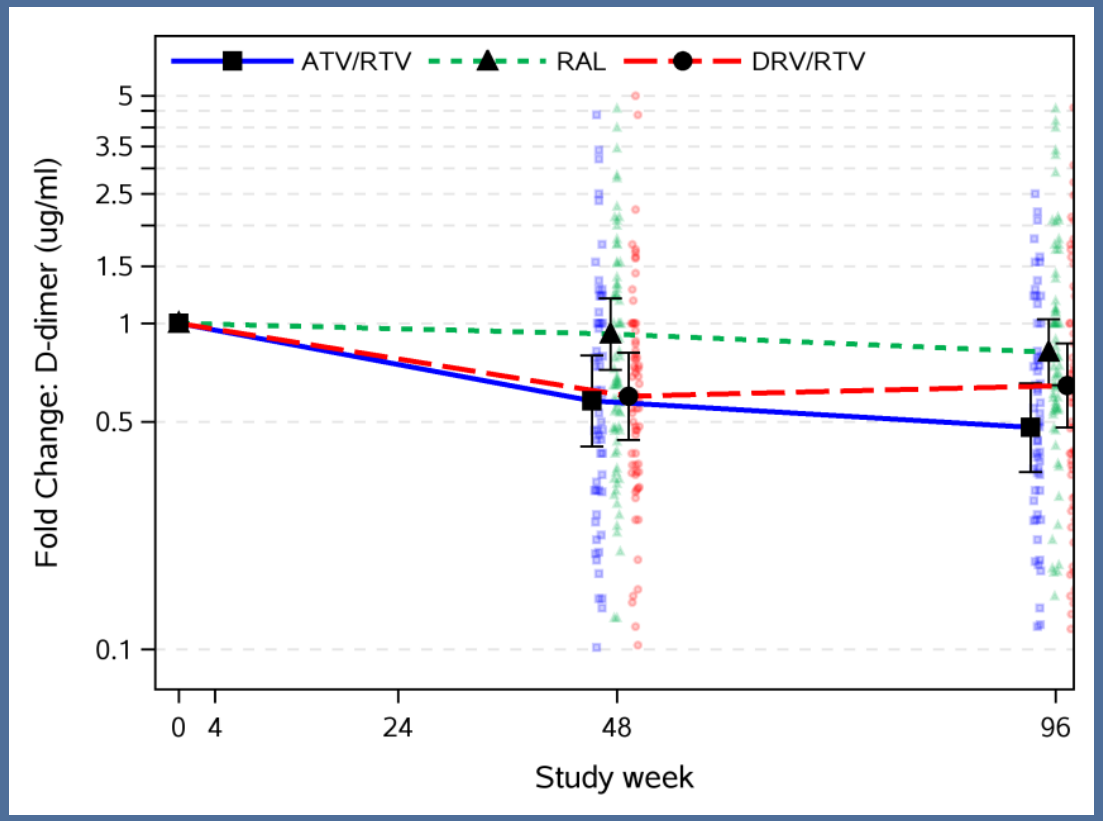


	Overall at Baseline
Median (Q1,Q3)	1.48 ug/ml (0.78, 3.18)

	Mean Fold Change (95% CI) from Baseline	
	Week 48	Week 96
ATV/r	0.57 (0.40,0.82)	0.64 (0.46,0.90)
RAL	0.78 (0.59,1.04)	0.66 (0.51,0.87)
DRV/r	0.90 (0.69,1.16)	1.21 (0.91,1.62)

Kelesidis, T CID 2015

Markers of Inflammation and Coagulation: D-dimer declined with ATV/r and DRV/r

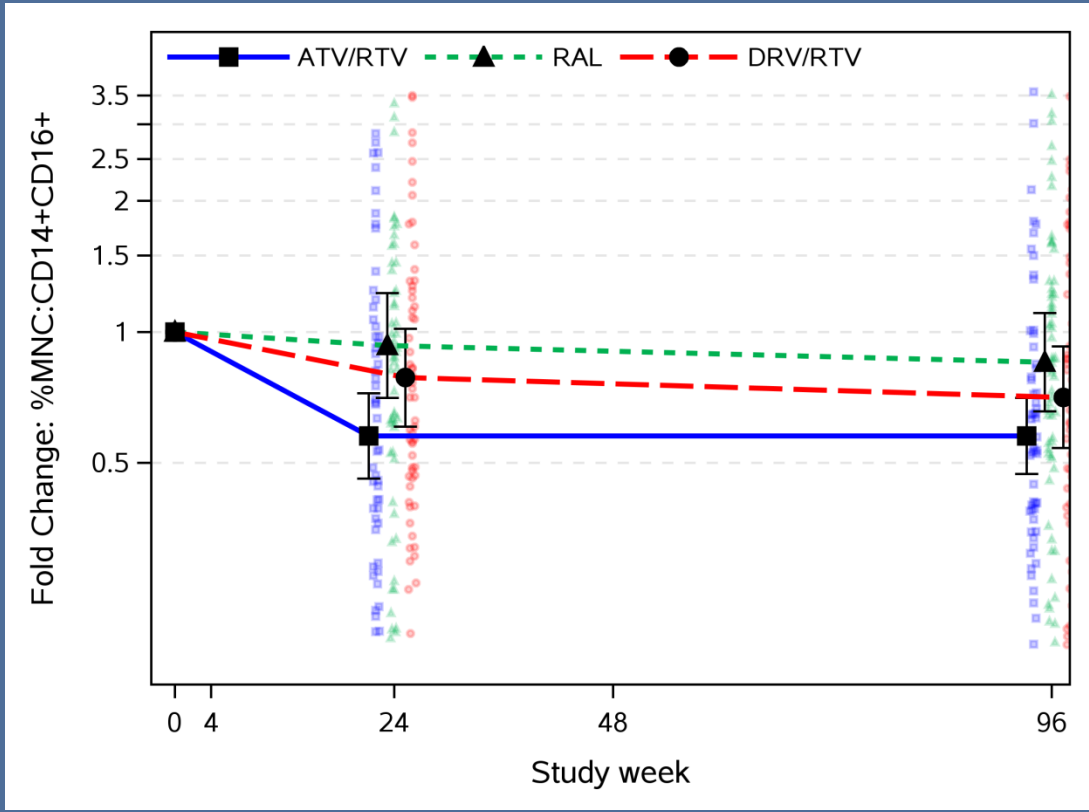


	Overall at Baseline
Median (Q1,Q3)	0.26 ug/ml (0.14, 0.56)

	Mean Fold Change (95% CI) from Baseline	
	Week 48	Week 96
ATV/r	0.58 (0.42,0.80)	0.48 (0.35,0.66)
RAL	0.93 (0.72,1.19)	0.82 (0.65,1.03)
DRV/r	0.60 (0.44,0.82)	0.65 (0.48,0.87)

Abstract WEAB0106LB

Markers of Macrophage Activation: pMNCs decreased more in ATV/r and DRV/r groups compared to RAL



Overall at Baseline

Median (Q1,Q3)	8.2% (5.7, 13.0)

Mean Fold Change (95% CI) from Baseline

	Week 48	Week 96
ATV/r	0.58 (0.46,0.72)	0.58 (0.47,0.70)
RAL	0.93 (0.71,1.23)	0.85 (0.66,1.10)
DRV/r	0.78 (0.61,1.02)	0.71 (0.54,0.93)

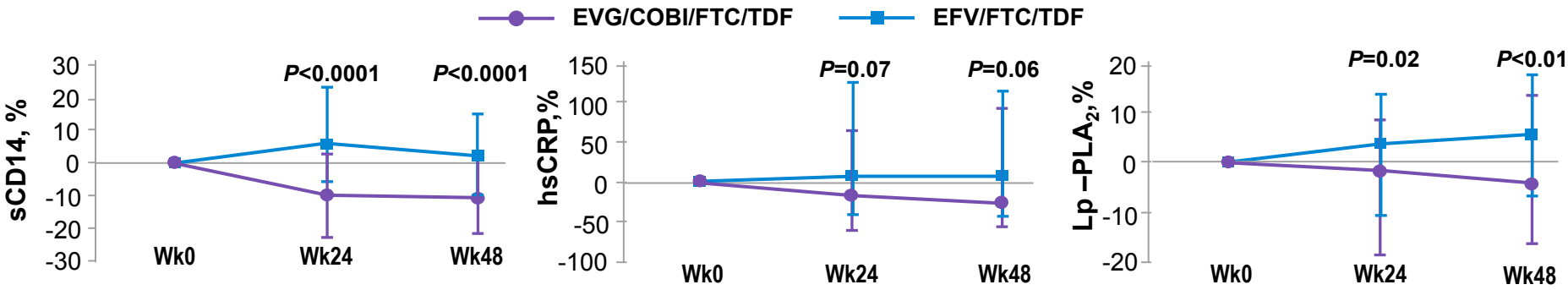
‡

Differences in Monocyte Activation and Vascular Inflammation with EVG vs. EFV

Sub-analysis of inflammatory and monocyte activation biomarkers in 100 ART-naïve subjects who achieved VL< 50 c/mL at Week 48 on STB or ATR

- Biomarkers of monocyte activation (sCD14, sCD163), systemic inflammation (sTNF-RI, IL-6, hsCRP) and vascular inflammation (Lp-PLA_2) at BL, W24, and W48
- STB led to greater decreases in sCD14, hsCRP and Lp-PLA_2 than ATR

Median change over 24 and 48 weeks for each biomarker, by group, %



- Randomization group independently predicted change in sCD14, and changes in monocyte activation independently predicted change in Lp-PLA_2

"There is a more favorable effect of EVG vs. EFV on immune activation, that may effect vascular inflammation"

EVG = elvitegravir; EFV = efavirenz; STB = EVG/COBI/FTC/TDF; ATR = EFV/FTC/TDF

Hileman C, et al. CROI 2015; Seattle, WA. #739

Intensification with MVC and RAL has not an impact on gut immune-reconstituion

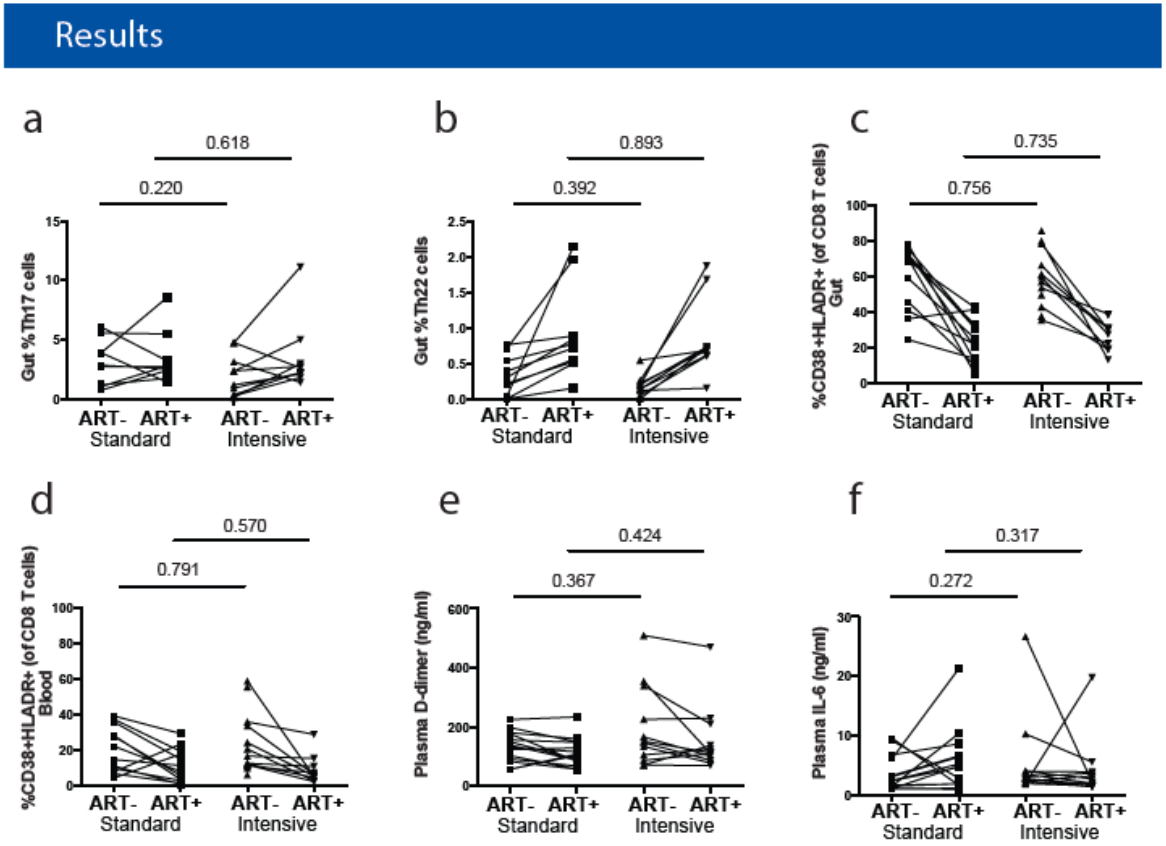


Figure 5: The frequency of gut (a) Th17 and (b) Th22 cells were similar between the standard and intensive ART arm at baseline and week 48. Similarly, there was no added improvement with (c) gut and blood (d) CD8 T cell immune activation or with plasma SNA biomarkers, (e) D-dimer and (f) IL-6 by ART intensification.

Management of the Treatment-Experienced Patient

Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression

(Last updated: April 8, 2015; last reviewed: April 8, 2015)

Section Only PDF (236 KB)
Full Guideline PDF (1.21 MB)
Recommendations Only PDF (88.9 KB)
Tables Only PDF (563 KB)

Panel's Summary and Recommendations

Panel's Summary and Recommendations

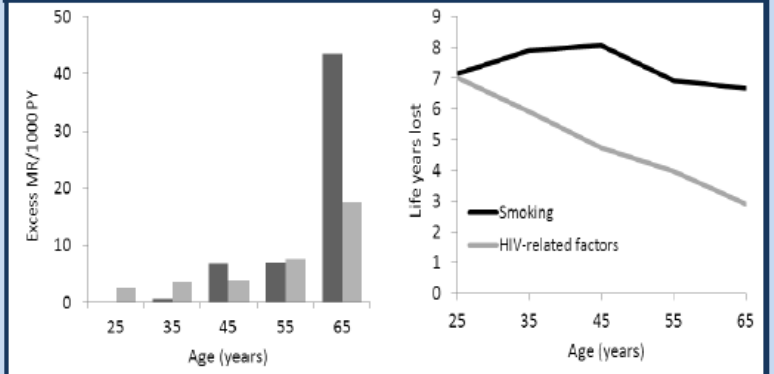
- Morbidity and mortality from several AIDS and non-AIDS conditions are increased in HIV-infected individuals despite antiretroviral therapy (ART)-mediated viral suppression, and are predicted by persistently low CD4 T lymphocyte (CD4) cell counts and/or persistent immune activation.
- ART intensification by adding antiretroviral (ARV) drugs to a suppressive ART regimen does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(AI)**.
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(BIII)**.
- No interventions designed to increase CD4 cell counts and/or decrease immune activation are recommended at this time (in particular, interleukin-2 is **not recommended [AI]**) because none has been proven to decrease morbidity or mortality during ART-mediated viral suppression.
- Monitoring markers of immune activation and inflammation is not recommended because no immunologically targeted intervention has proven to improve the health of individuals with abnormally high biomarker levels, and many markers that predict morbidity and mortality fluctuate widely in individuals **(AII)**.
- Because there are no proven interventions to improve CD4 cell recovery and/or inflammation, efforts should

  focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and exercise; treating hypertension, hyperlipidemia) **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Impact of smoking on life expectancy (ART-CC)

Figure 1: Excess mortality rates (bars) and numbers of life years lost (lines) in association with smoking and HIV among HIV-infected men, stratified by age



Age-specific mortality rates (MR) were calculated as deaths per 1000 person-years (PY). Excess MRs were estimated by subtraction of MRs of smokers from that of non-smokers and of HIV-infected individuals from that of the French background population. In the latter analyses mortality rates in the HIV infected population were adjusted for smoking frequency using weighted averages. Life expectancies were estimated using abridged life tables and numbers of life years lost were calculated by subtraction of life expectancies of smokers from non-smokers and of HIV-infected from the French background population.

Table 2: Cause-specific mortality rate ratios (95%CI) by smoking status

	All cohorts		Cohorts with info. on current, previous and never-smokers		
	Deaths	Smoker vs. non-smoker	Deaths	Current vs. never	Previous vs. never
All-cause mortality	520	1.94 (1.56-2.41)	301	1.70 (1.23-2.34)	0.92 (0.64-1.34)
AIDS-related deaths	152	1.37 (0.93-2.02)	99	1.21 (0.73-2.01)	0.54 (0.28-1.03)
Non-AIDS related deaths	276	2.61 (1.88-3.61)	153	2.45 (1.49-4.03)	1.40 (0.81-2.42)
Non-AIDS malignancies	94	3.13 (1.80-5.45)	43	2.42 (1.03-5.68)	0.94 (0.34-2.64)
Cardiovascular disease	39	6.28 (2.19-18.0)	27	8.82 (1.15-67.8)	4.55 (0.55-37.6)
Non-AIDS infections	26	2.38 (0.88-2.46)	10	3.98 (0.47-15.8)	1.38 (0.12-15.8)
Liver disease	19	8.70 (1.14-66.6)	14	3.44 (0.42-28.4)	1.46 (0.15-14.4)
Other	66	1.42 (0.81-2.49)	29	1.08 (0.40-2.93)	0.66 (0.22-1.98)
Non-AIDS, not classified	32	2.56 (0.96-6.83)	30	1.90 (0.61-5.96)	2.34 (0.73-7.43)
Accident/violence/suicide/abuse	36	2.30 (0.92-5.77)	24	2.14 (0.60-7.60)	0.38 (0.06-2.36)
Unknown	56	1.38 (0.78-2.46)	25	0.93 (0.30-2.87)	1.27 (0.41-3.92)

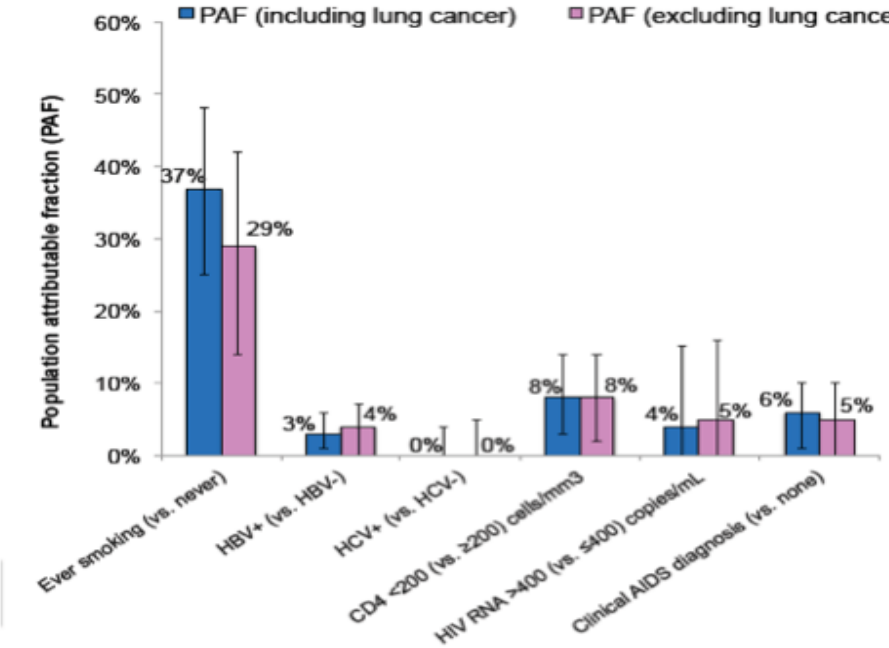
Mortality rate ratios adjusted for gender, age (time-updated), route of transmission, CD4 count at baseline, AIDS at baseline, years on ART (time-updated) and calendar year of ART

Helleberg et al. poster 559

Smoking outweights HIV related risk factors for non-AIDS cancers in the NA-accord

Figure 1: Population attributable fraction (PAF) and 95% confidence intervals for smoking and HIV-related risk factors, NADC with and without lung cancer

The PAF of smoking declines from 37% to 29% when lung cancers are removed from the NADC outcome. Regardless, smoking has a higher PAF than any of the HIV-related risk factors.



Non-AIDS-defining cancers (including lung cancer)						
Prevalence	64%	6%	20%	25%	64%	21%
aHR*	1.82	1.60	1.00	1.34	1.07	1.24
(95% CI)	(1.41, 2.35)	(1.22, 2.10)	(0.82, 1.22)	(1.11, 1.62)	(0.89, 1.29)	(1.03, 1.49)

Non-AIDS-defining cancers (excluding lung cancer)						
Prevalence	64%	6%	20%	25%	64%	21%
aHR*	1.54	1.68	0.99	1.34	1.08	1.21
(95% CI)	(1.18, 2.00)	(1.26, 2.26)	(0.79, 1.23)	(1.09, 1.65)	(0.89, 1.33)	(0.99, 1.48)

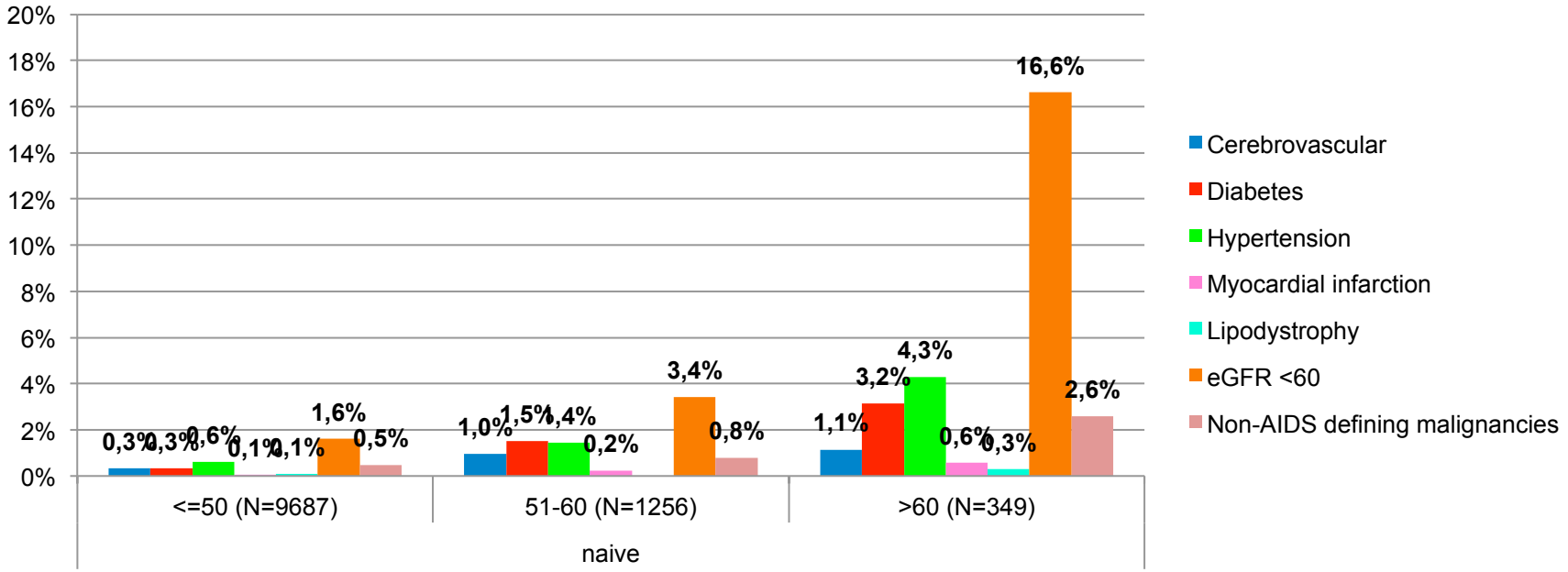
*aHRs were adjusted for age, sex, race, and all the risk factors shown in the figure.

Althoff and coworkers explained that these population-attributable fractions mean, for example, that getting adolescents at risk for HIV infection to avoid smoking could prevent up to 37% of non-AIDS cancers if they became infected.

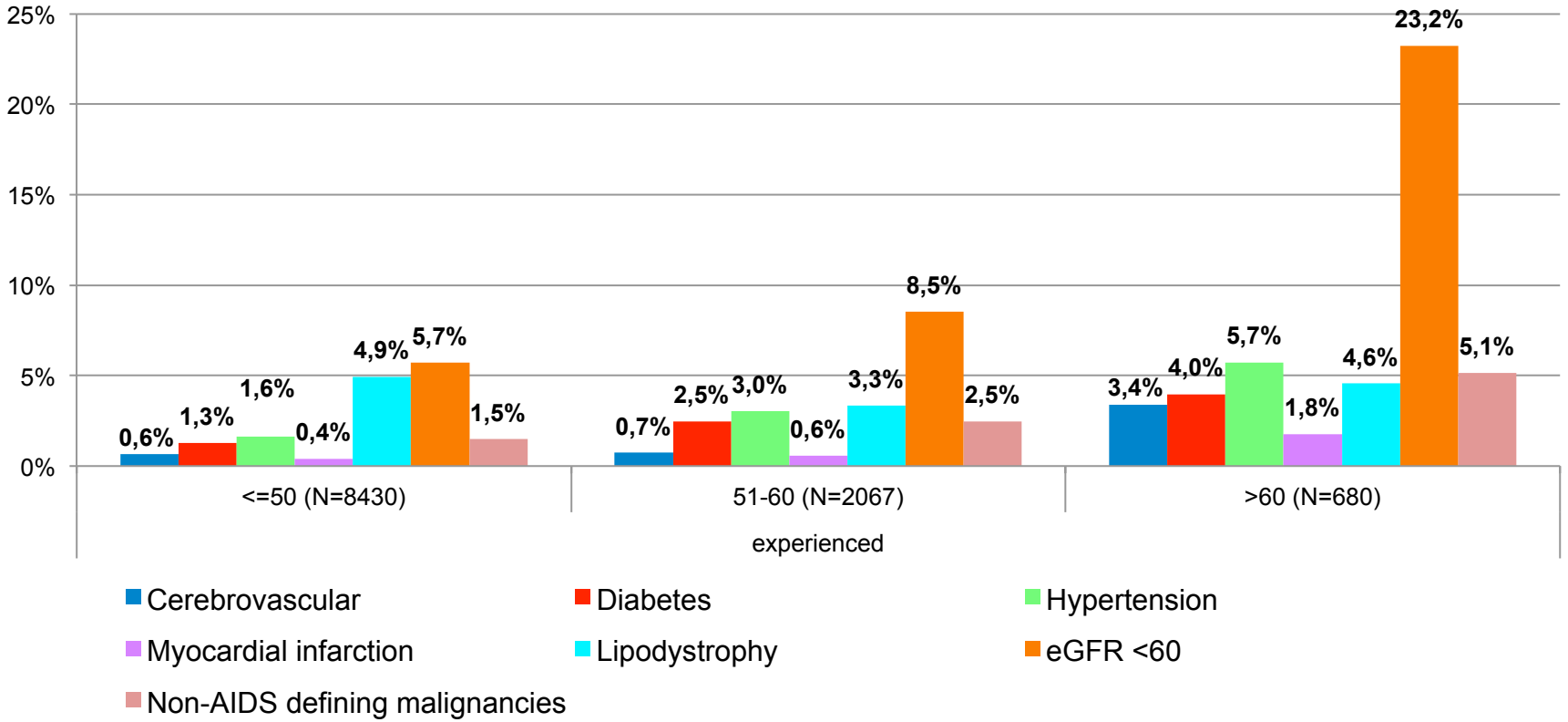
Among infected people, using antiretroviral therapy to maintain a high CD4 count ...and an undetectable viral load could prevent up to 8% of non-AIDS cancers.

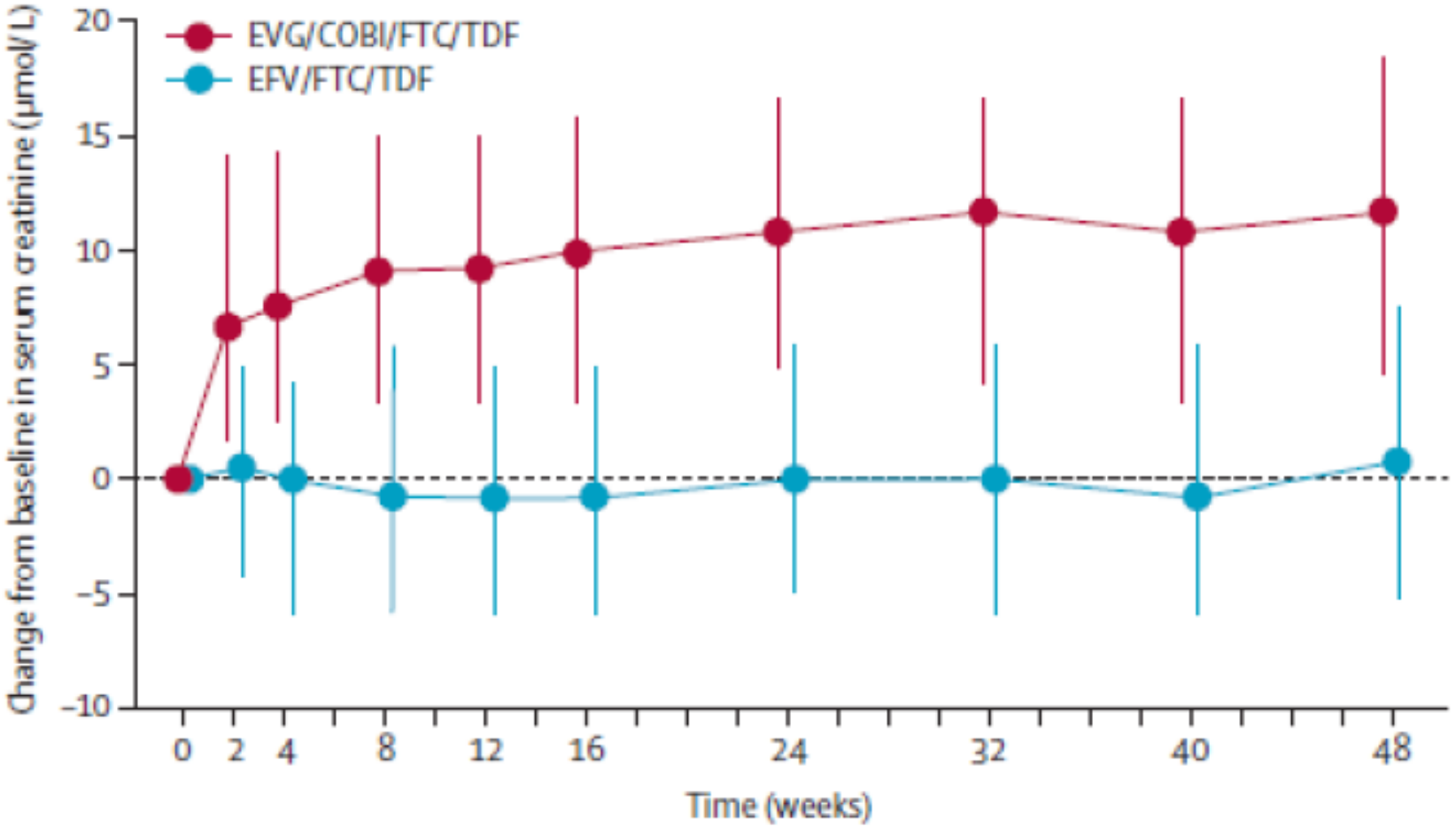
Althoff et al.

Prevalence of different non-AIDS related co-morbidities at different age strata in naive patients



Prevalence of different non-AIDS related co-morbidities at different age strata in ART-treated patients

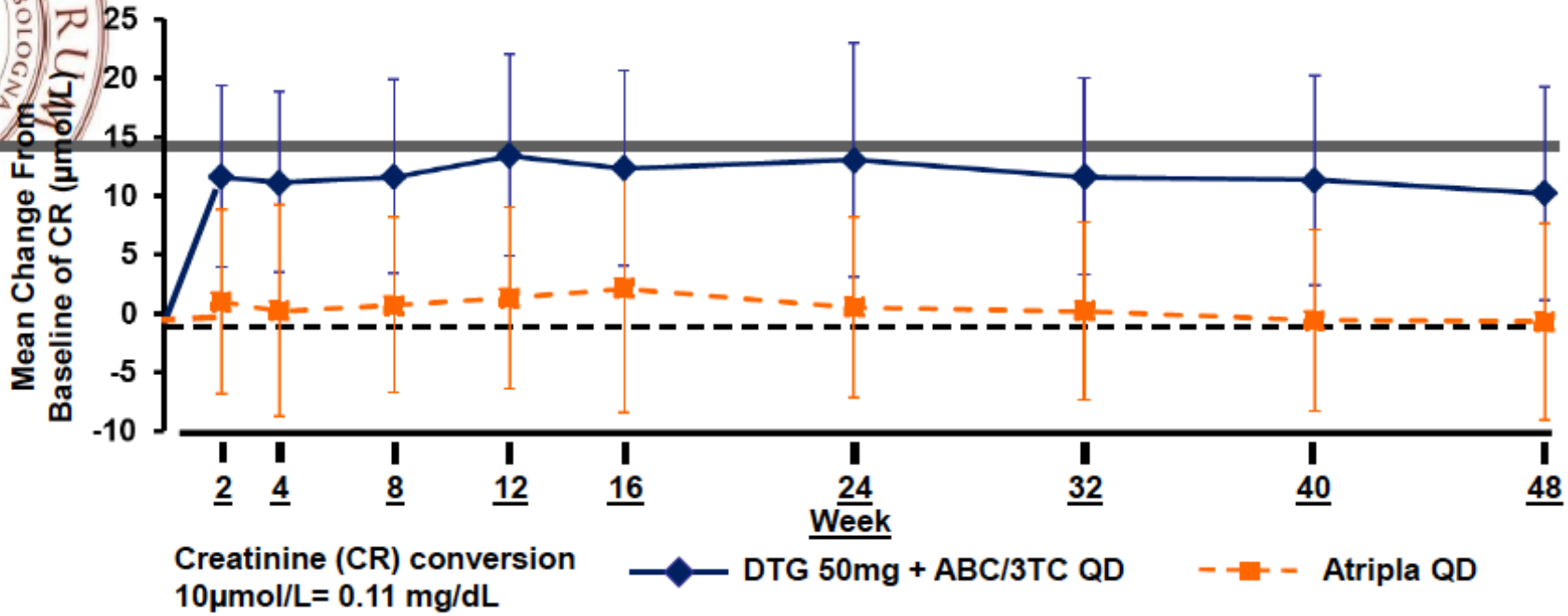




Number of patients										
EVG/COBI/FTC/TDF	348	341	345	341	337	335	328	323	320	320
EFV/FTC/TDF	352	340	340	336	327	323	317	313	309	307

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

Dolutegravir Renal Safety



	DTG 50 mg+ABC/3TC QD	Atripla QD
Urine albumin/creatinine		
Median change (IQR) from baseline (mg/mmol CR) to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

Small increase in creatinine due to blockade of Cr secretion[1]

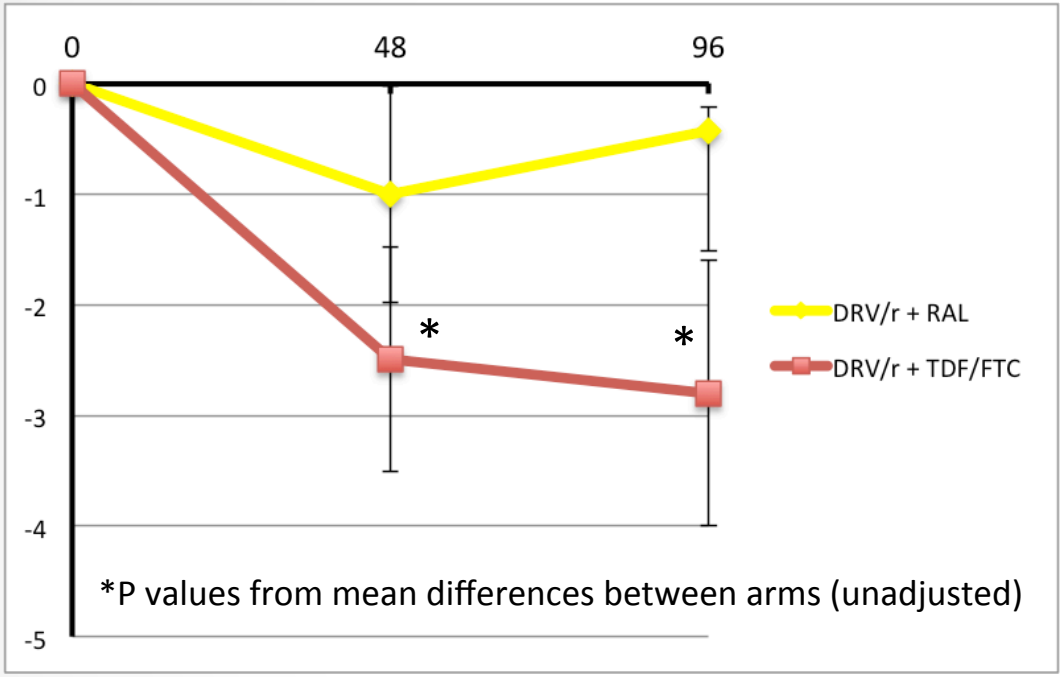
DTG does not affect actual glomerular filtration rate (GFR)[1]

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

1. Koteff, J. et al. Br J Clin Pharmacol. 2012 Aug. DOI: 10.1111/j.1365-2125.2012.04440.x

NEAT001/ANRS143

Mean % Change in lumbar spine BMD

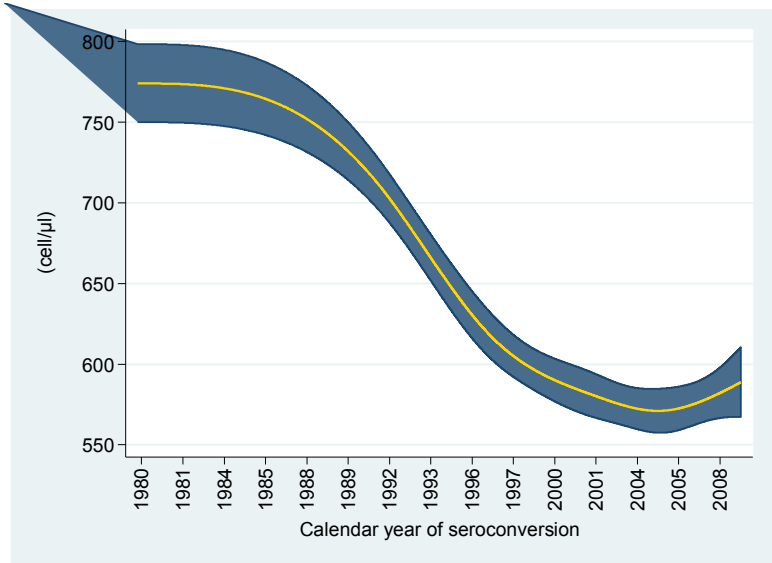


- Use of the nucleos(t)ide sparing regimen DRV/r + RAL was associated with significantly less bone mineral density (hip, lumbar spine) loss at W48 and W96 weeks than a regimen of TDF/FTC + DRV/r in first line ART.
- During 96 weeks no difference in osteopenia/osteoporosis nor fractures was found.

	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =70	51	-1.0 (-1.98, -0.02)	48	-0.43 (-1.51, 0.65)
DRV/r + TDF/FTC n = 76	63	-2.49 (-3.51, -1.47)	57	-2.8 (-4.0, -1.6)
Mean difference (95% CI); p	- 1.49 (-2.94, -0.04); p = 0.046*		-2.37 (-4.0, -0.74); p = 0.0054*	

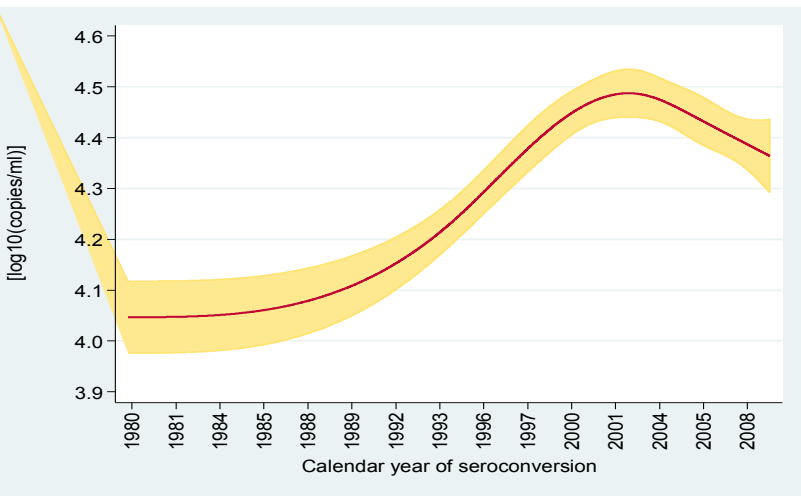
Changes in HIV virulence?

Changes in CD4 cell count at SC



Time to needing ART halved

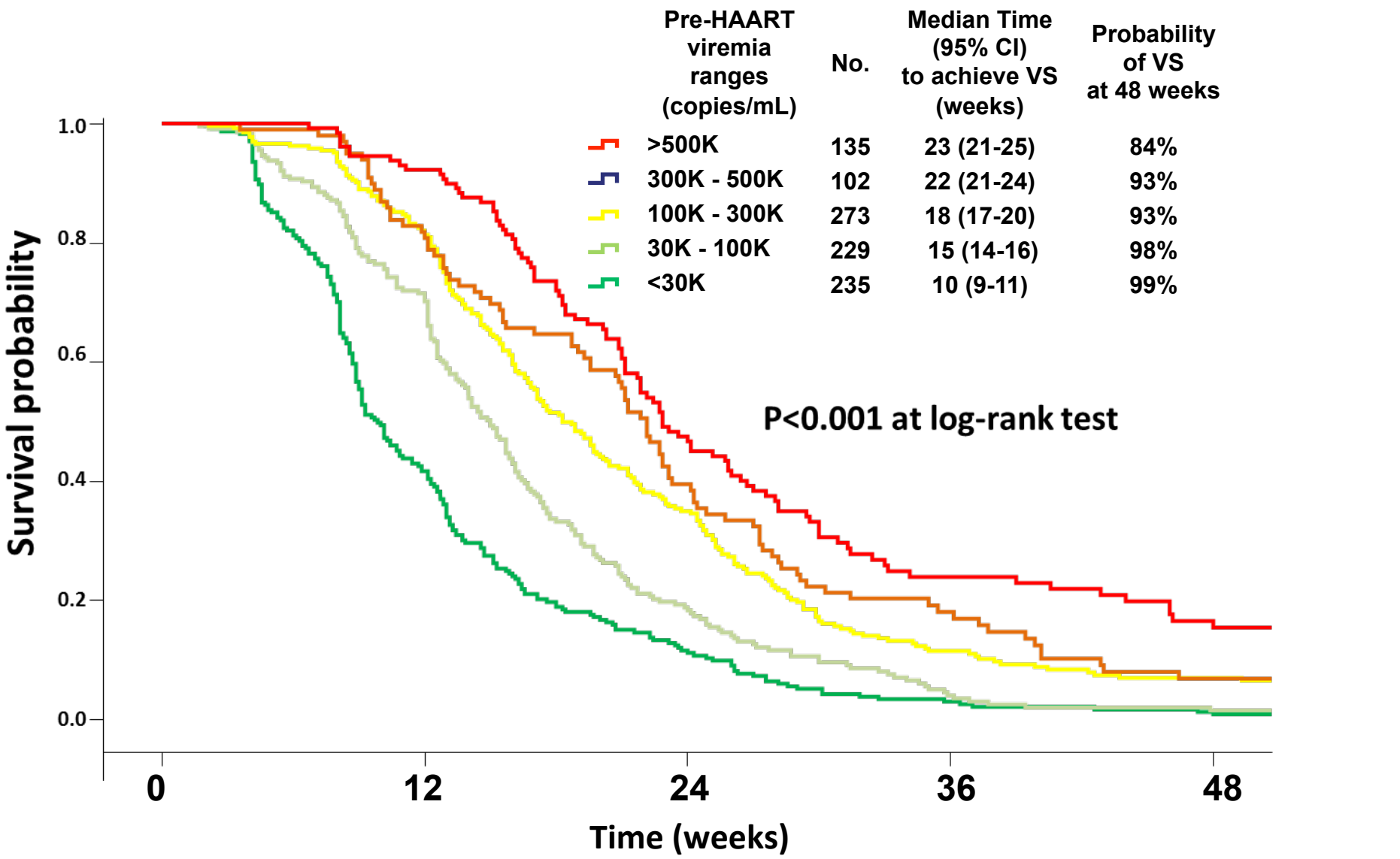
Changes in viral load set-point



44% increase in virus transmissibility

Pantazis *et al Lancet HIV* 2014

The time to achieve virological undectability and the rate of success at 48 weeks are pre-HAART viremia dependent



Santoro M, et al. Antiviral Therapy 2013

Risk of virological success on the basis of baseline viral load

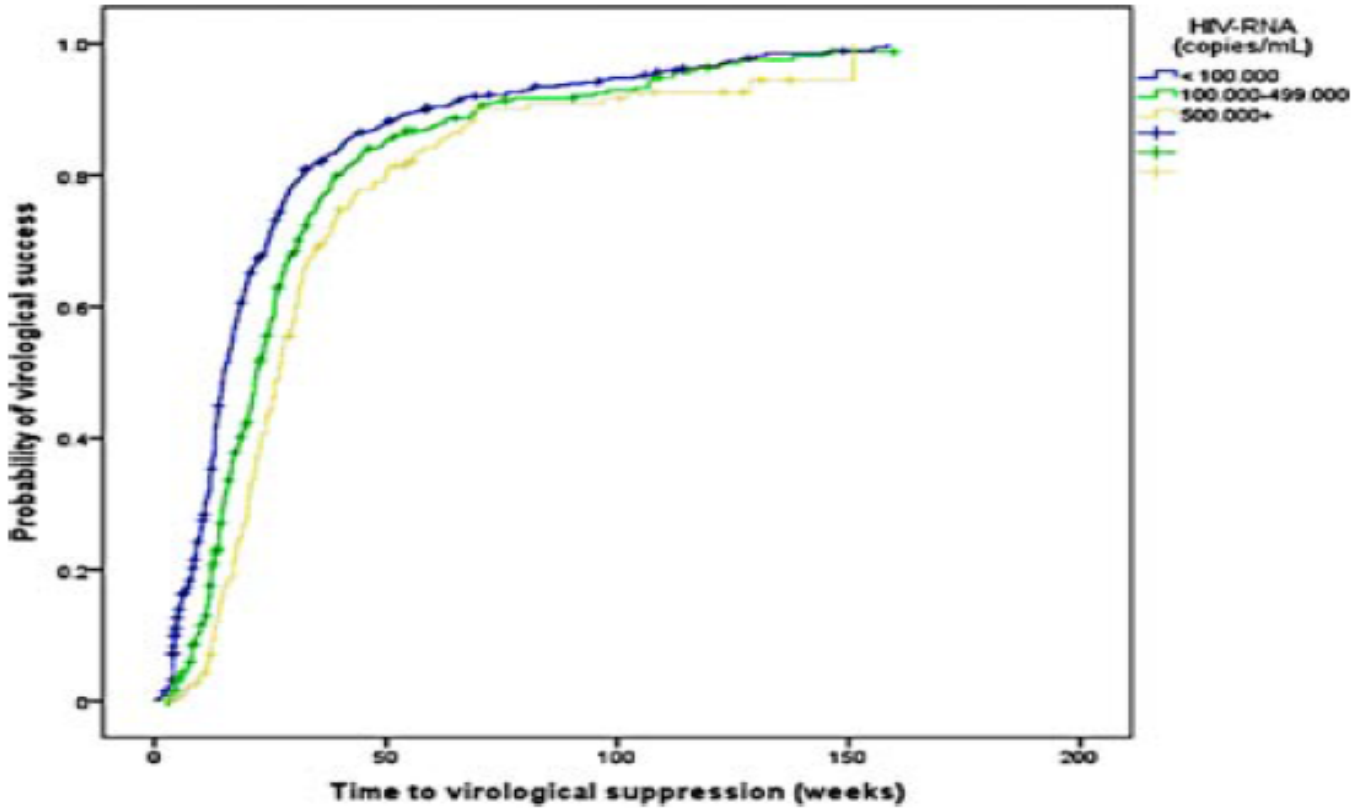


Fig. 1. Kaplan–Meier curve of time to virological success (first plasma HIV-1 RNA value <50 copies/ml) based on baseline viral load stratum.

Di Biagio A et al. JMV 2014

TABLE II. Variables Associated With Virological Success

	Univariate		Multivariate*	
	HR (95 % CI)	*P*-value	HR (95% CI)	*P*-value
Baseline HIV RNA (copies/ml)				
<100,000	1.00 (Ref)	<0.001	1.00	<0.001
100,000–499,999	0.73 (0.64–0.83)		0.76 (0.65–0.88)	
≥500,000	0.67 (0.56–0.79)		0.52 (0.42–0.64)	
wGSS				
≥3	1.00 (Ref)	0.05	1.00 (Ref)	0.003
<3	0.74 (0.54–1.00)		0.58 (0.40–0.83)	
NRTI backbone of initial regimen				
TDF/FTC	1.00 (Ref)	0.021	1.00 (Ref)	0.73
ABC/3TC	1.17 (0.98–1.39)		1.07 (0.88–1.30)	
ZDV/3TC	0.91 (0.79–1.04)		1.04 (0.84–1.28)	
Other	0.86 (0.71–1.03)		1.16 (0.88–1.54)	
Gender				
Male vs. female	0.84 (0.73–0.96)	0.008	0.76 (0.64–0.90)	0.001
3rd drug of initial regimen				
bPI	1.00 (Ref)	0.038	1.00	<0.001
NNRTI	0.96 (0.85–1.09)		0.98 (0.83–1.14)	
INI	2.02 (1.23–3.31)		3.23 (1.84–5.68)	
Other	1.02 (0.80–1.32)		1.32 (0.96–1.82)	

Time to achieve HIV RNA <50 copies/ml. Univariate and multivariate Cox regression (N = 1,305).
Ref, reference category for interpretation of odds-ratios (OR); wGSS, weighted genotypic susceptibility score; NRTI, nucleoside reverse transcriptase inhibitors; TDF/FTC, tenofovir/emtricitabine; ABC/3TC, abacavir/lamivudine; ZDV/3TC, zidovudine/lamivudine; bPI, boosted protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; INI, integrase inhibitor.
*Variables were mutually adjusted in the multivariate model that also included transmission mode, presence of transmitted drug resistance, baseline $CD4^+$ and viral subtype.

Di Biagio A et al. JMV 2014

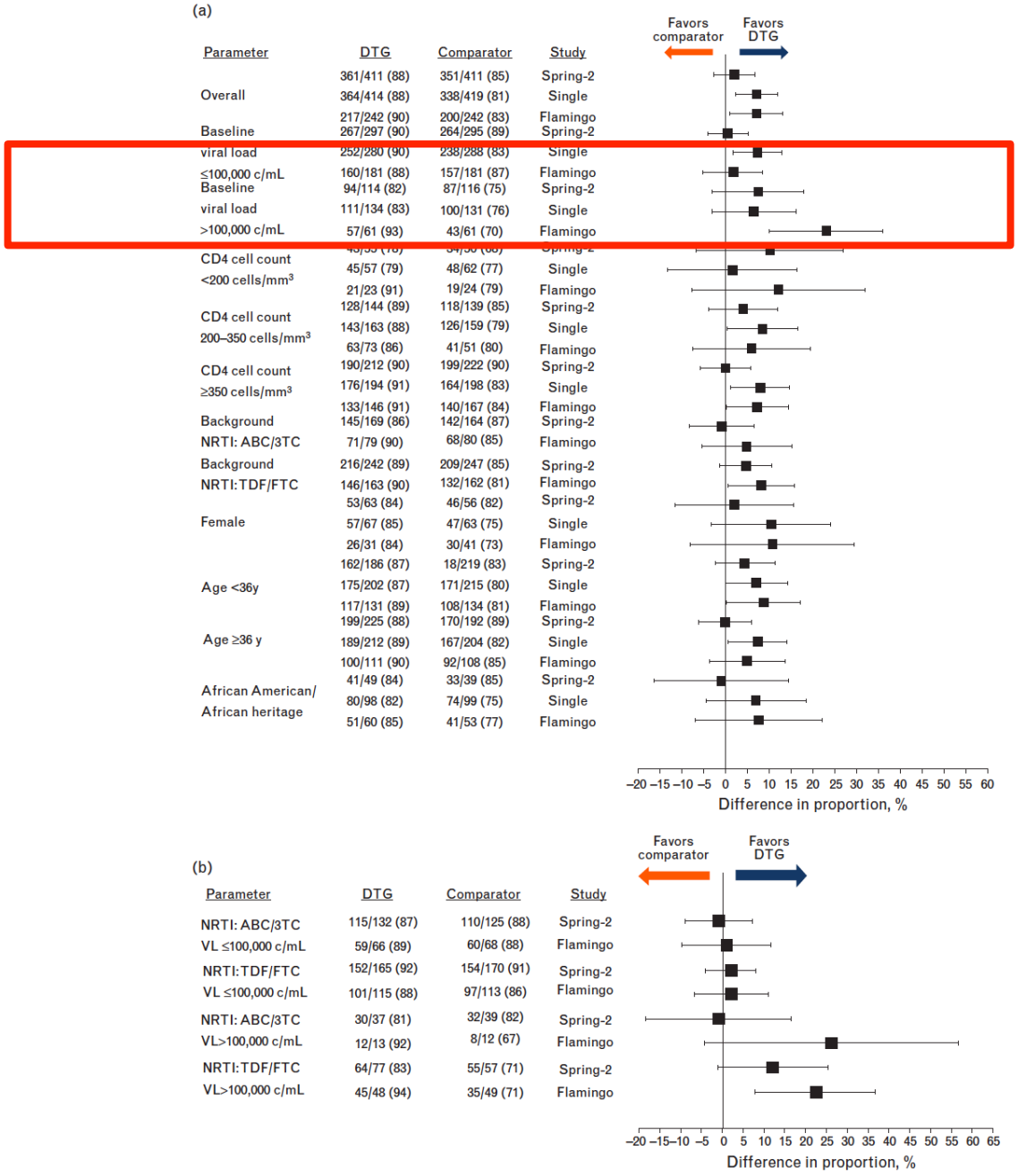


Fig. 1. Snapshot response rates by subgroup in each study; (a) univariate and (b) bivariate summaries by baseline viral load and NRTI backbone. Specific subgroups for male and white participants are omitted from (a): these subgroups comprised more than 75% of the study populations, and their results mirrored those in the overall population. ABC/3TC, abacavir/lamivudine; DTG, dolutegravir; NRTI, nucleoside reverse transcriptase inhibitor; TDF/FTC, tenofovir/emtricitabine.

Raffi F et al. AIDS 2014

Short communication

No advantage of quadruple- or triple-class antiretroviral therapy as initial treatment in patients with very high viraemia

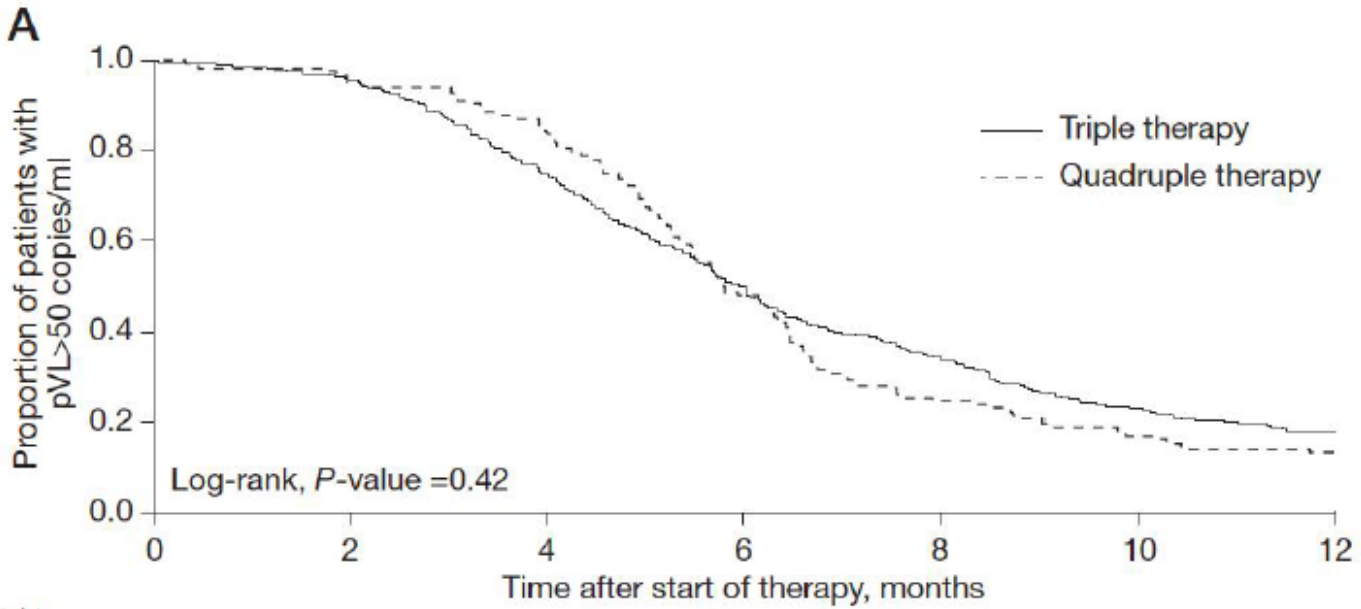
Marlous L Grijsen[1], Rebecca Holman[2], Luuk Gras[2], Ferdinand WNM Wit[3], Andy IM Hoepelman[4], Guido E van den Berk[5], Frank de Wolf[2], Jan M Prins[1], the ATHENA National Observational Cohort Study*

[1]Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, University of Amsterdam, Center for Infection and Immunity Amsterdam, Amsterdam, the Netherlands
[2]HIV Monitoring Foundation, Amsterdam, the Netherlands
[3]Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands
[4]Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, the Netherlands
[5]Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

- Observational cohort study
- Inclusion criteria: treatment naive patients, HIV-RNA ≥500,000 cp/ml, initiation of quadruple or triple cART between 2001 and 2011
- 675 patients included: 19% in quadruple and 81% in triple cART

(Grijsen ML et al., Antiviral Ther 2012)

Figure 1. Kaplan–Meier curves of the probability of achieving a viral suppression



Patients remaining, *n*							
Triple	548	516	398	254	167	106	79
Quadruple	125	118	103	57	29	19	14

- 22 (18%) pts on quadruple and 63(12%) on triple interrupted the treatment because of drug toxicity (p=0.06)
- In the adjusted Cox analysis quadruple was not associated with time to viral suppression

(Grijsen ML et al., Antiviral Ther 2012)

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**

This study was unique in measuring not only routine virologic and immunologic responses but also determining levels of plasma viremia with the single copy assay (SCA), measuring levels of cell associated HIV-1 DNA and RNA by polymerase chain reaction (PCR), and directly measuring the levels of virus in the latent reservoir after approximately 2 years of suppressive therapy.

We also performed comprehensive quantitative and qualitative immune responses to therapy, including levels of naive and central memory CD4+ T cells and assessed markers of immune activation before and during therapy.

Conclusions: Intensified 5-drug cART initiated during early infection fails to significantly further impact virologic or immunologic responses beyond those achieved with standard 3-drug Pi based cART

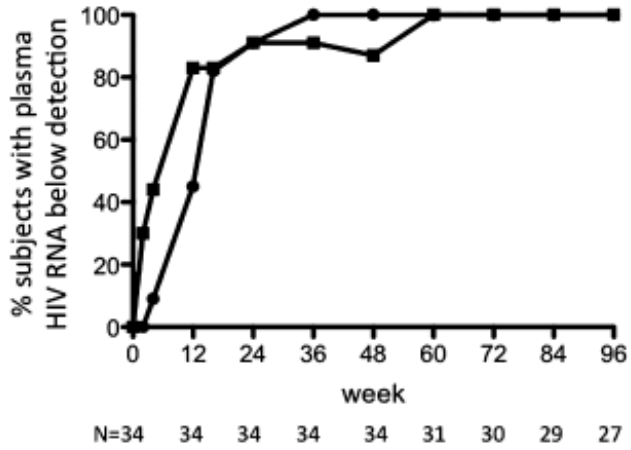
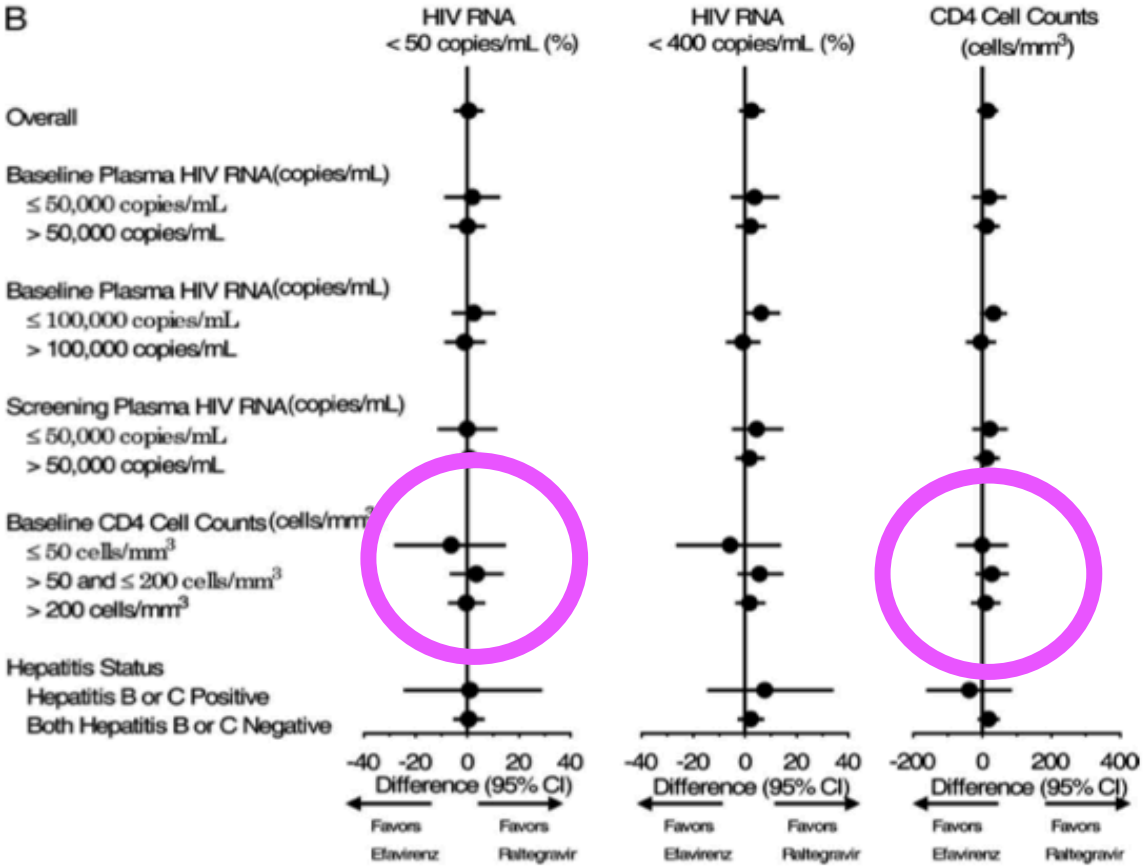


FIGURE 2. The percent of subjects with plasma HIV-1 RNA levels below the level of detection during 96 weeks of treatment with 3-drug therapy (circles) and 5-drug therapy (squares). Number of subjects included in the analysis is shown below the *x* axis.

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

Raltegravir Versus Efavirenz Regimens in Treatment-Naive HIV-1–Infected Patients: 96-Week Efficacy, Durability, Subgroup, Safety, and Metabolic Analyses

Jeffrey L. Lennox, MD, Edwin DeJesus, MD,† Daniel S. Berger, MD,‡ Adriano Lazzarin, MD,§ Richard B. Pollard, MD,‖ Jose Valdez Ramalho Madruga, MD,¶ Jing Zhao, PhD,# Hong Wan, MS,# Christopher L. Gilbert, BS,# Hedy Teppler, MD,# Anthony J. Rodgers, MS,# Richard J. O. Barnard, PhD,# Michael D. Miller, PhD,# Mark J. DiNubile, MD,# Bach-Yen Nguyen, MD,# Randi Leavitt, MD, PhD,# and Peter Sklar, MD, MPH#, for the STARTMRK Investigators***

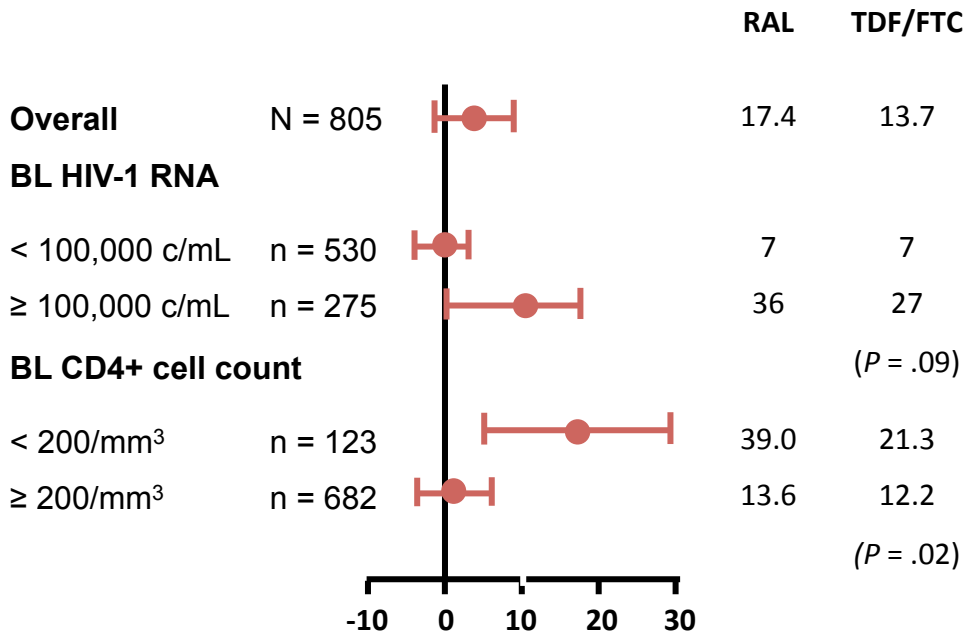


J Acquir Immune Defic Syndr. 2010;55:39-48

NEAT: RAL + DRV/RTV Noninferior to TDF/FTC + DRV/RTV in Naive Pts at 96 Wks

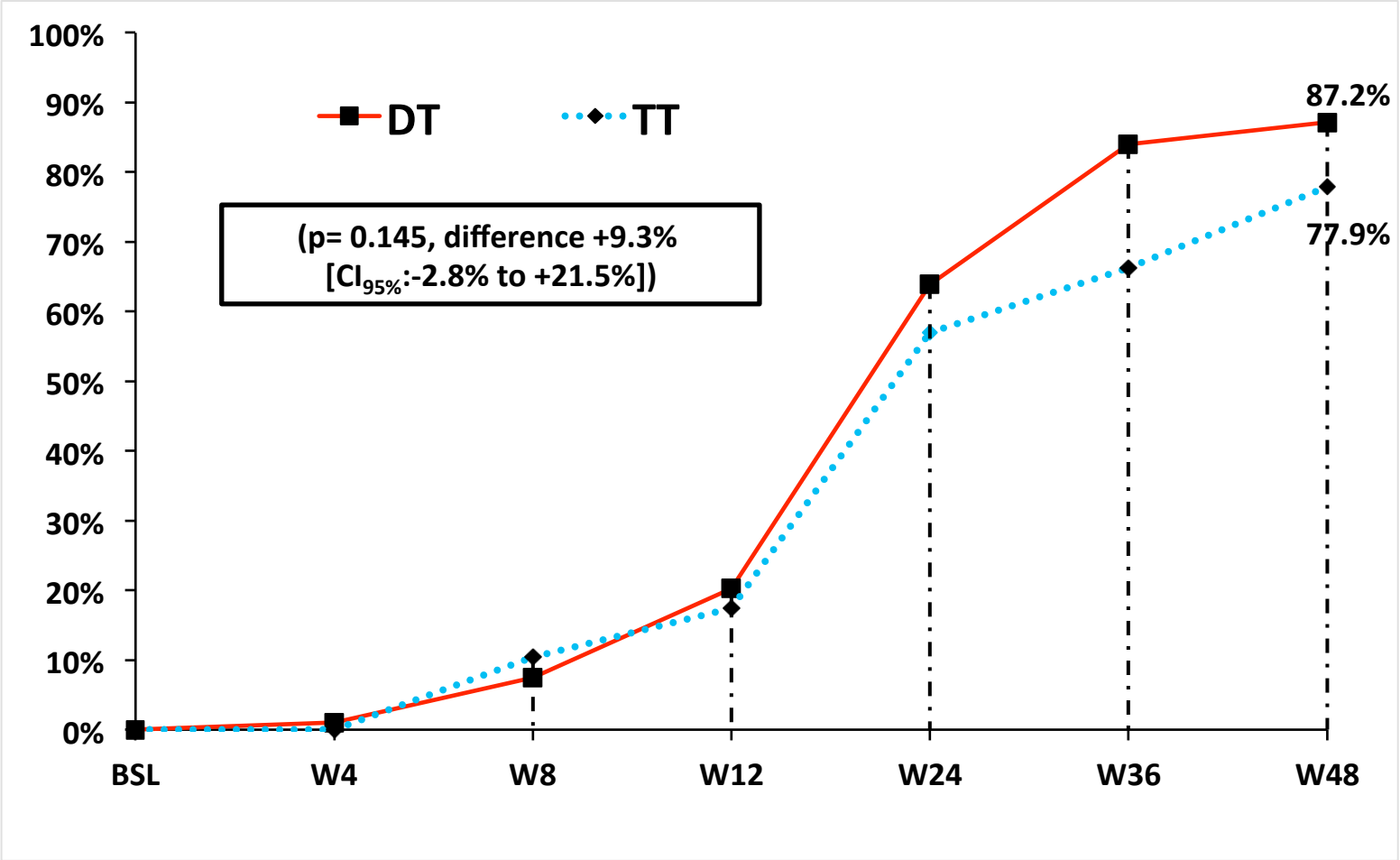
- Randomized, open-label phase III study of DRV/RTV + RAL vs DRV/RTV + TDF/FTC in ART-naive pts

Primary Endpoint at Wk 96: Adjusted Difference Estimate (95% CI)
RAL - TDF/FTC

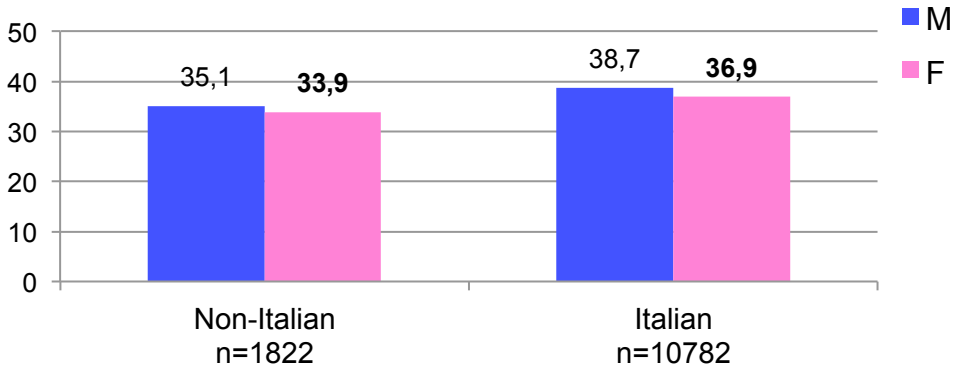


Raffi F, et al. CROI 2014. Abstract 84LB. Reproduced with permission.

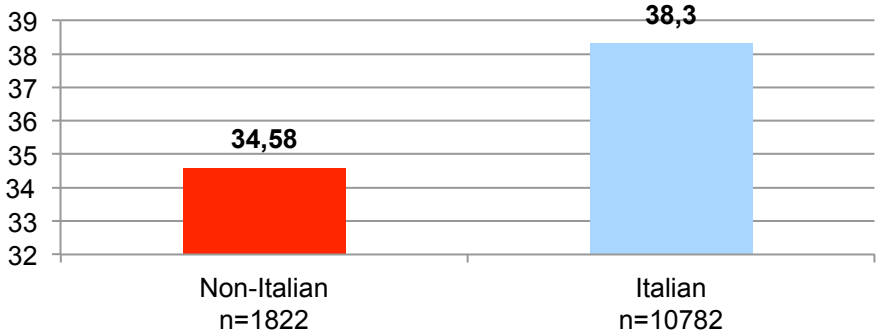
Viral load <50 copies/mL at week 48 (ITTe), baseline VL > 100.000 copies/mL



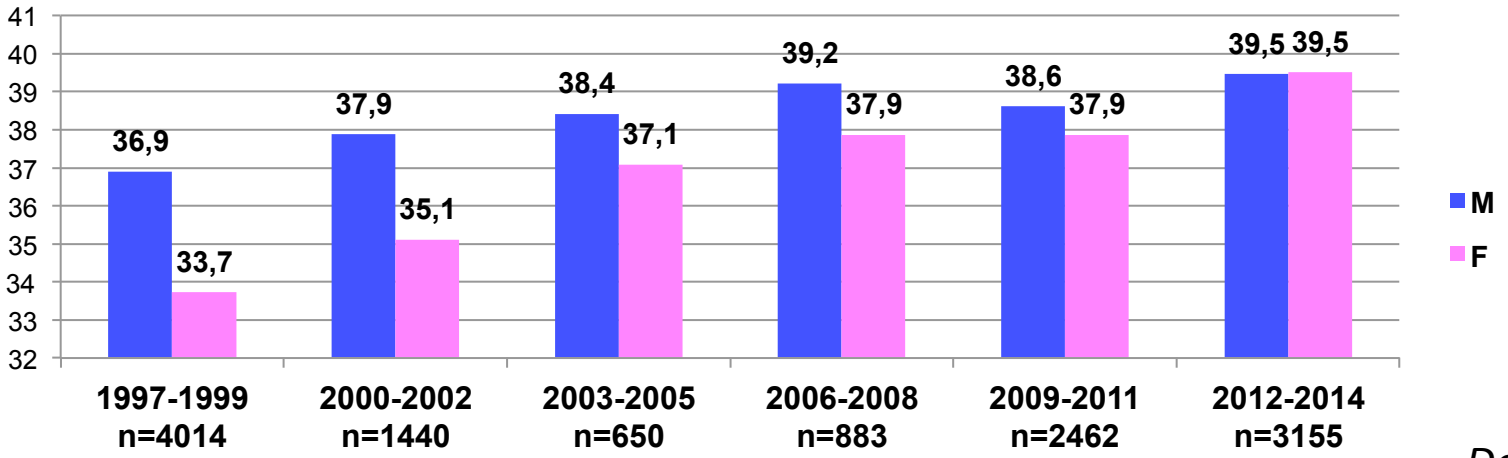
Mean age according to nationality and gender



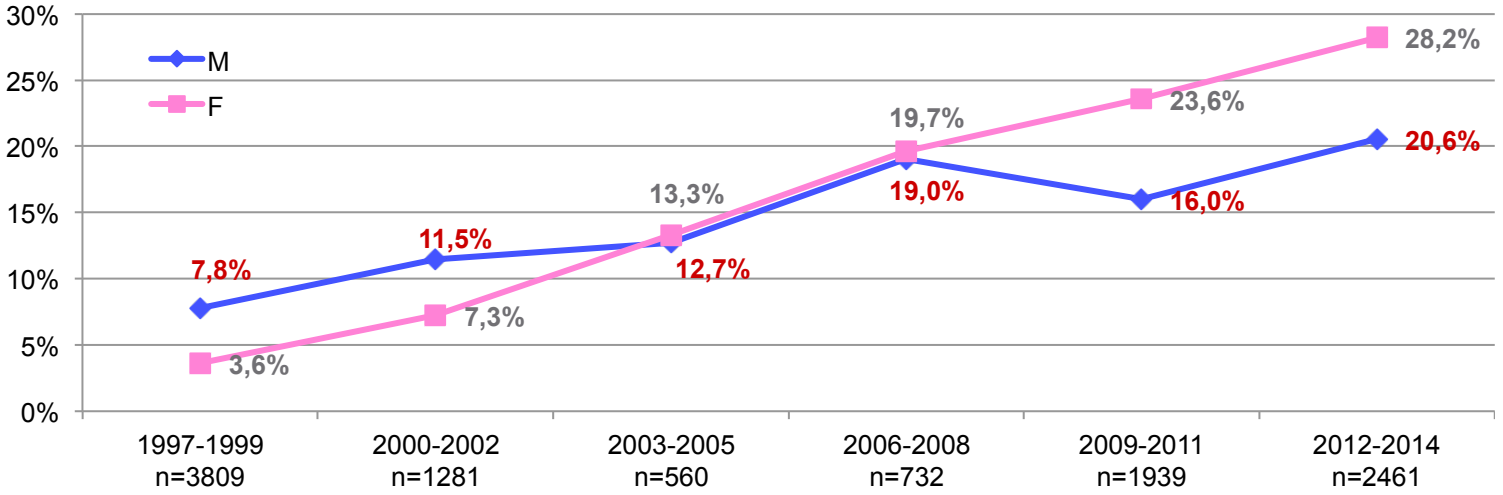
Mean age according to nationality



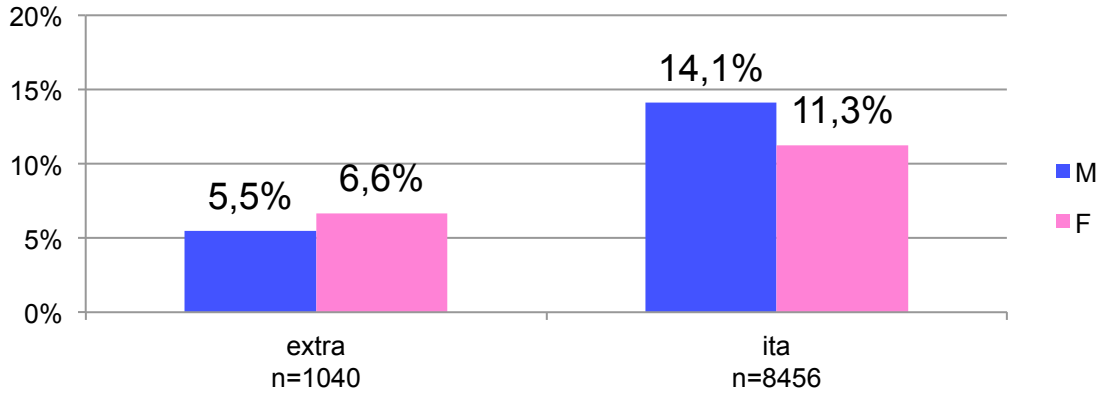
Mean age according to calendar year of enrollment and gender



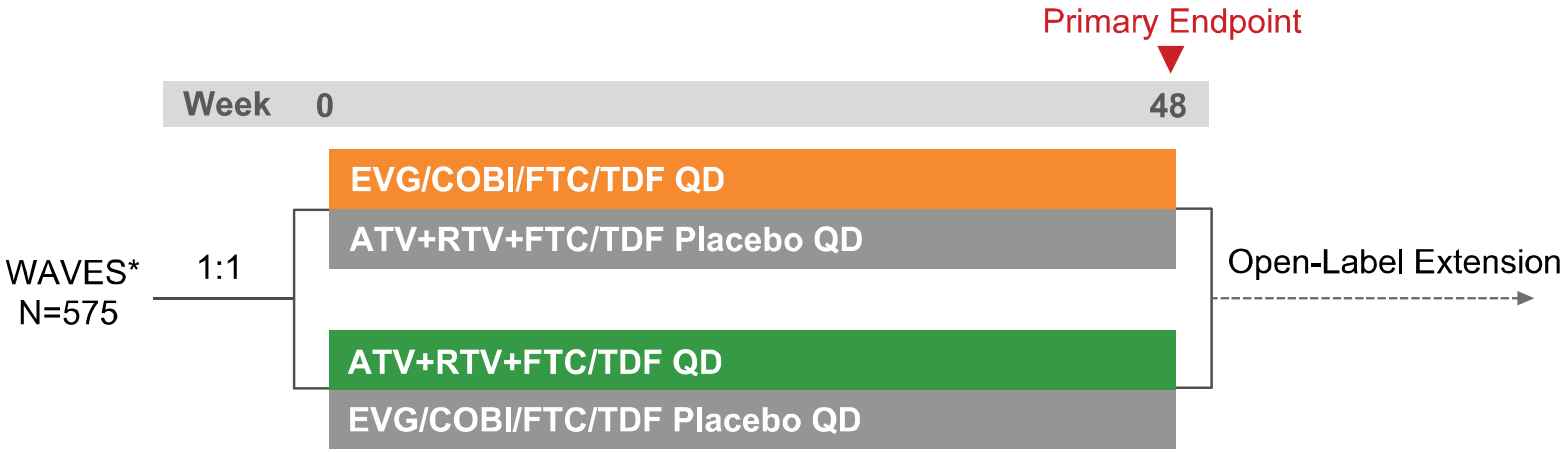
Proportion of italian patients aged 50 or more according to gender and to period of enrolment



Proportion patients aged 50 or more according to gender and to nationality



Study Design



- Key eligibility criteria
  - HIV-1 RNA ≥500 copies/mL
  - Estimated glomerular filtration rate (eGFR) ≥70 mL/min
  - No history of ART
  - Sensitivity to FTC, TDF, and ATV
- Primary endpoint: proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 (Food and Drug Administration [FDA] snapshot analysis)
- Stratification
  - HIV-1 RNA (≤100,000, >100,000–≤400,000, or >400,000 copies/mL)
  - Race (black or nonblack)

*Study ongoing.

Table 6. What to Start: Initial Combination Regimens for Antiretroviral-Naive Pregnant Women (page 1 of 2)

These recommendations are for pregnant women who have never received antiretroviral therapy (ART) previously (i.e., antiretroviral-naive) and are predicated on lack of evidence of resistance to regimen components. See Table 7 for more information on specific drugs and dosing in pregnancy. Within each drug class, regimens are listed alphabetically, and the order does not indicate a ranking of preference. It is recommended that women who become pregnant while on a stable ARV regimen with viral suppression remain on that same regimen.

Drug	Comments
Preferred Regimens Regimens with clinical trial data in adults demonstrating optimal efficacy and durability with acceptable toxicity and ease of use, PK data available in pregnancy, and no evidence to date of teratogenic effects or established adverse outcomes for mother/fetus/newborn. To minimize the risk of resistance, a PI regimen is preferred for women who may stop ART during the postpartum period.	
Preferred Two-NRTI Backbone	
ABC/3TC	Available as FDC. Can be administered once daily. ABC **should not be used** in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction. ABC/3TC with ATV/r or with EFV is not recommended if pretreatment HIV RNA >100,000 copies/mL.
TDF/FTC or 3TC	TDF/FTC available as FDC. Either TDF/FTC or TDF and 3TC can be administered once daily. TDF has potential renal toxicity, thus TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.
ZDV/3TC	Available as FDC. NRTI combination with most experience for use in pregnancy but has disadvantages of requirement for twice-daily administration and increased potential for hematologic toxicities.
Preferred PI Regimens	
ATV/r plus a Preferred Two-NRTI Backbone	Once-daily administration. Extensive experience in pregnancy. Maternal hyperbilirubinemia
DRV/r plus a Preferred Two-NRTI Backbone	Better tolerated than LPV/r. PK data available. Increasing experience with use in pregnancy. Must be used twice daily in pregnancy.
Preferred NNRTI Regimen	
EFV plus a Preferred Two-NRTI Backbone **Note:** May be initiated after the first 8 weeks of pregnancy	Concern because of birth defects seen in primate study; risk in humans is unclear (see Teratogenicity and Table 7). Postpartum contraception must be ensured. Preferred regimen in women who require co-administration of drugs with significant interactions with PIs or the convenience of co-formulated, single-tablet, once-daily regimen.
Preferred Integrase Inhibitor Regimen	
RAL plus a Preferred Two-NRTI Backbone	PK data available and increasing experience in pregnancy. Rapid viral load reduction. Useful when drug interactions with PI regimens are a concern. Twice-daily dosing required.
Alternative Regimens Regimens with clinical trial data demonstrating efficacy in adults but one or more of the following apply: experience in pregnancy is limited, data are lacking or incomplete on teratogenicity, or regimen is associated with dosing, formulation, toxicity, or interaction issues	
PI Regimens	
LPV/r plus a Preferred Two-NRTI Backbone	Abundant experience and established PK in pregnancy. More nausea than preferred agents. Twice-daily administration. Once-daily LPV/r is not recommended for use in pregnant women.
NNRTI Regimen	
RPV/TDF/FTC (or RPV plus a Preferred Two-NRTI Backbone)	RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm^3. Do not use with PPIs. PK data available in pregnancy but relatively little experience with use in pregnancy. Available in co-formulated single-pill once daily regimen.

CONCLUSIONI

Raltegravir e dolutegravir rappresentano sicuramente la prima scelta nel paziente co-infetto sulla base delle interazioni farmacologiche con i DAA.

Per quanto riguarda le co-morbosità non vi sono evidenze che favoriscano questa classe rispetto alle altre, ma dovremo aspettare un più prolungato periodo di osservazione. L'effetto sulla creatinina di dolutegravir ed elvitegravir rendono difficile la gestione nel paziente anziano, cosa che non si verifica con raltegravir.

Nel paziente ad alta viremia sono molto importanti, ma con gli attuali dati (aspettiamo EACS per dolutegravir+3TC) vanno utilizzati in triplice terapia.

Nella donna in gravidanza I dati a nostra disposizione riguardano raktegravir e lo rendono fondamentale soprattutto nelle diagnosi tardive.

Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare

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