6th Infectivology Today®

L'infettivologia del 3° millennio: AIDS ed altro

Tossicità della cART

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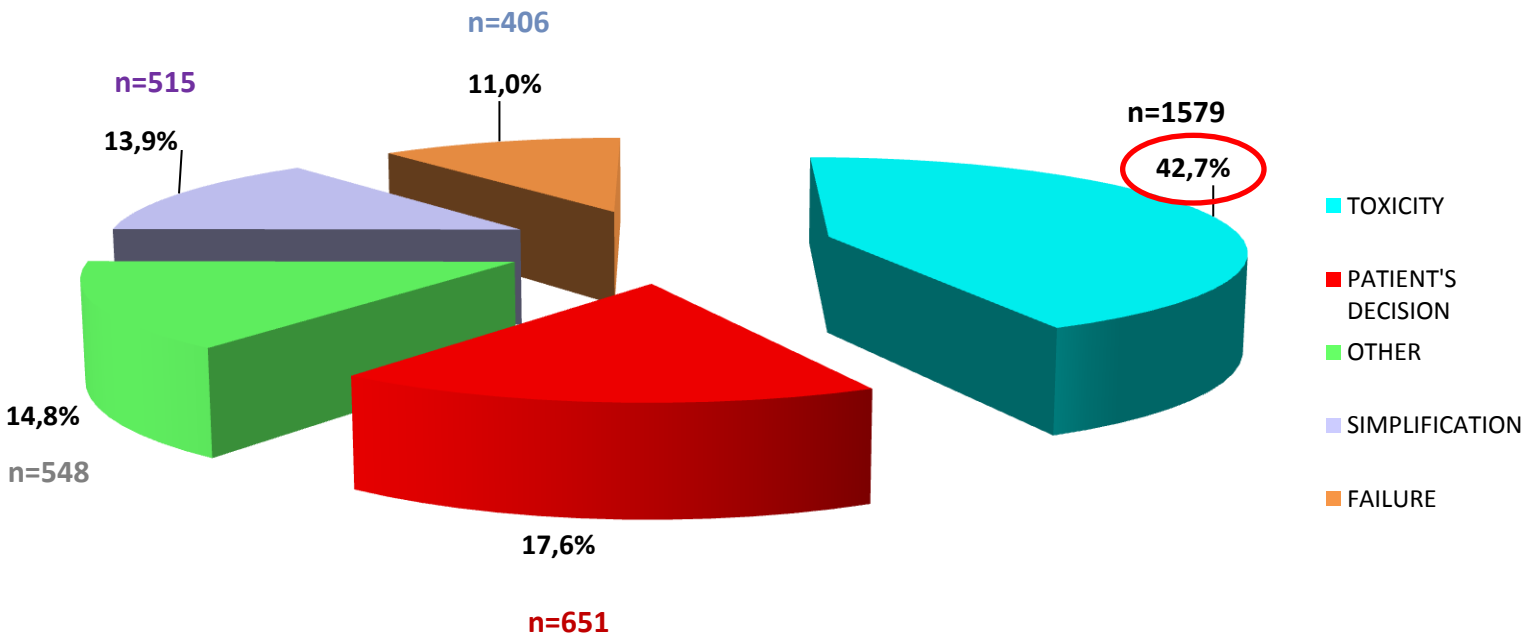
Paestum,16 maggio 2014

Italia Cohort Naive Antiretrovirals

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

Distribution of reason for ever stopping the drugs included in the first regimen in 3699 patients



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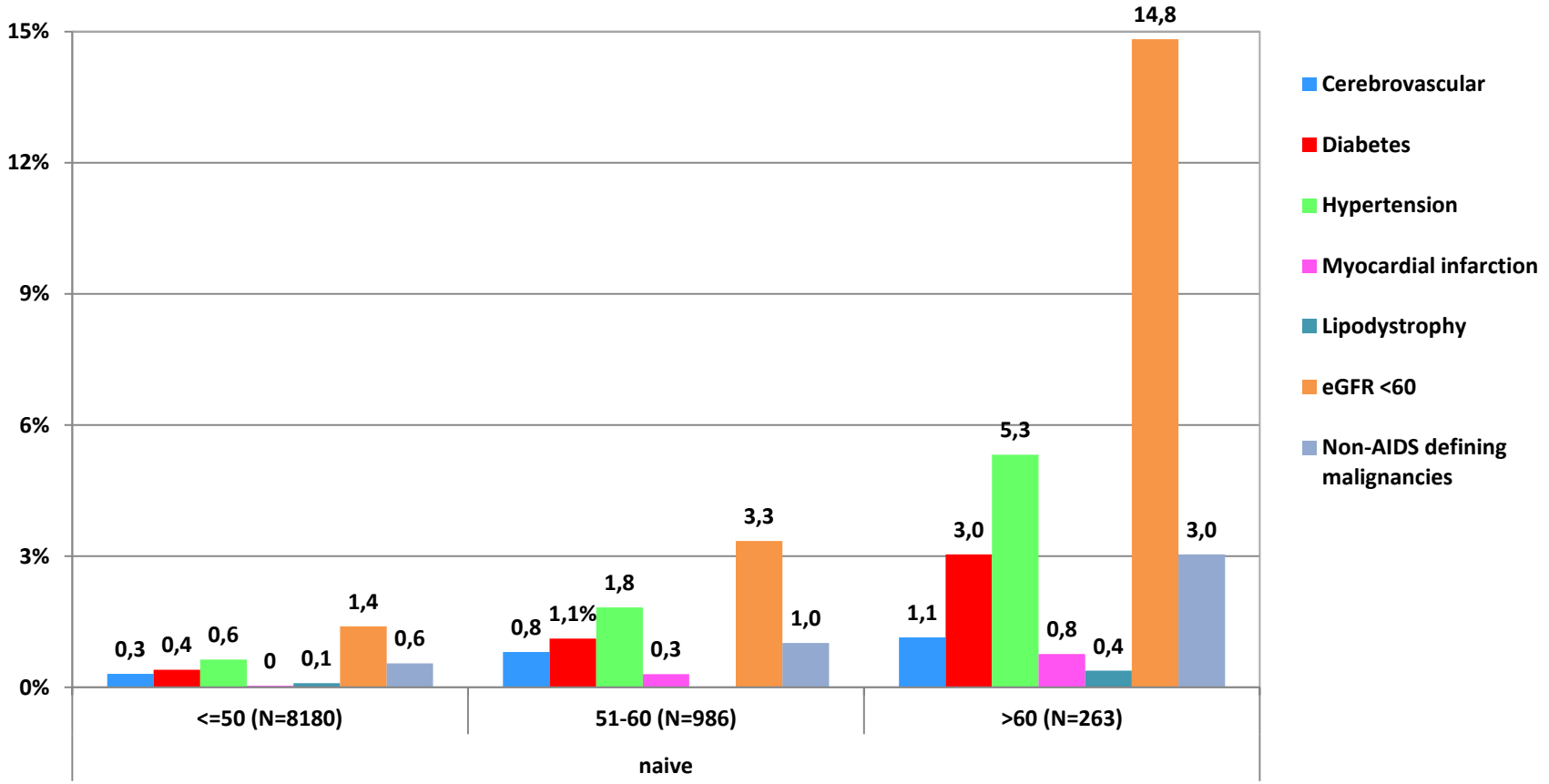
Italian Cohort Naive Antiretrovirals

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

Icona: prevalence of different non-AIDS related comorbidities at different age strata in naive patients



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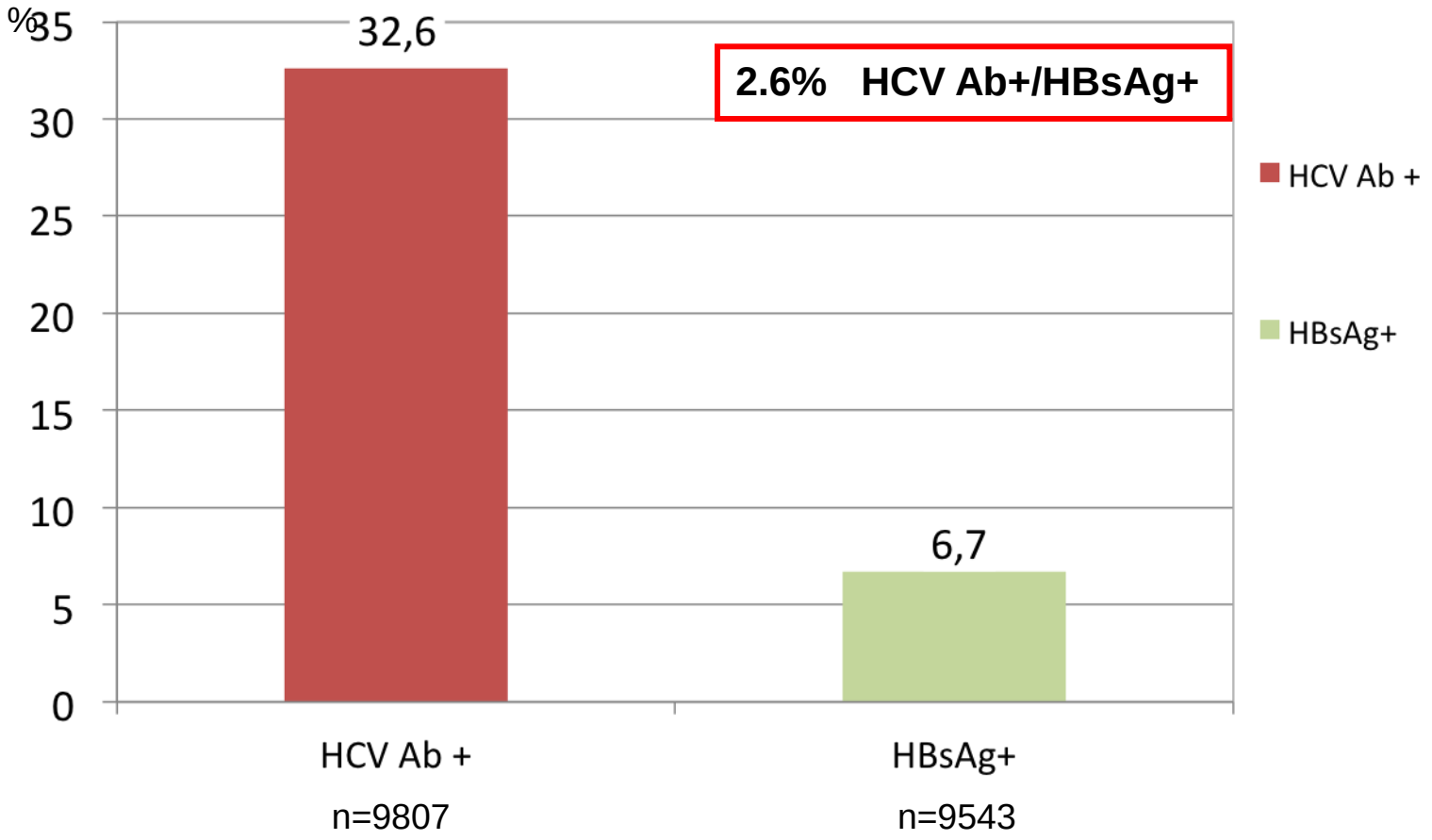
cART e tossicità epatica

Italian Cohort of Antiretroviral Naive Patients

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

HBsAg and HCV Ab positivity in 10986 patients



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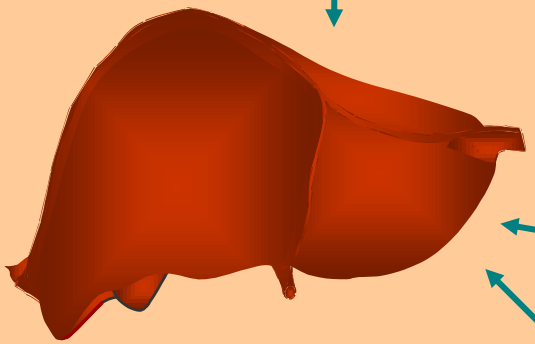
Factors affecting the liver in HIV patients



HBV or HCV
(HDV)

HIV

HIV Direct Toxicity?

NASH

Immune Restoration "Cytotoxicity"?

cART

Alcohol
Illicit Drugs
Medications

Drug-Related Hepatotoxicity

ART Exposure per year
Univariate analyses : (RR, 1.00; 95% CI, 0.93-1.07)
Adjusted RR (latest CD4 count & others) RR, 1.11; (95% CI, 1.02-1.21; *P*=.02)

Modified from: Weber J, et al.: The D.A.D.Study. Arch Intern Med 2006;166:1632–1641

DILI: meccanismi di epatotossicità

Table 1. Mechanisms of liver toxicity by antiretroviral class

	Mechanisms of HAART-Related Liver Toxicity				
Antiretroviral Class	**Hypersensitivity Reactions**	**Mitochondrial Toxicity**	**Lipid/Sugar Metabolism Disturbances and Steatosis**	**Direct Liver Cell Stress**	**Immune Reconstitution in Viral Hepatitis Coinfection(s)**
Nucleos(t)ide reverse transcriptase inhibitors	Abacavir (associated with HLB5701)	Possible for all D-drugs > the others Reported with: Zidovudine Stavudine Didanosine Lamivudine	D-drugs likely Other?	Didanosine	All
Non-nucleoside reverse transcriptase inhibitors	All		Possible for all	Nevirapine Efavirenz	All
Protease inhibitors	Fosamprenavir Darunavir		Possible for all Ritonavir-boosted PIs > non-ritonavir-boosted PIs	Ritonavir Tipranavir	All
Fusion inhibitor					All
CCR5 blocker	Maraviroc				All
Integrase inhibitor					All

D-drugs: dideoxinucleosides (didanosine, stavudine, zalcitabine); zalcitabine has been removed from the market.

Nunezet al.: Hepatology 2010

Association between dideoxinucleotide analogues (d-Drugs) and End-Stage-Liver-Diseases (EDSL) (D.A.D. Study Group)

Table: Associations between current and cumulative exposure to d-drugs and rate of ESLD

			Adjusted for:	
			Exposure to other NRTIs, PIs & NNRTIs	Exposure to other NRTIs, PIs & NNRTIs & potential confounders[c]
	Rate /1000 PY[a] (95% CI[a])	Relative rate[b] (95% CI)	Relative rate (95% CI)	Relative rate (95% CI)
Never received d-drugs	0.042 (0.031-0.052)	0.75 (0.41-1.38)	0.74 (0.40-1.36)	1.35 (0.73-2.49)
Currently on d-drugs	0.086 (0.050-0.122)	Ref.	Ref.	Ref.
Stopped d-drugs & off for:				
≥0, <2 years	0.167 (0.111-0.222)	2.28 (1.32-3.94)	2.31 (1.33-4.02)	2.01 (1.17-3.48)
≥2, <4 years	0.144 (0.093-0.196)	1.90 (1.09-3.32)	1.97 (1.12-3.47)	1.91 (1.09-3.36)
≥4, <6 years	0.172 (0.113-0.230)	2.23 (1.29-3.85)	2.38 (1.36-4.16)	2.45 (1.40-4.28)
≥6, <8 years	0.114 (0.066-0.183)	1.51 (0.79-2.86)	1.66 (0.86-3.20)	1.75 (0.91-3.38)
≥8 years	0.067 (0.033-0.119)	0.91 (0.44-1.91)	1.01 (0.47-2.18)	1.09 (0.51-2.36)
Cumulative exposure (/year) to d-drugs	n/a	1.07 (1.01-1.12)	1.07 (1.01-1.14)	1.07 (1.01-1.13)

[a]PY: person-years; CI: confidence interval; [b] adjusted for time since stopping d-drug and cumulative exposure to d-drug; [c]Age, injection drug use as mode of HIV acquisition, previous AIDS diagnosis, viral hepatitis C/B coinfection, latest CD4 count, time since stopping d-drug and cumulative exposure to d-drug; no significant associations were seen between ESLD and calendar year, gender, cohort, smoking status, ethnicity or latest HIV RNA level and so models do not include adjustment for these factors.

Conclusions: Cumulative use of d-Drugs, but not other drugs, was associated with increased ESDL rates, which were not reversible upon cessation. The higher rates in those stopping d-drugs may suggest selective discontinuation in those at higher risk of ESLD. Our study suggest that d-drugs may be avoided if possible, particularly in those with viral hepatitis.

Ryom L.. et al. CROI 2014. Abstract 787

cART e rischio cardiovascolare

Italian Cohort Naive Antiretrovirals

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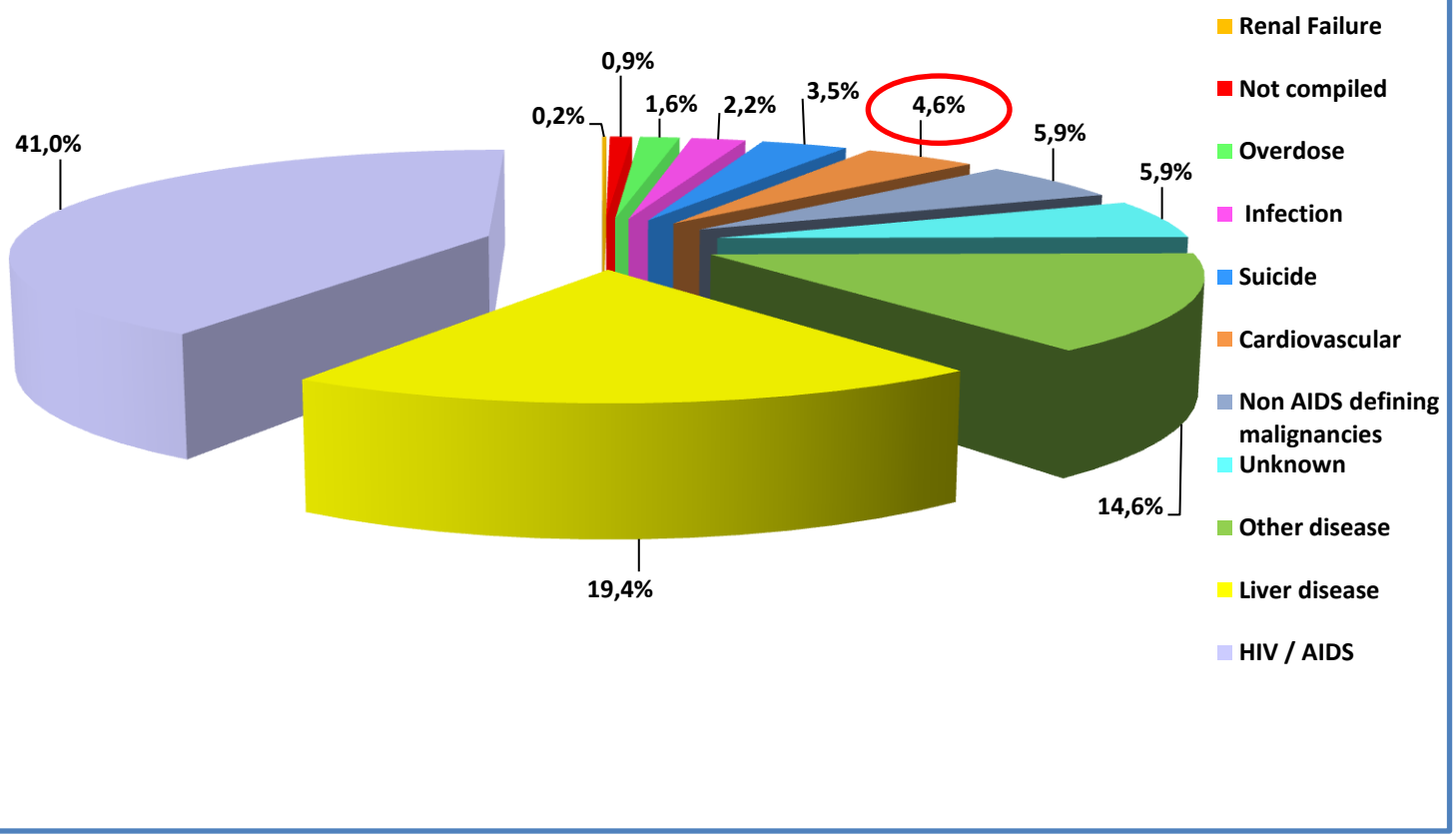
Italian Cohort of Antiretroviral Naïve Patients

Cause of death



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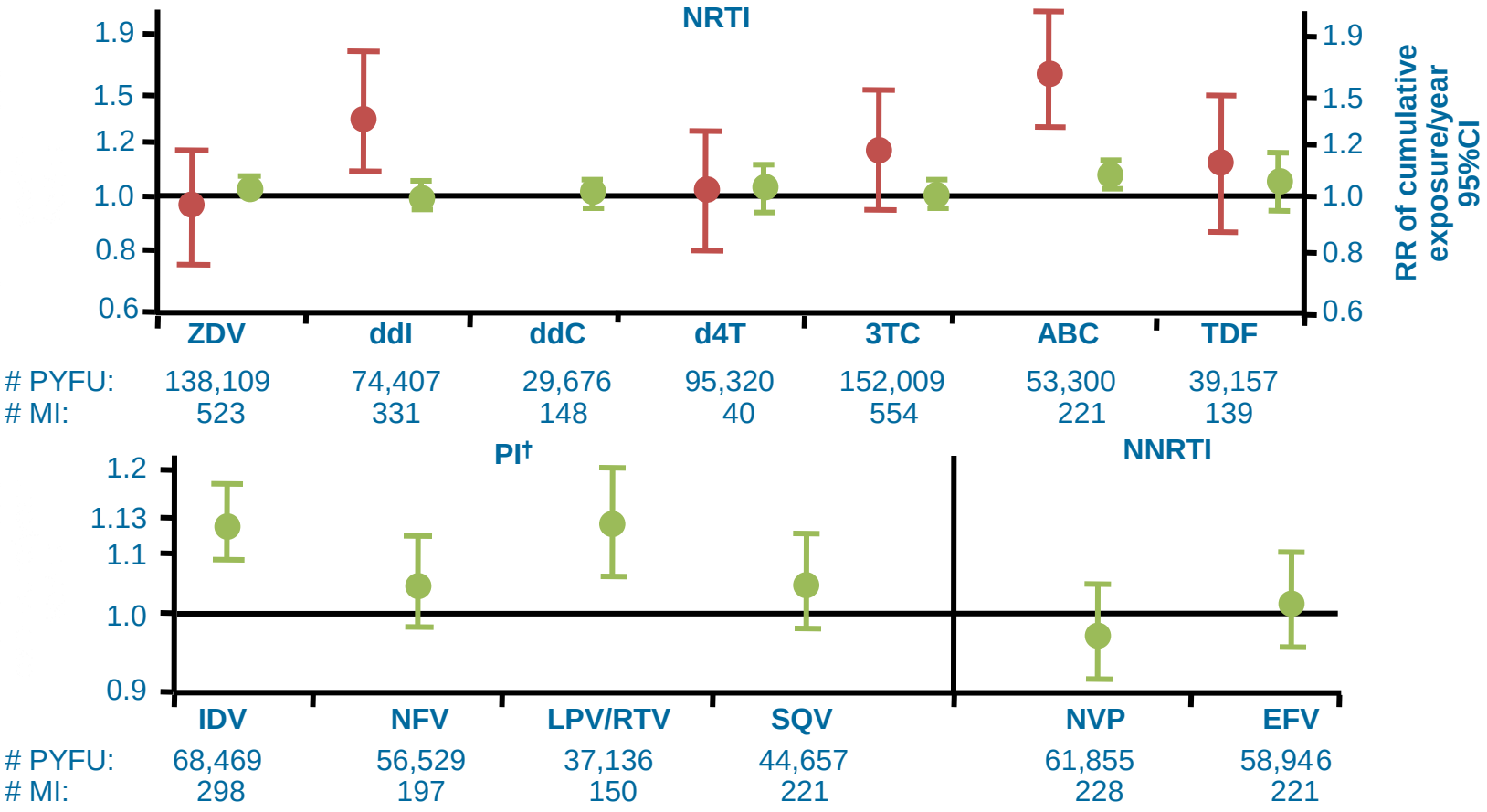
D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI



*Current or within last 6 months. †Approximate test for heterogeneity: *P* = 0.02

Lundgren JD, et al. CROI 2009. Abstract 44LB.

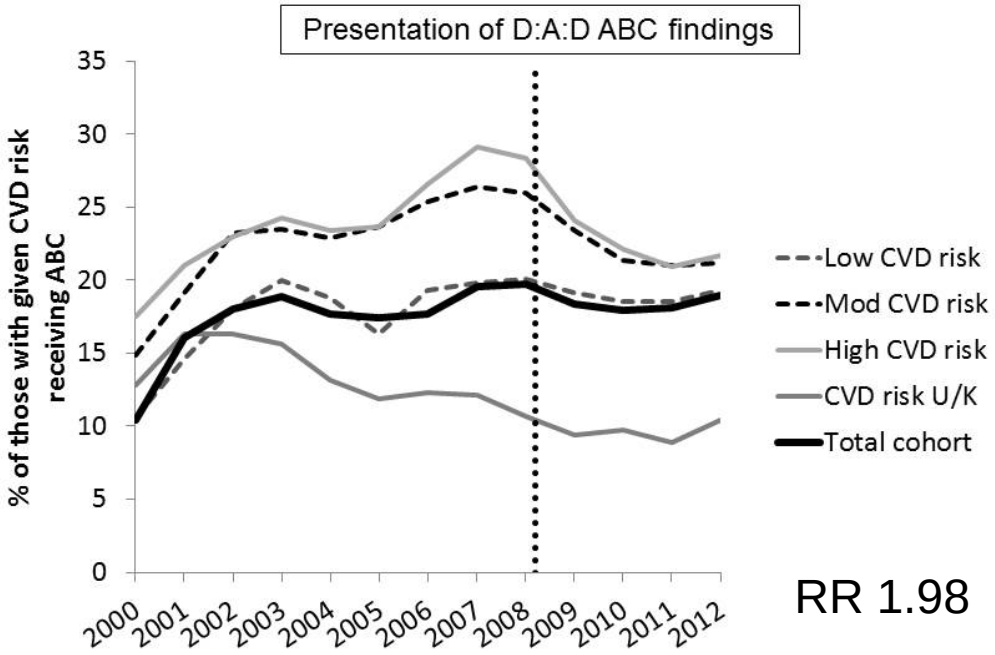
FDA Drug Safety Communication: Safety Review update of Abacavir and possible increased risk of heart attack

No statistically significant association between MI and the abacavir-containing regimen was detected

•Data from 26 RCTs conducted from 1996 to 2010 (16 trials from the drug manufacturer database, 5 from the AIDS Clinical Trials Group (ACTG), and 5 from academic centers were included in the meta-analysis conducted by FDA.

D.A.D.: Is There Continued Evidence for an Association Between Abacavir and Myocardial Infarction Risk?

Figure: Use of ABC in D:A:D cohort over time



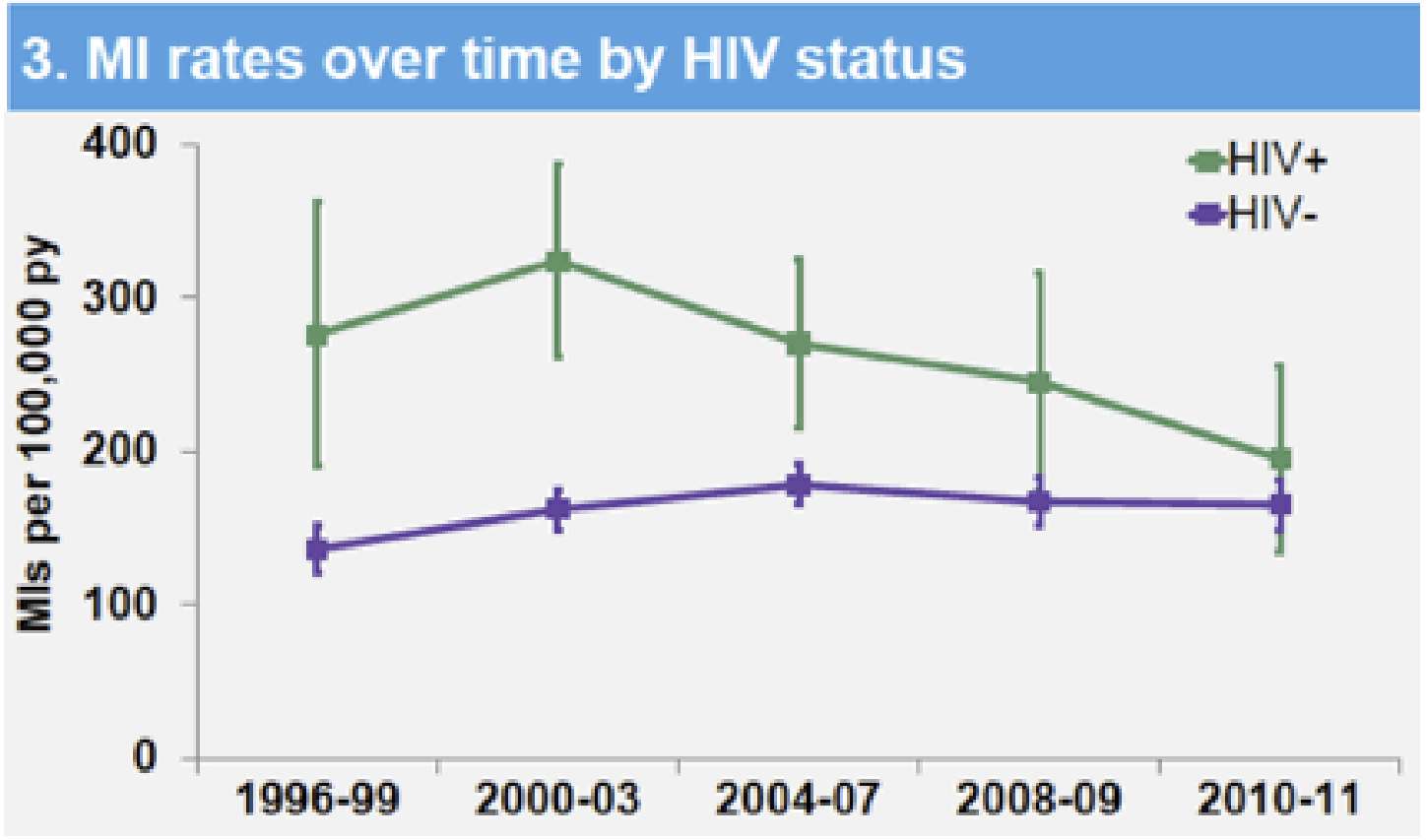
RR 1.98

Conclusions: Despite channelling of ABC away from those at higher CVD risk since 2008, we continue to observe an association between ABC use and MI risk.

Whilst confounding cannot be ruled out in any cohort study, this argues against channelling bias as an explanation for our findings

Sabin C, et al. CROI 2014. Abstract 747LB.

Risk of heart attack and stroke now no different for HIV+ and HIV- patients (Kaiser permanente group)



Klein D, et al. CROI 2014. Abstract 737.

Immunodeficiency and Risk of Myocardial Infarction among HIV-positive 1 Individuals withAccess to Care

Michael J. Silverberg, PhD, MPH1, Wendy A. Leyden, MPH1, Lanfang Xu, MS2, Michael A. 6 Horberg, MD MAS3, Chun R. Chao, PhD2, William J. Towner, MD4, Leo B. Hurley, MPH1, 7 Charles P. Quesenberry, Jr, PhD1, and Daniel B. Klein, MD

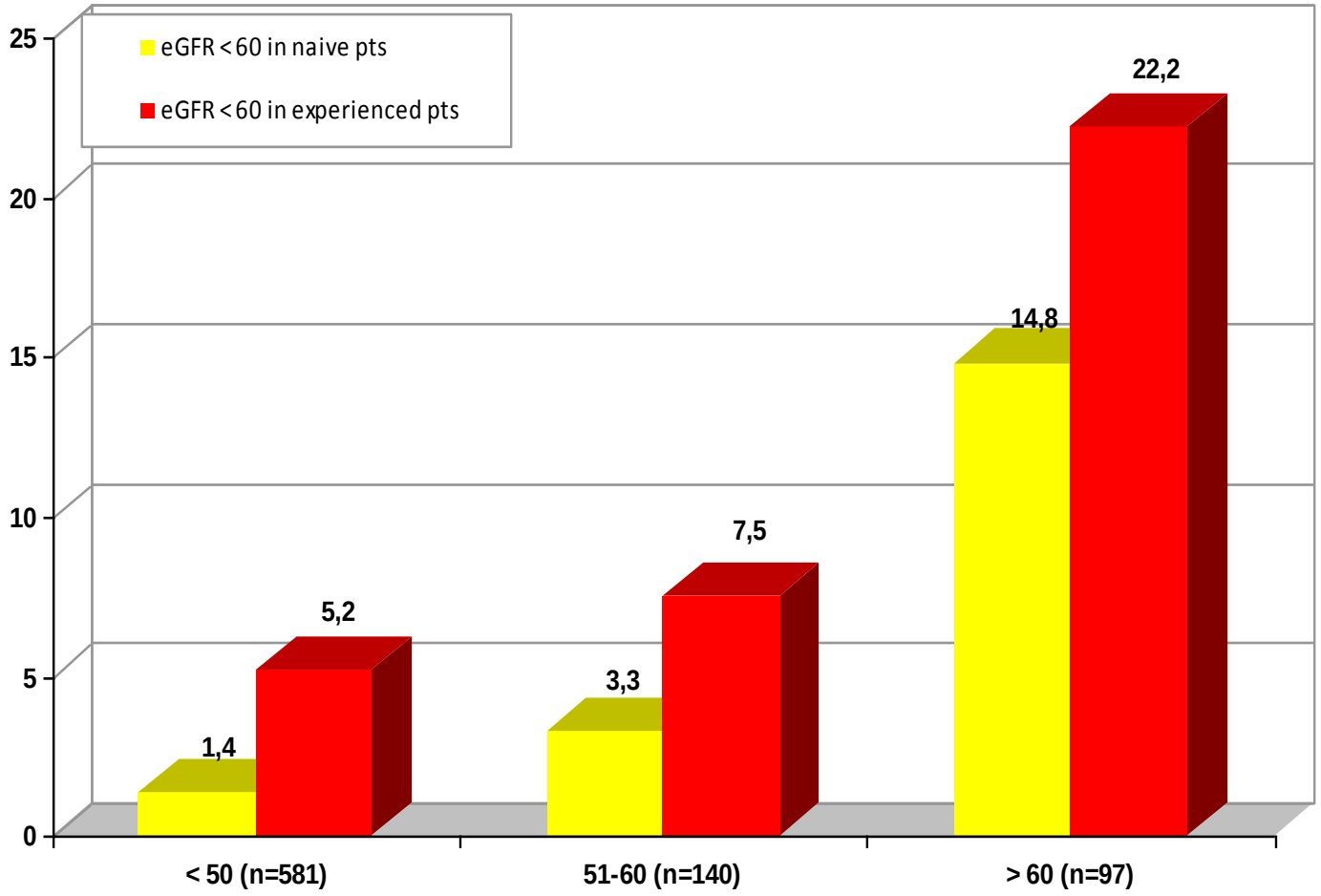
- **44% increased risk of MIs among HIV+ subjects compared with HIV- subjects**
- **nadir CD4 but not recent CD4, was independently associated with MIs among HIV+ individuals, suggesting the higher MI risk in this population may not be easily reversible**
- **HIV+ subjects with recent or nadir CD4≥500 cells/μL had similar MI rates compared with HIV- subjects.**
- **These results strengthen recommendations for earlier ART initiation**

JAIDS 2013. Publish Ahead of Print DOI: 10.1097/QAI.0000000000000009

cART e tossicità renale

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

Icona: prevalence of CKD according to age **in naive and experienced patients**



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Risk Factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors

Vasantha Jotwani, MD,[1,2] Yongmei Li, PhD,[1] Carl Grunfeld, MD, PhD,[3] Andy I. Choi, MD, MAS,[4†] and Michael G. Shlipak, MD, MPH[1,2]

22,156 HIV-infected veterans in "Veterans' Affairs medical system" between 1996 and 2004

Table 2. Risk Factors for ESRD in HIV-Infected Veterans

Risk Factors	Multivariate-Adjusted Model[a] HR (95% CI)	*P*	Competing-Risks Analysis[b] Sub-HR (95% CI)	*P*
Baseline age quartile				
<38 y	1.00 (reference)		1.00 (reference)	
38-44 y	0.90 (0.65-1.25)	0.5	0.84 (0.60-1.18)	0.3
45-49 y	0.59 (0.42-0.82)	0.002	0.55 (0.38-0.78)	0.001
≥50 y	0.36 (0.26-0.51)	<0.001	0.33 (0.23-0.48)	<0.001
Race				
White	1.00 (reference)		1.00 (reference)	
Black	3.06 (2.22-4.22)	<0.001	3.24 (2.18-4.82)	<0.001
Baseline hypertension	1.87 (1.46-2.40)	<0.001	2.04 (1.56-2.68)	<0.001
Diabetes	1.69 (1.32-2.16)	<0.001	1.54 (1.15-2.08)	0.004
Cardiovascular disease	2.17 (1.72-2.74)	<0.001	1.78 (1.34-2.36)	<0.001
Dyslipidemia	1.16 (0.91-1.49)	0.2	1.46 (1.11-1.94)	0.007
CD4 count				
>350 cells/μL	1.00 (reference)	—	1.00 (reference)	—
200-350 cells/μL	0.92 (0.65-1.29)	0.6	0.92 (0.64-1.32)	0.7
<200 cells/μL	1.54 (1.17-2.02)	0.002	1.30 (0.97-1.76)	0.08
Viral load				
<500 copies/mL	1.00 (reference)	—	1.00 (reference)	—
500-3,999 copies/mL	0.89 (0.60-1.32)	0.6	0.81 (0.52-1.27)	0.4
4,000-29,999 copies/mL	1.42 (0.99-2.03)	0.06	1.28 (0.88-1.87)	0.2
≥30,000 copies/mL	2.01 (1.46-2.76)	<0.001	1.44 (1.02-2.03)	0.04
Hepatitis C virus	1.90 (1.52-2.38)	<0.001	1.95 (1.53-2.50)	<0.001
Hypoalbuminemia[c]	2.14 (1.80-2.54)	<0.001	1.99 (1.69-2.34)	<0.001
Baseline eGFR				
≥60 mL/min/1.73 m^2	1.00 (reference)	—	1.00 (reference)	—
30-59 mL/min/1.73 m^2	6.43 (4.81-8.58)	<0.001	5.24 (3.72-7.39)	<0.001
<30 mL/min/1.73 m^2	28.09 (20.29-38.88)	<0.001	20.87 (13.73-31.73)	<0.001
Baseline proteinuria				
0 mg/dL	1.00 (reference)		1.00 (reference)	
30-100 mg/dL	5.63 (4.29-7.38)	<0.001	5.25 (3.88-7.11)	<0.001
300-1,000 mg/dL	18.09 (12.96-25.23)	<0.001	18.26 (12.40-26.89)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Proportional hazards multivariate analysis adjusted for baseline age, race, body mass index, baseline eGFR, baseline proteinuria, baseline hypertension, diabetes, cardiovascular disease, CD4 lymphocyte count, HIV viral load, hepatitis C infection, hypoalbuminemia (serum albumin <3.5 mg/dL), and receipt of ACE inhibitor.

[b]Adjustment for the competing risk of death using Fine-Gray analysis. Competing-risks model estimates sub-HR for ESRD accounting for competing risk of death before ESRD.

[c]Serum albumin level <3.5 mg/dL.

Am J Kidney Dis. 2012;

Evaluation of glomerular filtration rate in HIV-1-infected patients before and after combined antiretroviral therapy exposure*

F Tordato,1 A Cozzi Lepri,2 P Cicconi,1 A De Luca,3 A Antinori,4 V Colangeli,5 A Castagna,6 P Nasta,7 N Ladisa,8 A Giacometti,9 A d'Arminio Monforte1 and A Gori1,10 for the ICONA Foundation Study Groupw

HIV Medicine (2011), 12, 4–13

1505 Patient characteristics according to estimated glomerular filtration rate (eGFR) at baseline and factors associated with an eGFR < 90 mL/min per 1.73 m^2 at baseline from fitting a logistic regression model

Characteristic	eGFR ≥ 90 mL/min/1.73 m^2	eGFR < 90 mL/min/1.73 m^2	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Number of patients	1142	363				
Age (years)						
Median (IQR)	38 (32, 43)	40 (36, 46)				
Per 10 years older			1.50 (1.32, 1.71)	0.000001	1.58 (1.37, 1.82)	0.000001
Gender [*n* (%)]						
Male	858 (75.1)	224 (61.7)	1.00		1.00	
Female	284 (24.9)	139 (38.3)	1.87 (1.46, 2.41)	0.000001	2.41 (1.75, 3.31)	0.000001

24%

Conclusions

We observed a relatively high rate of mild renal dysfunction in the absence of ART. In addition to traditional risk factors such as older age and diabetes/hypertension, female gender and current use of ddI, tenofovir and protease inhibitors were associated with a greater risk of decreased renal function as measured by eGFR.

Association of tenofovir exposure with kidney disease risk in HIV infection

Rebecca Scherzer[a], Michelle Estrella[b], Yongmei Li[a], Steven G. Deeks[c], Carl Grunfeld[a] and Michael G. Shlipak[a]

AIDS 2012, **26**:867–875

10,841 from the Veterans Health Administration who initiated ART from 1997–2007

Table 4. Association of cumulative antiretroviral exposure (per year) with risk[a] of kidney disease outcomes, ordered by prevalence of use.

Antiretroviral	% of participants with any exposure at end of study (10841 pts)	Proteinuria		Rapid Decline[c]		Chronic Kidney Disease	
		Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Tenofovir	39.7	1.34 (1.25, 1.45)	<0.0001	1.11 (1.03, 1.18)	0.0033	1.33 (1.18, 1.51)	<0.0001
Lamivudine	89.5	0.98 (0.94, 1.03)	0.50	1.02 (0.97, 1.06)	0.44	0.93 (0.85, 1.02)	0.11
Zidovudine	68.3	0.98 (0.93, 1.03)	0.42	0.98 (0.93, 1.02)	0.29	0.89 (0.81, 0.98)	0.020
Efavirenz	49.0	0.94 (0.90, 0.99)	0.026	1.01 (0.97, 1.05)	0.64	0.88 (0.79, 0.98)	0.018
Stavudine	43.0	1.02 (0.97, 1.07)	0.54	1.02 (0.97, 1.06)	0.43	0.98 (0.89, 1.07)	0.61
Ritonavir[b]	35.7	1.18 (1.09, 1.27)	<0.0001	0.96 (0.89, 1.04)	0.34	0.97 (0.84, 1.14)	0.74
Nelfinavir	31.6	0.99 (0.95, 1.04)	0.68	1.02 (0.98, 1.06)	0.39	1.01 (0.92, 1.11)	0.76
Abacavir	29.6	1.01 (0.96, 1.07)	0.73	1.01 (0.96, 1.06)	0.65	1.07 (0.97, 1.18)	0.20
Indinavir	24.6	1.04 (0.99, 1.09)	0.15	0.99 (0.95, 1.04)	0.67	1.16 (1.06, 1.27)	0.0019
Didanosine	23.0	0.94 (0.88, 1.00)	0.051	0.98 (0.93, 1.04)	0.49	0.95 (0.84, 1.07)	0.37
Nevirapine	22.8	1.01 (0.96, 1.06)	0.69	1.02 (0.97, 1.06)	0.52	0.93 (0.84, 1.03)	0.18
Atazanavir	17.1	0.93 (0.79, 1.08)	0.34	1.22 (1.07, 1.40)	0.0035	0.96 (0.77, 1.18)	0.69
Lopinavir/r	15.3	0.77 (0.68, 0.86)	<0.0001	1.05 (0.94, 1.17)	0.39	1.21 (0.91, 1.60)	0.18
Saquinavir	10.7	0.91 (0.83, 0.99)	0.035	1.00 (0.92, 1.08)	0.97	0.89 (0.72, 1.09)	0.24
Amprenavir	4.3	0.90 (0.78, 1.05)	0.20	1.03 (0.90, 1.18)	0.67	1.17 (0.94, 1.46)	0.16
Fosamprenavir	3.3	0.91 (0.63, 1.32)	0.63	1.29 (0.90, 1.85)	0.16	1.00 (0.67, 1.47)	0.98
Zalcitabine	1.5	1.11 (0.92, 1.35)	0.29	0.91 (0.72, 1.14)	0.41	1.24 (0.70, 2.19)	0.46
Delavirdine	1.5	1.10 (0.90, 1.35)	0.35	0.85 (0.66, 1.10)	0.21	1.24 (0.84, 1.81)	0.28
Tipranavir	0.6	0.87 (0.29, 2.68)	0.81	0.34 (0.05, 2.34)	0.27	0.06 (0.00, 66.0)	0.43

Conclusions: Tenofovir exposure was independently associated with increased risk for three types of kidney disease events, and did not appear to be reversible. Because subtle kidney function decline affects long-term morbidity and mortality, the balance between efficacy and probable adverse effects requires further study.

Exposure to Antiretrovirals (ARVs) and Risk of Renal Impairment among HIVpositive Persons with Normal Baseline Renal Function: the D:A:D study

Lene Ryom1, Amanda Mocroft2, Ole Kirk1,8, Signe W Worm1, David A Kamara2, Peter Reiss3, Michael Ross4, Christoph A Fux5, Philippe Morlat6, Olivier Moranne7, Colette Smith2 and Jens D Lundgren1,8 on behalf of the D:A:D study group

Also: CROI 2013 Atranta. Paper # 810

22,603 pazienti della Coorte DAD (49,734), quelli con almeno 3 misurazioni di creatinina disponibili. e una eGFR> 90 di baseline.

Vennero quindi automaticamente **esclusi** gli AA, HCV, HBV, fumatori, AIDS, CVD, DM, IA, IDU.

Quindi la **coorte analizzata** era prevalentemente rappresentata da maschi bianchi con età media di 39 anni (IQR 33-44) e MSM

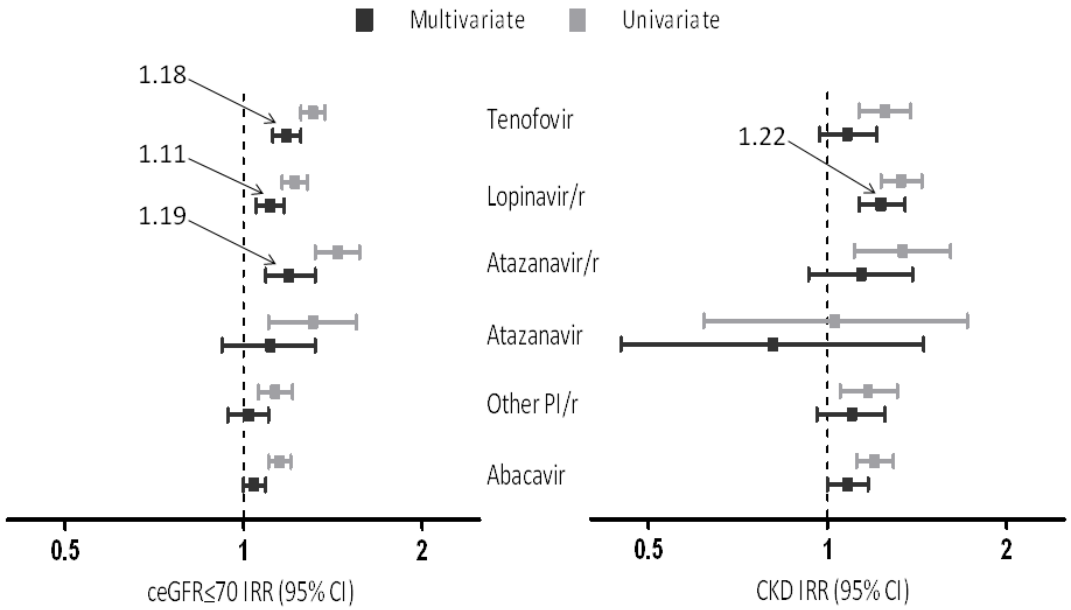


Figure 2. ARV exposure (per year) & incidence rate ratios of confirmed eGFR<70 & CKD from eGFR>90

Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of transmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +, Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables.

Exposure to Antiretrovirals (ARVs) and Risk of Renal Impairment among HIVpositive Persons with Normal Baseline Renal Function: the D:A:D study

Lene Ryom1, Amanda Mocroft2, Ole Kirk1,8, Signe W Worm1, David A Kamara2, Peter Reiss3, Michael Ross4, Christoph A Fux5, Philippe Morlat6, Olivier Moranne7, Colette Smith2 and Jens D Lundgren1,8 on behalf of the D:A:D study group

Also: CROI 2013 Atranta. Paper # 810

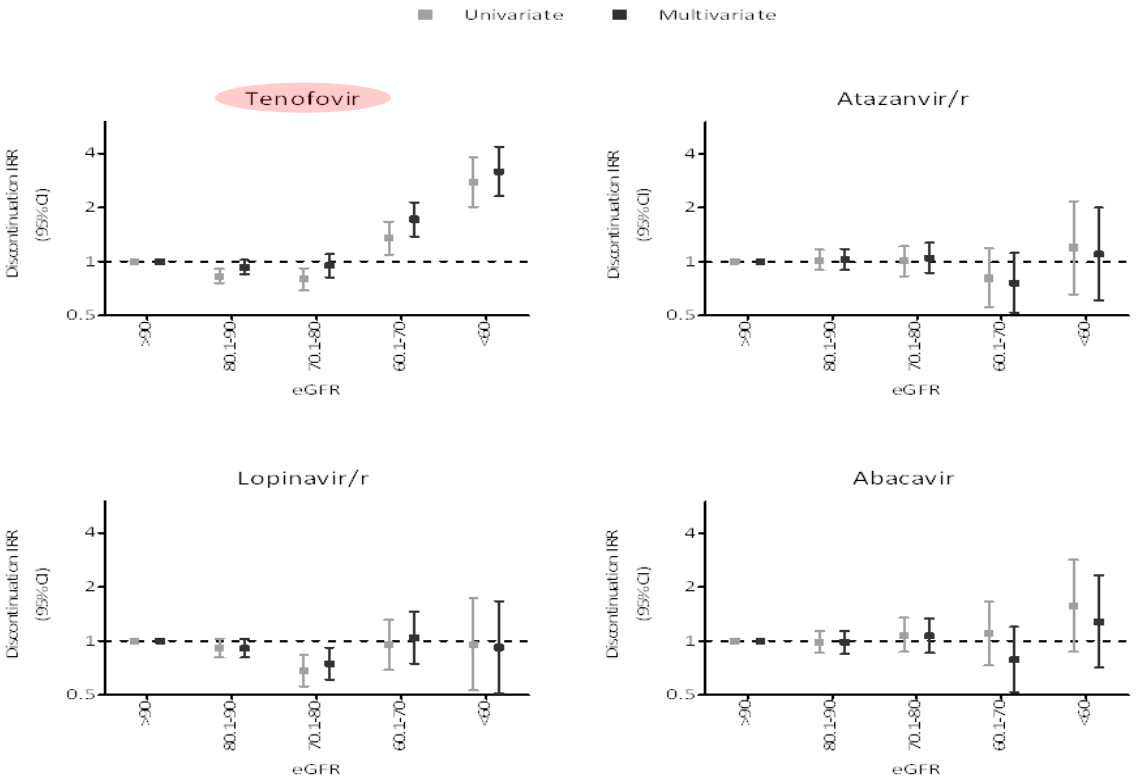
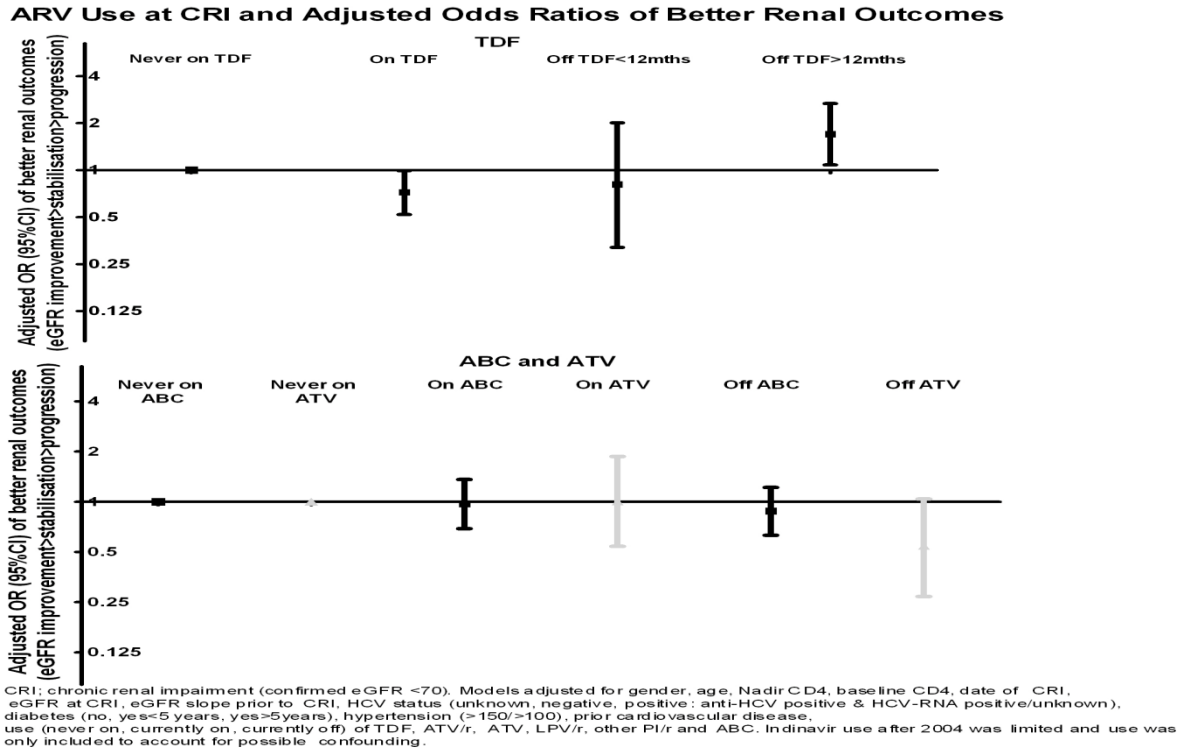


Figure 1. ARV discontinuation rates & eGFR levels

Models adjusted for baseline eGFR (per 5 ml/min higher), age (per 10 years), gender, ethnicity (Caucasian, of African origin, unknown), HIV mode of ransmission (MSM, heterosexual, intravenous drug use (IDU), unknown or other), CD4 nadir, enrolment cohort, baseline date. Prior AIDS, HCV (defined by anti-HCV and HCV-RNA positive/unknown) +, HBV (defined by HBsAg positive, HBeAg positive or HBV-DNA positive/anti-HBe positive) +, smoking status +, hypertension +, diabetes +, CVD +, CD4 (per doubling) +. Viral load (per log 10 increase) +, and cumulative exposure (per year) + to ATV, ATV/r, LPV/r, TDF, ABC, IDV and other PI/r. + included as time-updated variables

Predictors of Progression, Stabilisation, or Improvement of eGFR After Chronic Renal Impairment (D.A.D. Study Group)



Conclusions: Use of TDF, ATV/r, LPV/r and other PI/r, older age, diabetes and slowly declining eGFR were associated with decreased odds of better eGFR outcomes in HIV-positive persons after CRI. TDF discontinuation prior to CRI was associated with better eGFR outcomes, suggesting TDF associated eGFR decline may be halted or reversed with early cessation. There was some suggestion that this may also be true for ATV/r, LPV/r and other PI/r.

Romy,L. et al. CROI 2014. Abstract 792

Abstract #: R-152

Reversibility of tenofovir-associated decline in renal function

Sophie Jose[1], Lisa Hamzah[2], Lucy Campbell[2], Dorothea Nitsch[3], Rachael Jones[4], Caroline Sabin[1] and Frank Post[2] for the UK Collaborative HIV Cohort (CHIC) Study

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Paper # 813

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UK Collaborative HIV Cohort (CHIC) : 2610 patients discontinued TDF, of whom 696 (80% male, 69% white, median age 4) had sufficient data to assess reversibility

Table 3: Factors associated with incomplete eGFR recovery

	Univariable			Multivariable		
	OR	CI	P	OR	CI	P
eGFR at TDF start per 10ml/min ↑	1.48	(1.03, 2.13)	0.033	2.76	(2.11, 3.62)	<0.0001
eGFR at TDF stop per 10ml/min ↑	0.73	(0.66, 0.81)	<0.0001	0.48	(0.40, 0.59)	<0.0001
Time on TDF *(years)*	1.36	(1.20, 1.54)	<0.0001	1.42	(1.21, 1.68)	<0.0001
Rapid decline on TDF *(Yes vs. No)*	4.66	(2.84, 7.66)	<0.0001	2.13	(1.12, 4.05)	0.022
Age *(10 years)*	1.53	(1.22, 1.92)	0.0002	1.78	(1.25, 2.54)	0.002

Covariates considered for multivariable analyses were: age; sex; ethnicity; exposure; antiretroviral-naive status at TDF start; eGFR at TDF start; eGFR at discontinuation; time exposed to TDF CKD; rapid eGFR decline; pre-TDF eGFR slope; during-TDF eGFR slope.

Conclusions:

In patients who discontinued TDF, eGFR recovery was incomplete in 9.2% of patients with available data.

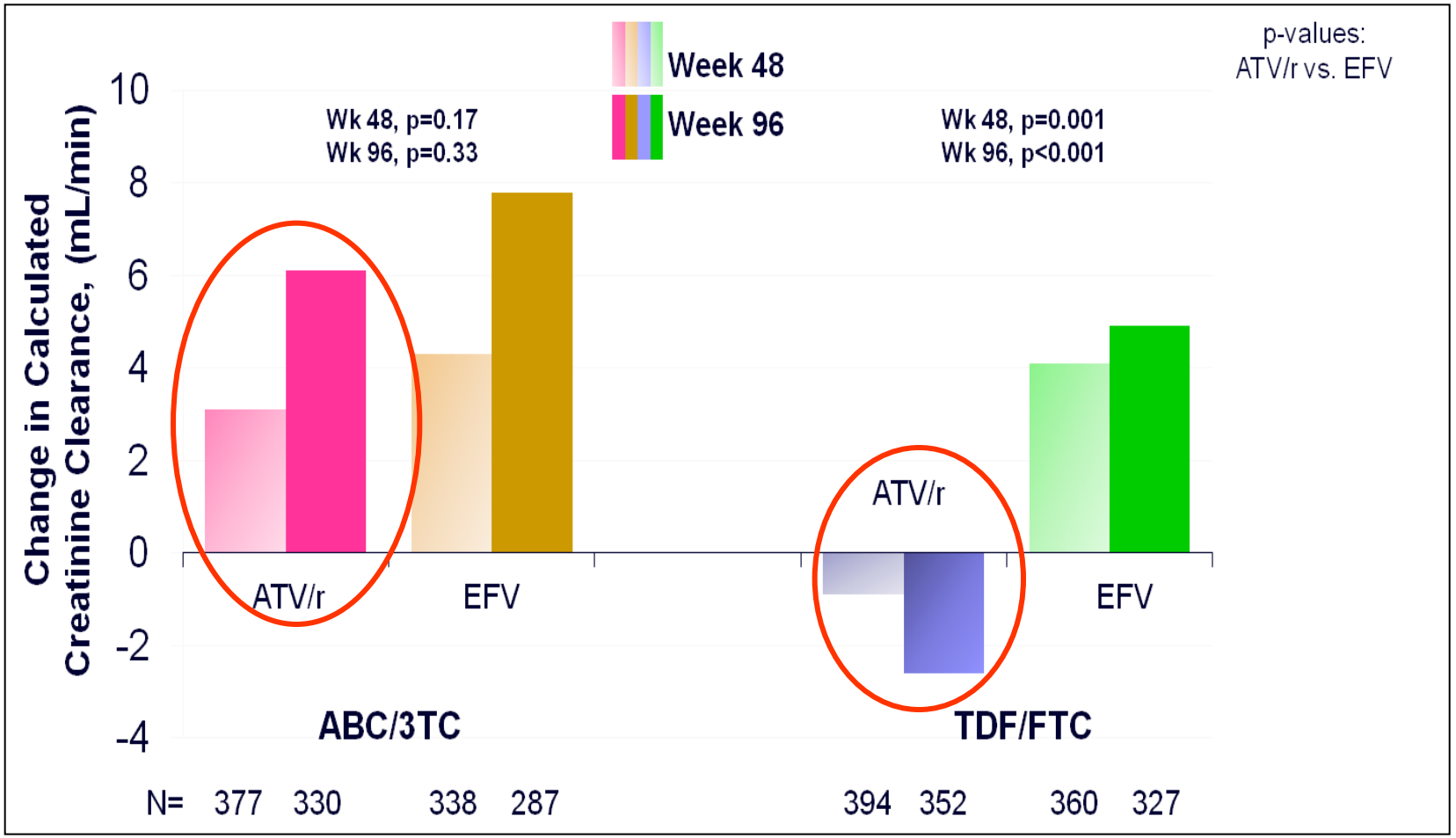
While this may reflect underlying CKD, alternatives to TDF should be considered in patients with progressive eGFR decline.

Factors associated with incomplete eGFR recovery were: a **hight eGFR at TDF start**, a **lover eGFR at TDF discontinuation**, **longer time exposed to TDF**, **rapid decline on TDF** and older age.

ACTG 5202 - ATV/r vs. EFV

Median Change in Creatinine Clearance

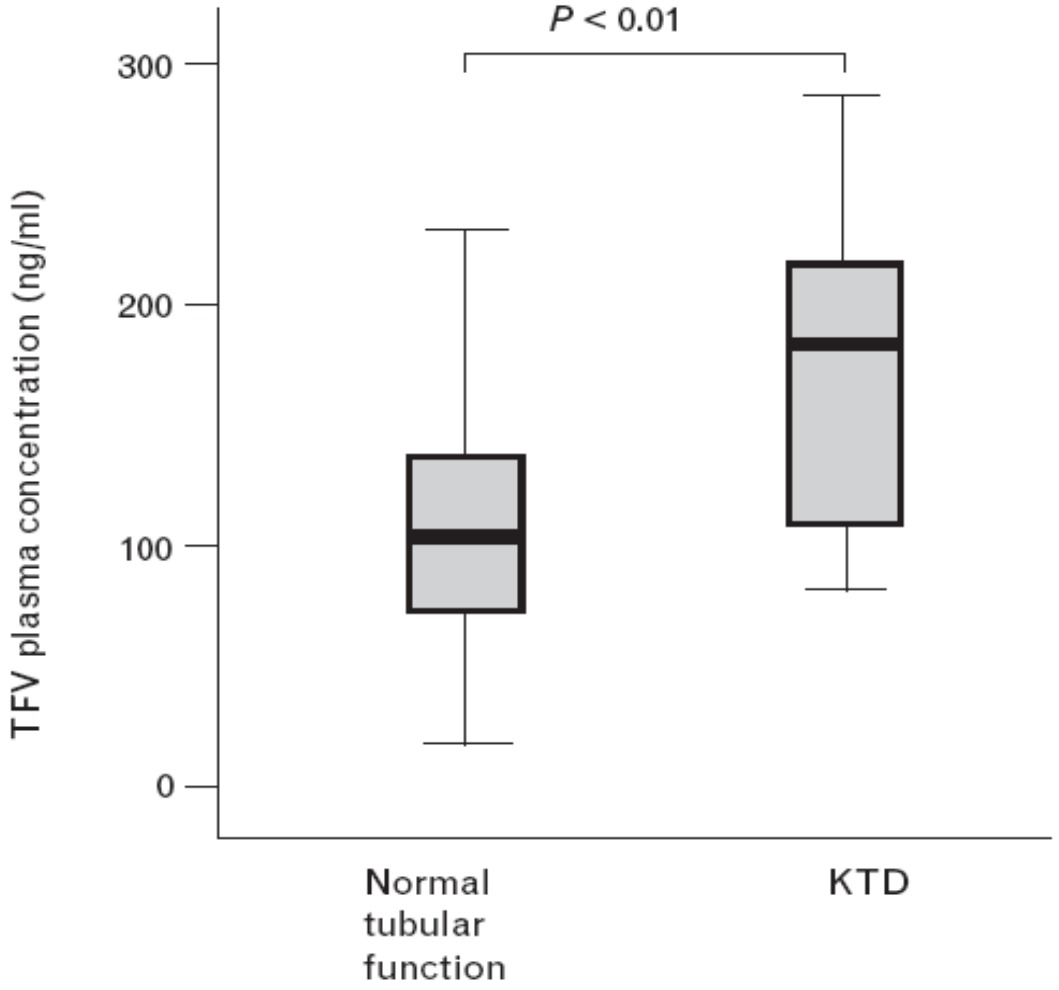
End of study: all patients (as treated)



Daar, E et al. 17th CROI 2010. Abstract 59LB

Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations

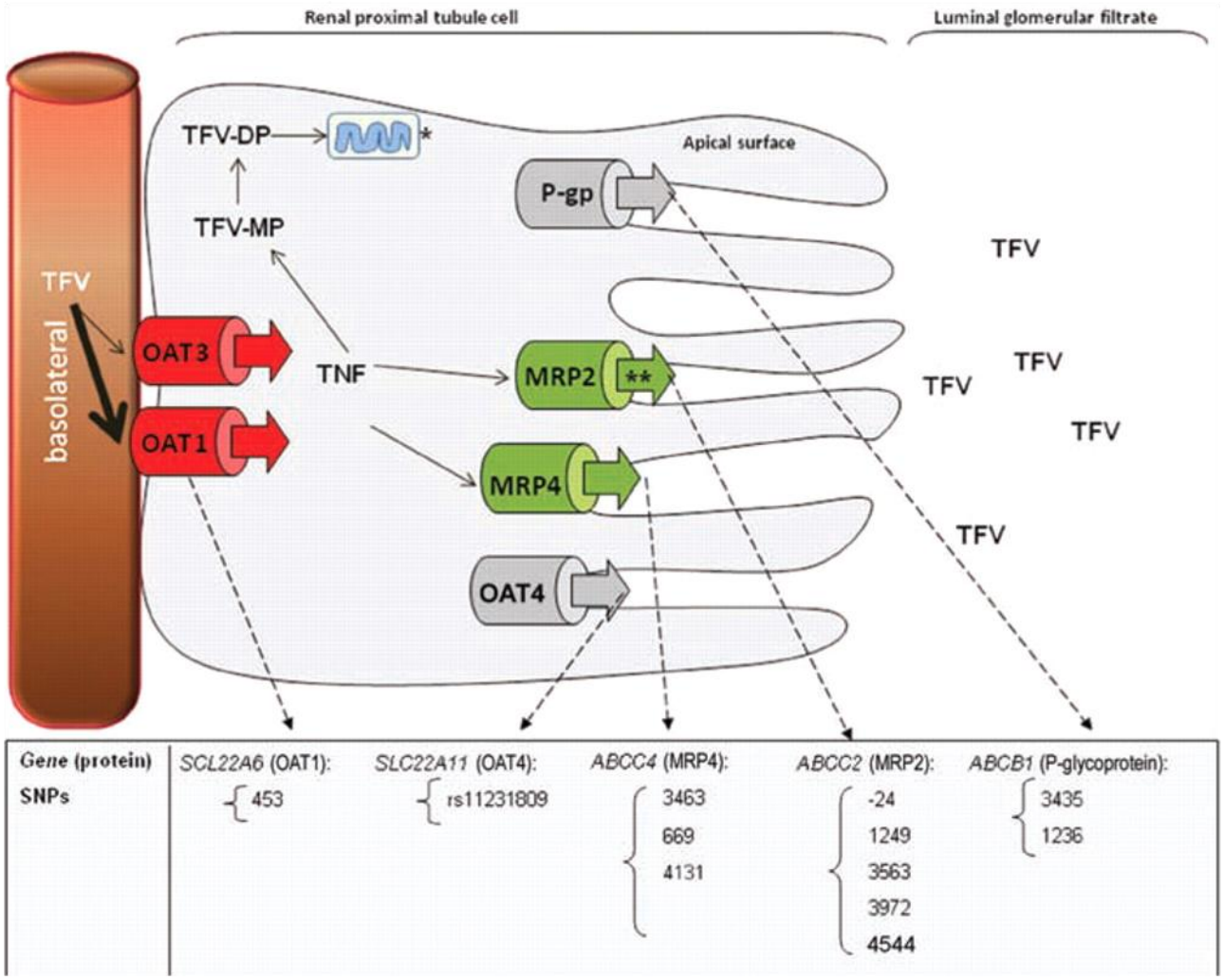
Sonia Rodríguez-Nóvoa[a], Pablo Labarga[a], Antonio D'Avolio[b], Pablo Barreiro[a], Marta Albalate[c], Eugenia Vispo[a], Carmen Solera[a], Marco Siccardi[b], Stefano Bonora[b], Giovanni Di Perri[b] and Vincent Soriano[a]



AIDS 2010, **24**:1063–1075

Clinical Infectious Diseases

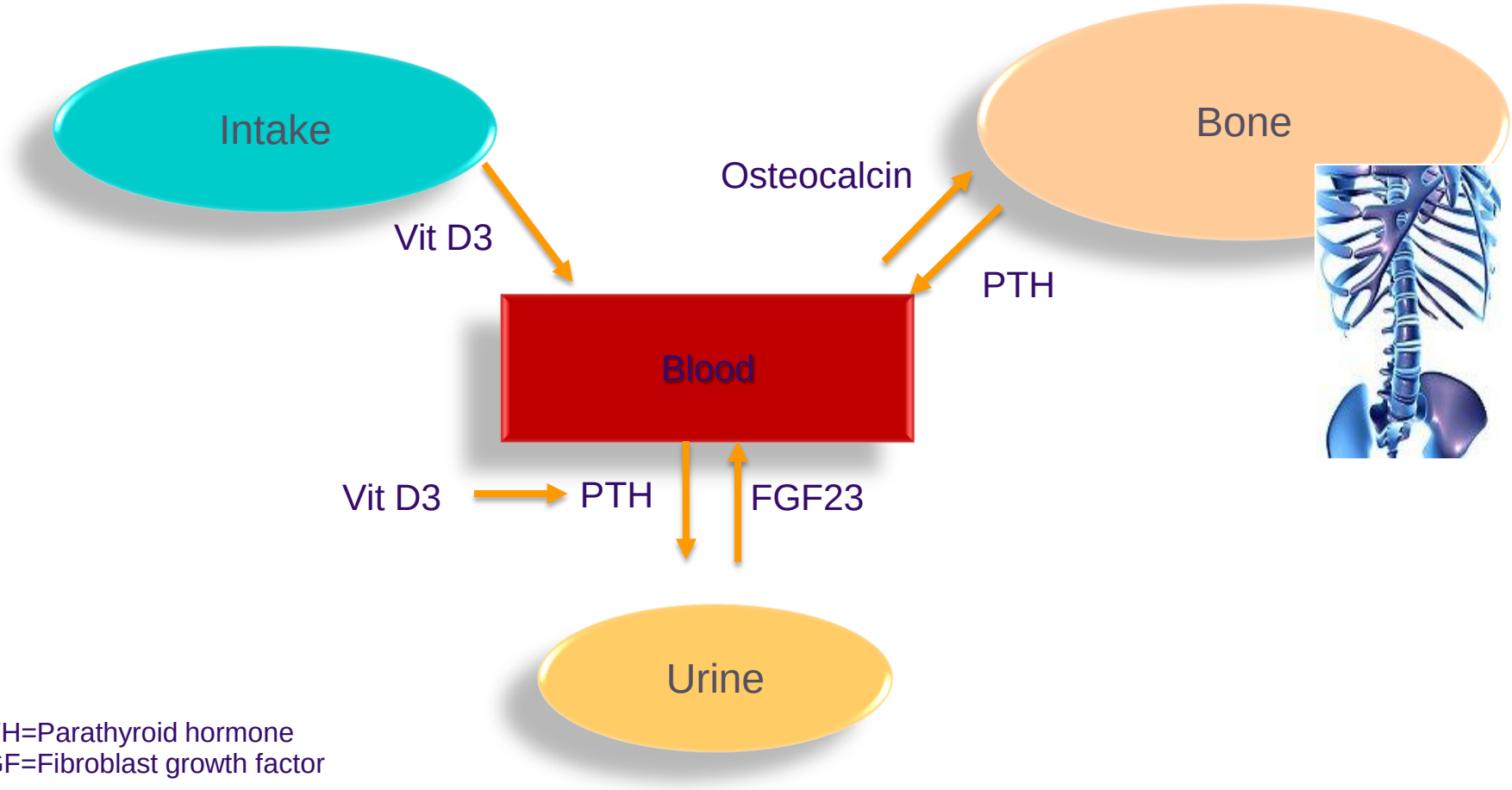
Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with Tenofovir: A Pharmacogenetic Study



Protein transporters involved in tenofovir (TFV) elimination at basolateral and luminal surface of the proximal renal tubule.

Rodríguez-Nóvoa S et al. Clin Infect Dis. 2009;48:e108-e116

Tubular lesions can be associated with Phosphaturia

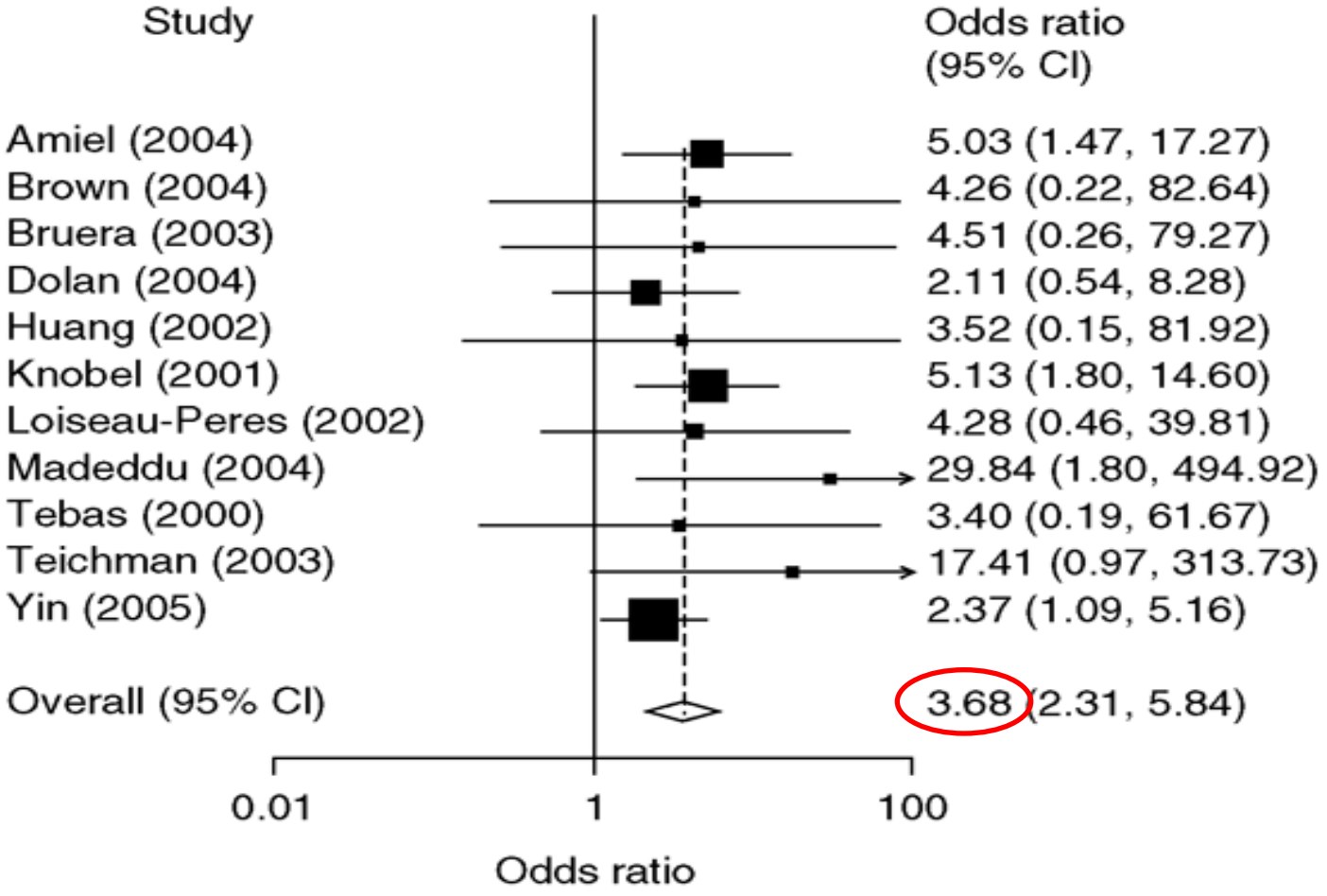


PTH=Parathyroid hormone
FGF=Fibroblast growth factor

Essig M, et al. *J Acquir Immune Defi Syndr.* 2007;46:256–8

cART e alterazione dell'omeostasi ossea

Odds of osteoporosis in HIV-infected patients compared with HIV-uninfected controls



Brown and Qaqish. *AIDS* 2006;20:2165-74

Low Bone Mineral Density is Associated with Increased Risk of Incident Fracture in HIV-infected Adults (HOPS & SUN Studies)

Table 4: Factors associated with incident fracture among the cohort (N=1,008 patients, 95 incident fractures)

Independent variables	Univariate HR (95% CI)	Multivariable HR (95% CI)
Age (per 10 years)	1.41 (1.13-1.76)*	1.35 (1.07-1.70)*
CD4+ count (per 100 cells/mm^3)	1.04 (0.97-1.11)	
Nadir CD4+ count (per 100 cells/mm^3)	1.00 (0.88-1.14)	
Female sex	0.66 (0.37-1.19)	
IDU HIV risk (vs. MSM HIV risk)	1.38 (0.66-2.87)	
Public insurance (vs. private/other)	1.26 (0.82-1.93)	
Hepatitis C	1.64 (0.99-2.71)	
Current/prior tobacco smoker	1.60 (1.05-2.44)*	1.53 (1.01-2.34)*
Osteopenia (hip T-score < -1.0)	1.21 (0.79-1.85)	1.04 (0.67-1.62)
Osteoporisis* (hip T-score < -2.5)	3.98 (1.96-8.11)*	3.03 (1.46-6.29)*

* p-value < 0.05

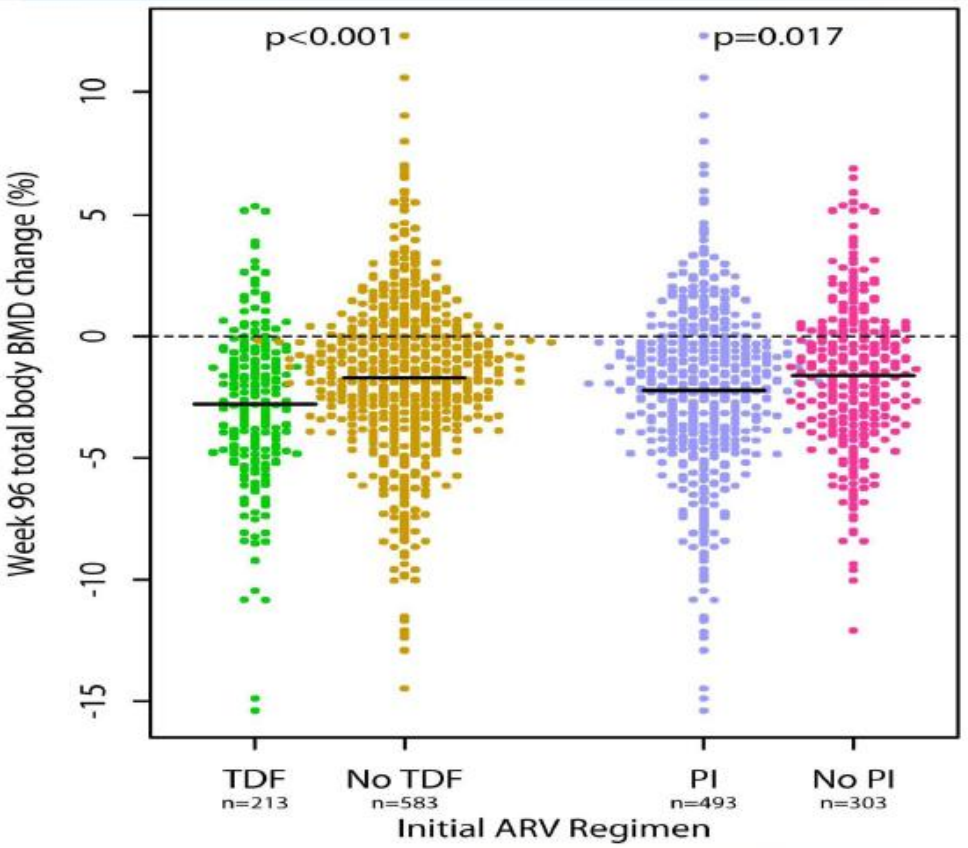
Abbreviations: HR, hazard ratio; CI, confidence interval; IDU, intravenous drug use; MSM, men who have sex with men.

Conclusions: In a large convenience sample of relatively young HIV-infected adults in the U.S., low baseline BMD and increasing age were strongly associated with elevated risk of incident fracture, highlighting the **potential value of DEXA screening** in this population..

Battalora,L. et al. CROI 2014. Abstract 781

Combined Analysis of ART-initiation Studies in the ACTG

Week 96 BMD Change by Initial ARV Regimen



Grant P, CROI 2013 # 823

Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents

Roger Bedimo, Naim M. Maalouf, Song Zhang, Henning Drechsler and Pablo Tebas

AIDS 2012, **26**:825–831

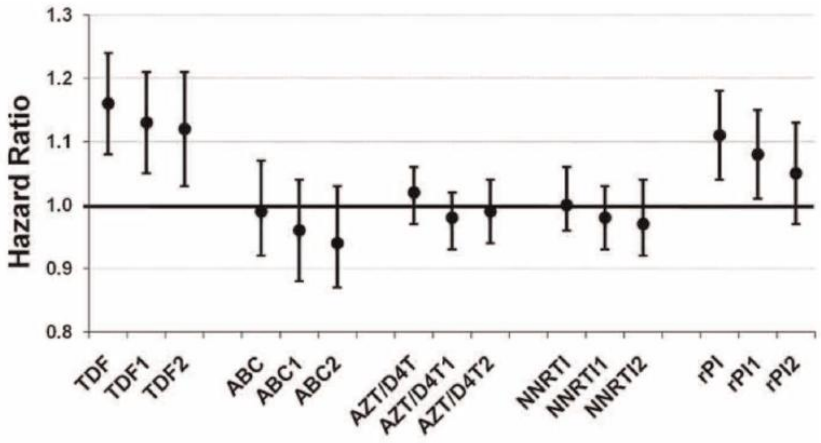


Fig. 2. Antiretroviral Exposure and Risk of Osteoporotic Fractures: 1996–2009. ABC, Abacavir; AZT/D4T, Zidovudine or Stavudine; NNRTI, Non-nucleoside reverse transcriptase inhibitors; rPI, ritonavir-boosted protease inhibitors; TDF, Tenofovir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, race, tobacco use, diabetes and BMI (MV Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concomitant exposure to other antiretrovirals.

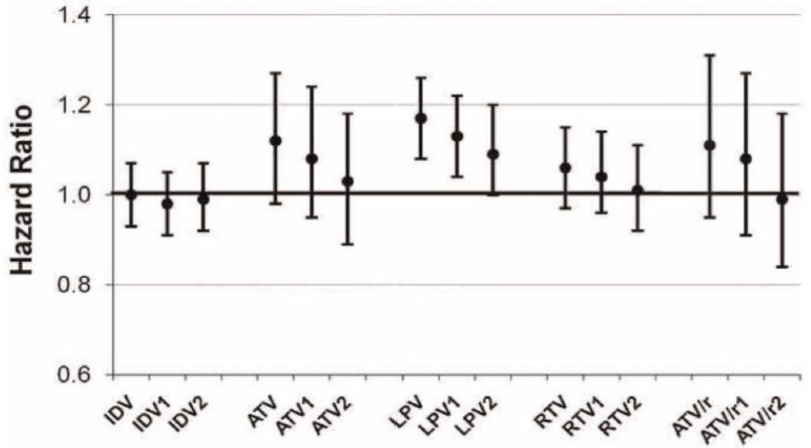


Fig. 3. Exposure to Specific Protease Inhibitors and Risk of Osteoporotic Fractures: HAART era (1996–2009). ATV, Atazanavir; ATV/r, ritonavir-boosted atazanavir; IDV, Indinavir; LPV, Lopinavir/Ritonavir; NFV, Nelfinavir; RTV, Ritonavir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, race, tobacco use, diabetes and BMI (MV Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concomitant exposure to other antiretrovirals.

Conclusion: Cumulative exposure to TDF and, among PIs, LPV/RTV were independently predictive of increased risk of OF in the HAART era.

Overall benefit of antiretroviral treatment on the risk of fracture in HIV: nested casecontrol analysis in a health-insured population

Linda M. Mundy, Ada O. Youk, Grace A. McComsey and Steve J. Bowlin

Objectives: Fractures are common and associated with multiple risk factors. We assessed the risks for fracture associated with time-dependent, differential antiretroviral drug exposures among a cohort of persons with human immunodeficiency virus (HIV) infection.

Design: Nested case-control study from an HIV cohort of 59,594 medically-insured persons with HIV infection enrolled in a medical care between January 1997 and March 2008.

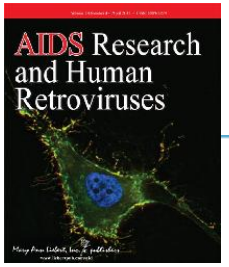
Methods: Cases were subjects with a low-impact, non-traumatic fracture identified by ICD-9-CM codes; non-cases were 1:4 matched and without fracture.

Results: Cases comprised 2,411 persons with HIV infection with fractures who were risk-set matched to 9,144 persons with HIV infection without fractures. Exposure to antiretroviral (ARV) therapy by drug class and by duration (any drug/class) was associated with reduced risk for fracture. Drug-specific ARV exposures over time identified an increased risk for fracture associated with darunavir, delavirdine and saquinavir while reduced risk was associated with efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine. An initial null risk became a reduced risk with increased duration for nevirapine. In a similar pattern, abacavir, didanosine, nelfinavir, ritonavir and stavudine were initially associated with increased risk for fracture, after which the risk became null with increased duration of exposure. Null or uncertain risk for fracture was associated with amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and zalcitabine.

Conclusions: ur findings suggest an overall reduced risk for facture in persons treated versus not treated with ARV drugs for HIV infection. Differential drug-specific exposure-response relationships for fracture will need to be further evaluated in other study populations.

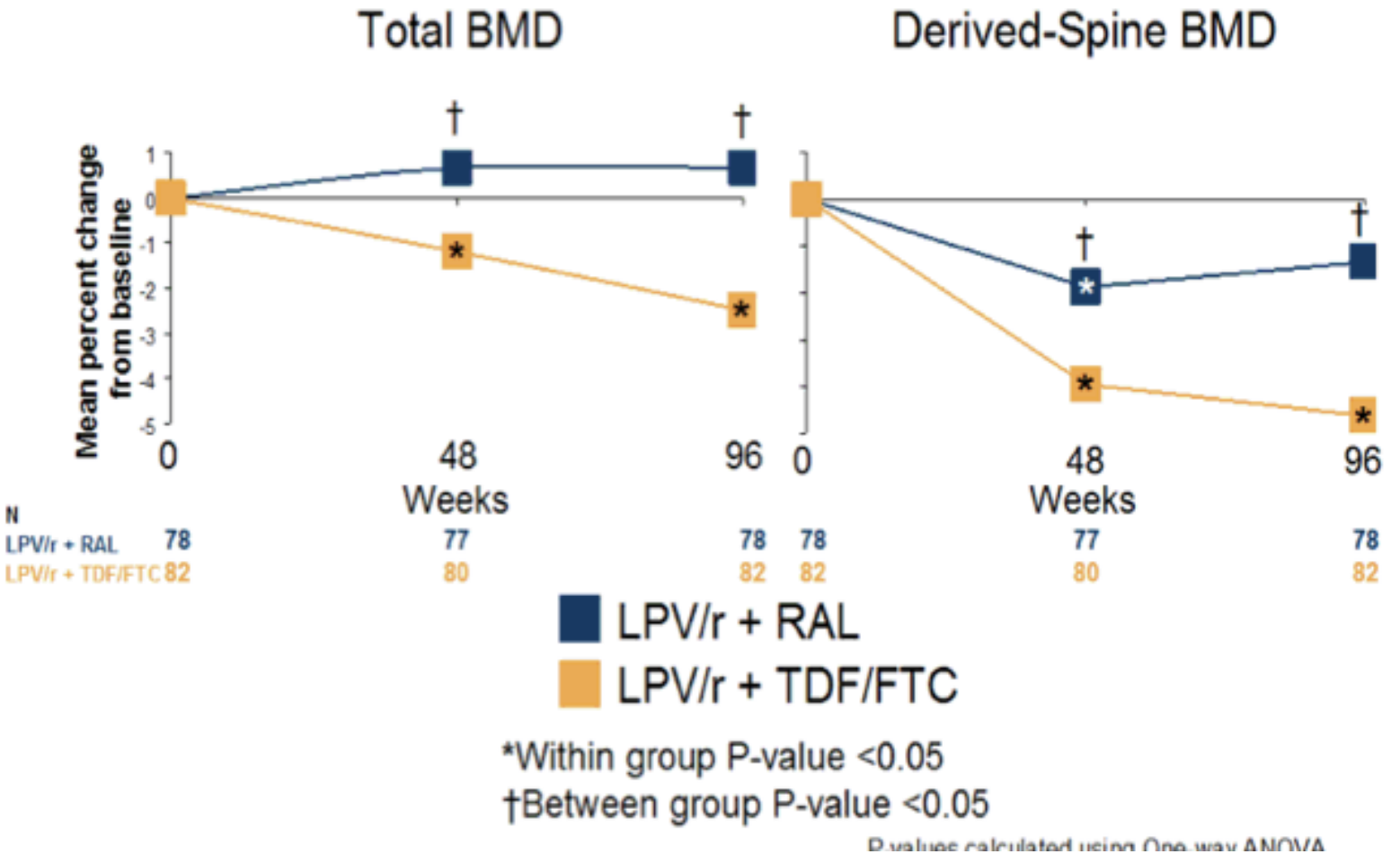
AIDS 2012, **26**:000–000

Keywords: antiretroviral drug, bone mineral density, fracture, HIV, risk



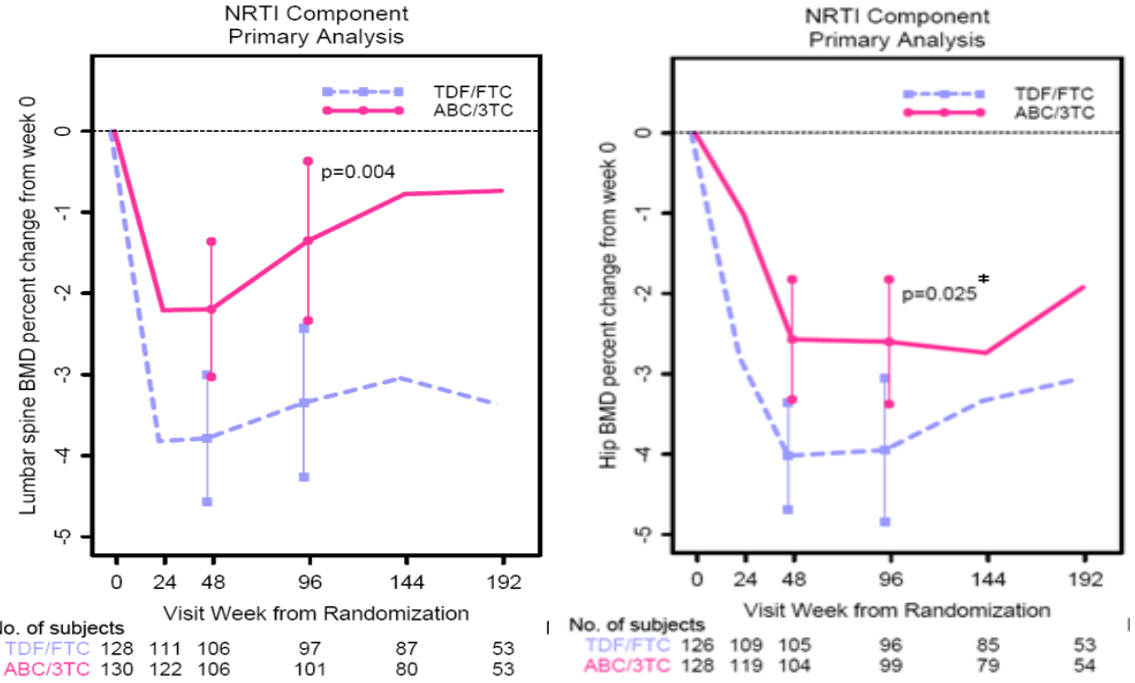
PROGRESS: BMD at Wk 96

Mean Percent Changes in Bone Mineral Density Analyzed Using DXA through 96 Weeks of Treatment



Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202

Grace A. McComsey,1 Douglas Kitch,2 Eric S. Daar,5 Camlin Tierney,2
Nasreen C. Jahed,7 Pablo Tebas,8 Laurie Myers,
9 Kathleen Melbourne,6 Belinda Ha,10 and Paul E. Sax3,4

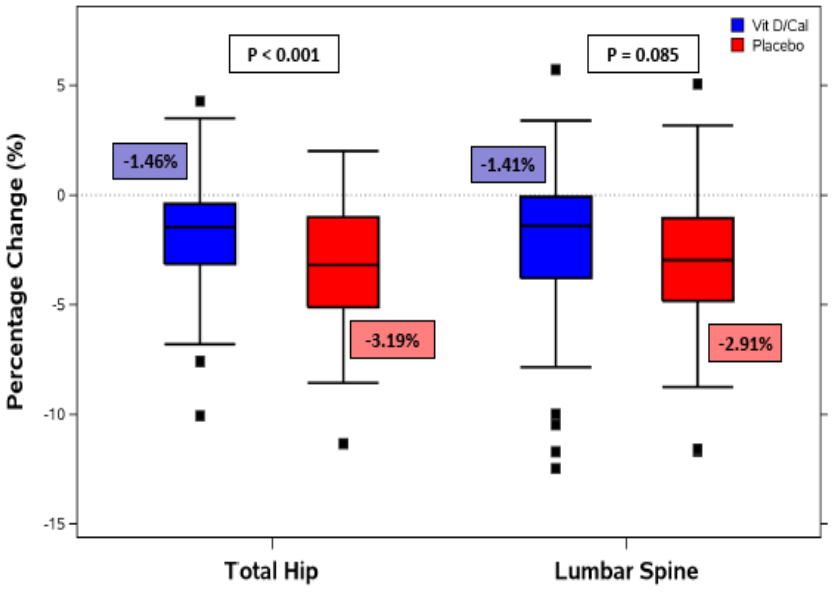


Conclusions. Compared with ABC-3TC, TDF-FTC–treated participants had significantly greater decreases in spine and hip BMD, whereas ATV/r led to more significant losses in spine, but not hip, BMD than EFV.

JID 2011:203 (15 June); 1791-1801

Vitamin D/Calcium Supplements Ease Bone Loss When Starting EFV/TDF/FTC

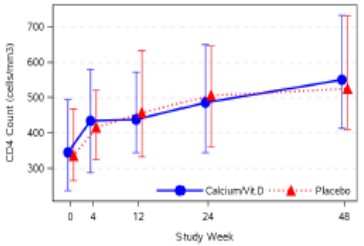
Percent Decline in BMD from Baseline to 48 Weeks



The lower and upper edges of the box indicate the first and third quartiles (the 25th and 75th percentiles); The line inside the box indicates the median value.

Other Findings

- HIV Parameters
  - 90% of subjects achieved virologic suppression
  - Similar CD4 increases in both arms
    - Vitamin D/Calcium: 192 c/mm³
    - Placebo: 201 c/mm³



- No differences in changes in inflammatory biomarkers between the two arms.
  - IL-6, sTNFr-I, sTNFr-II, sCD14
- No differences in changes in metabolic parameters
  - Lipids, glucose, weight
- Safety
  - 103 subjects (62%) experienced at least one adverse events.
    - 50 subjects in vitamin D/Ca arm (33 with Grade ≤ 2, 15 with Grade 3)
    - 53 subjects in placebo arm (33 with Grade ≤ 2, 15 with Grade 3)
  - No cases of hypercalcemia
  - 1 incident nephrolithiasis in placebo arm
  - 1 death on vitamin D/calcium arm

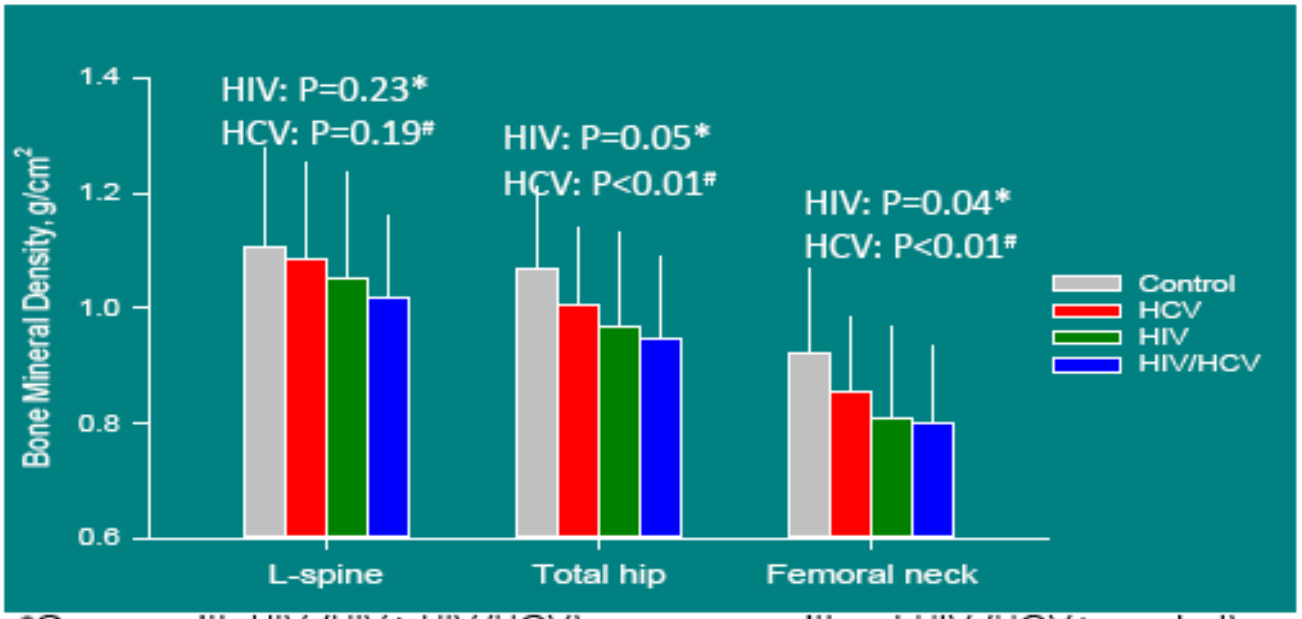
Conclusions: Daily high-dose vitamin D and calcium supplements reduced total hip bone loss 50% in a 48-week placebo-controlled trial that enrolled people starting efavirenz plus tenofovir/emtricitabine

Overton ET, et al. CROI 2014. Abstract 133.

Mechanism of Bone Disease in HIV and HCV: Impact of Tenofovir Exposure and Severity of Liver Disease

A. HIV and HCV Independently Lower BMD

Controlling for age, race and BMI (**model 1**)



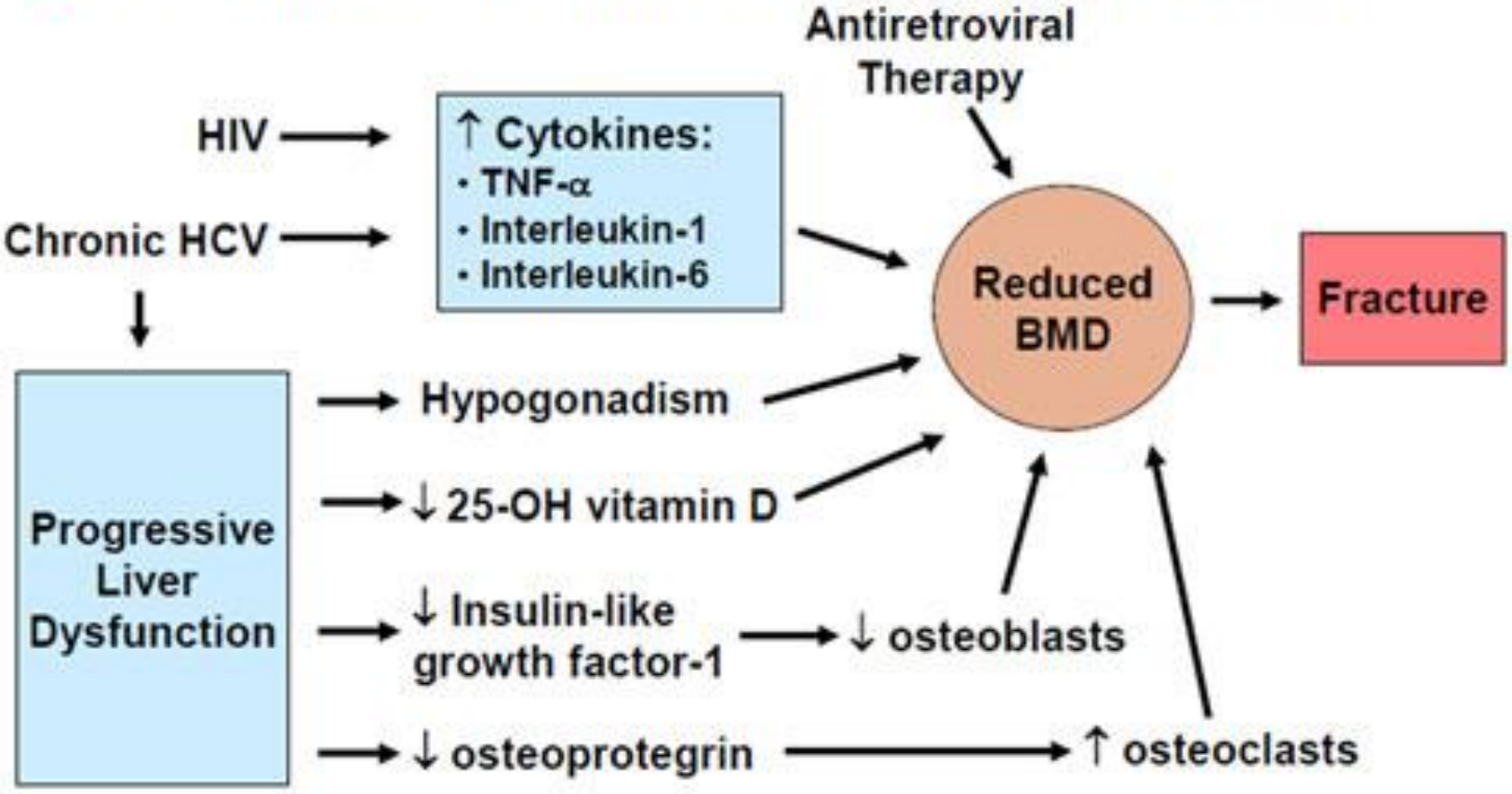
*Groups with HIV (HIV+ HIV/HCV) vs. groups without HIV (HCV+ control)

Groups with HCV (HCV+ HIV/HCV) vs. groups without HCV (HIV + control)

Conclusions: The impact of HIV on BMD appears to be explained (at least in large part) by TDF exposure and higher bone turnover. HCV association with BMD is independent of the severity of liver disease, as measured by APRI score.

Curell,J.et al. CROI 2014. Abstract 783.

- HIV and HCV infections are each associated with reduced bone density
- Coinfection might exacerbate bone loss and increase fracture risk
- Below is a model for mechanisms for low bone density and fracture:

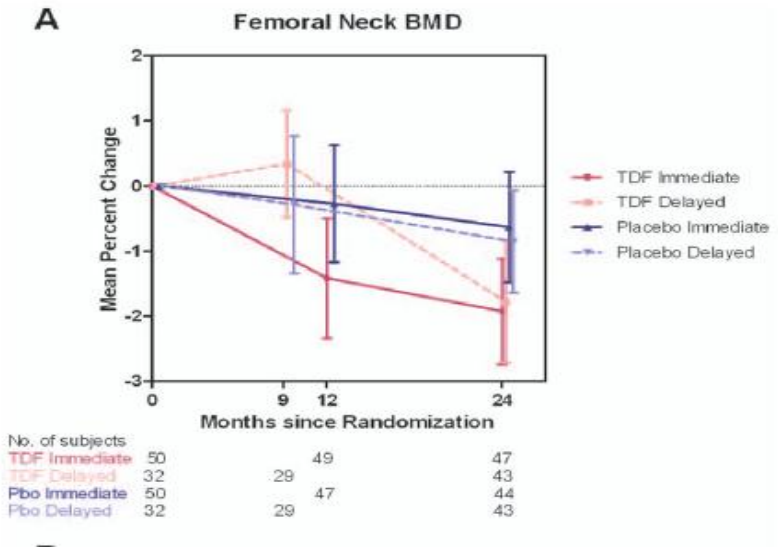


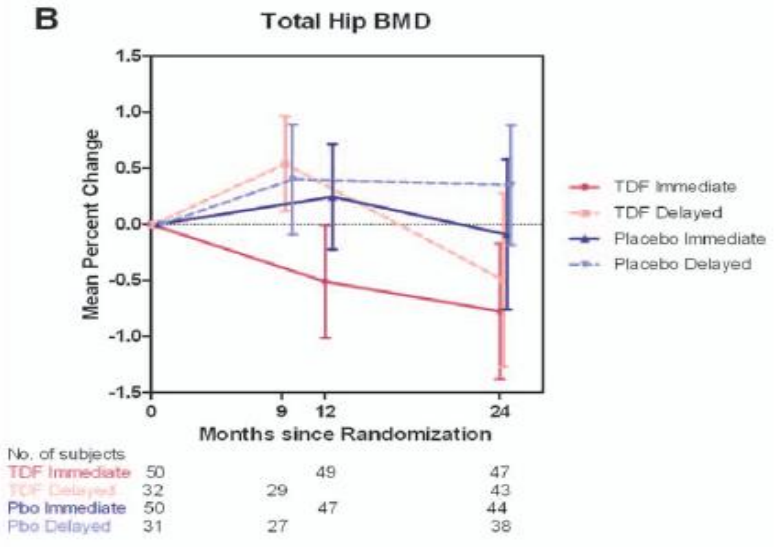
OPEN ACCESS Freely available online

PLoS one

Bone Mineral Density in HIV-Negative Men Participating in a Tenofovir Pre-Exposure Prophylaxis Randomized Clinical Trial in San Francisco

Albert Y. Liu[1,2]*, Eric Vittinghoff[2], Deborah E. Sellmeyer[3], Risha Irvin[1], Kathleen Mulligan[2], Kenneth Mayer[4], Melanie Thompson[5], Robert Grant[2,6], Sonal Pathak[7], Brandon O'Hara[7], Roman Gvetadze[7], Kata Chillag[8], Lisa Grohskopf[8], Susan P. Buchbinder[1,2]





In summary, we found a significant proportion of HIV uninfected men had low BMD at baseline. Low BMD was associated with methamphetamine and inhalant use. Similar adverse effects of TDF on BMD were seen in this cohort of HIV uninfected MSM as seen in antiretroviral treatment studies of TDF-based regimens in HIV-infected individuals. These data suggest that low BMD may pre-date HIV infection among men at risk for acquisition of HIV, and use of tenofovir in these individuals leads to a small but statistically significant decline in BMD. The decline was not associated with an elevated fracture risk during the study.

Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate (Pediatric HIV/AIDS Cohort study - PHACS Study)

Maternal ARV Regimens (Regimens taken by ≥ 3% of women)

Study Arm	Maternal ARV regimen	N (%)
TDF Arm (n=74)	TDF-FTC-ATVr	38 (52%)
	TDF-FTC-DRVr	12 (16%)
	TDF-FTC-RAL	6 (8%)
	TDF-FTC-LPVr	4 (5%)
	Other	14 (19%)
No-TDF Arm (n=69)	ZDV-3TC-LPVr	27 (41%)
	ABC-3TC-ZDV	14 (21%)
	ZDV-3TC-DRVr	4 (6%)
	Other	24 (32%)

Multivariable Model: Adjusted Mean BMC Lower in TDF Arm

	Adjusted* Mean Difference in BMC	P value
Whole-body BMC	6.4g lower in TDF arm (95%CI: 2.1, 10.7)	0.004
	Reminder: Unadjusted mean BMC diff: 7.8g	

*Adjusted for:
- site;
- infant gestational age, body length, race/ethnicity and age at DXA;
- maternal boosted PI use, age, and smoking.

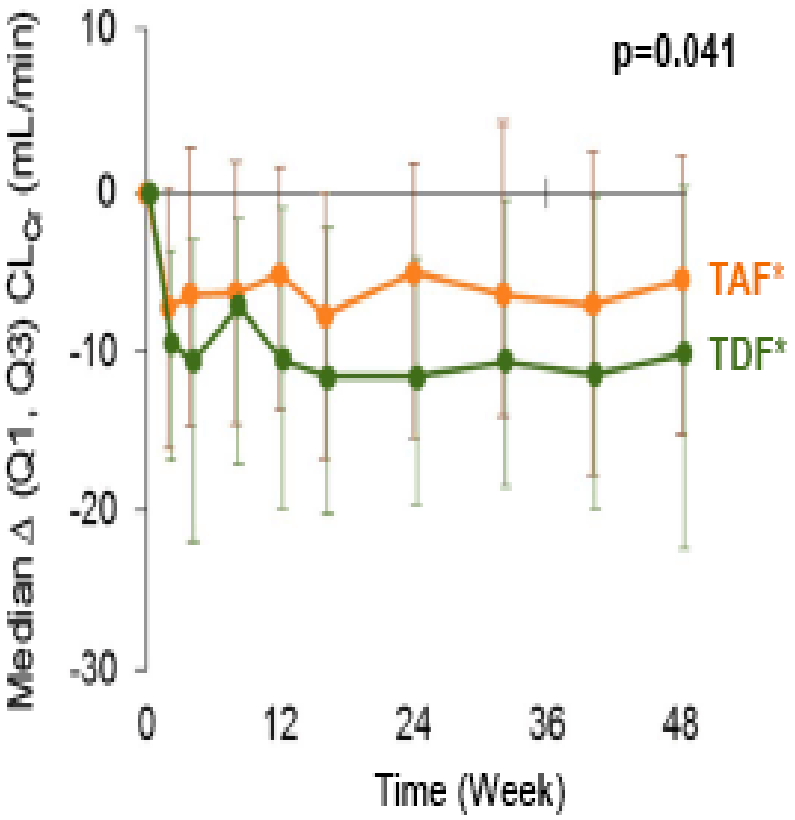
Similar results when whole-body BMC analyzed without head

Conclusions: Conclusions: Maternal TDF use is associated with a significant reduction in neonatal BMC that persists after adjustment for other factors. The duration and clinical significance of this finding merit evaluation in longitudinal studies.

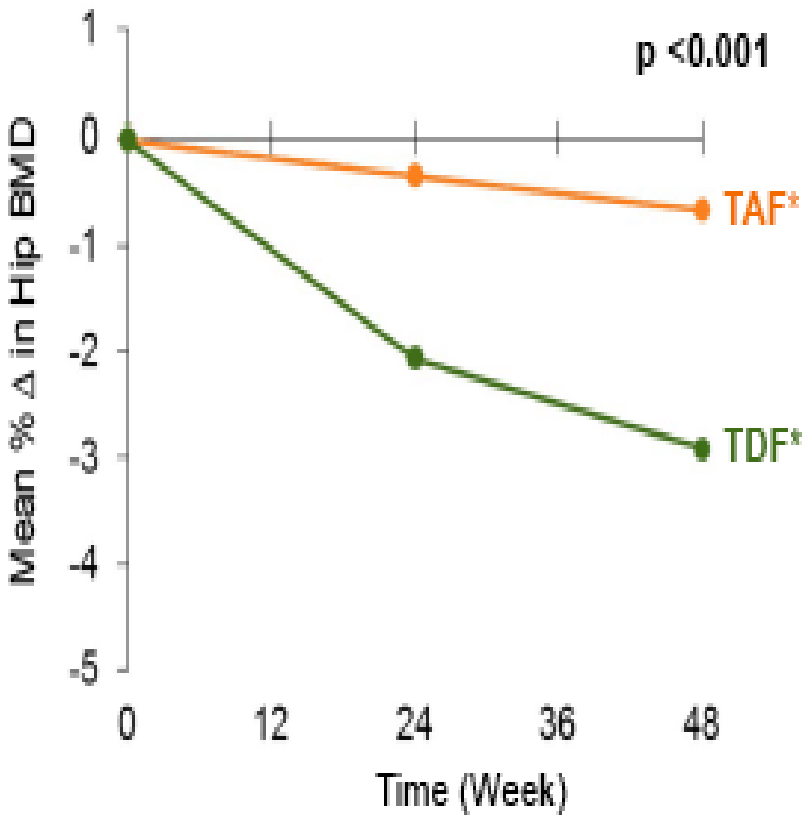
Siberry GK, et al. CROI 2014. Abstract 71LB.

Safety of TAF in HIV Infection (Phase 2)

Creatinine Clearance



Hip Bone Mineral Density



Challenge	Management (cART)
High CV Risk/Lipids	↓Ritonavir; PIs; Abacavir???
Hepatitis/Cirrhosis	↓Liver Toxicity; "Good PK"
Older Age	↓Ritonavir; "Good PK"; Simple
Pregnancy	↑Safety; "Good PK"
Osteopenia/Osteoporosis	↓TDF; Non-HAART Issues (Vit D, etc)
Renal Insufficiency	↓TDF
Polypharmacy	↓Ritonavir; Good Interaction Profile
Neurocognitive Disorder	↑CNS Penetration; ↓Neurotoxicity
Psychiatric Disease	↓EFV? Good Interaction Profile; Simple
Poor Adherence	STR, Tolerable, High Genetic Barrier
Advanced HIV Disease	↑Efficacy (Low CD4; High VL)
Lipoatrophy	↓Thymidine analogs. 3rd drug?
Cost	↓Price

Ministero della Salute

SCHEDA UNICA DI SEGNALAZIONE DI SOSPETTA REAZIONE AVVERSA (ADR)

(da compilarsi a cura dei medici o degli altri operatori sanitari e da inviare al Responsabile di farmacovigilanza della struttura sanitaria di appartenenza)

1. INIZIALI DEL PAZIENTE __ __	2. DATA DI NASCITA	3. SESSO	4. DATA INSORGENZA REAZIONE	5. ORIGINE ETNICA	CODICE SEGNALAZIONE

6. DESCRIZIONE DELLA REAZIONE ED EVENTUALE DIAGNOSI* ** se il segnalatore è un medico*

7. GRAVITA' DELLA REAZIONE:

◊ **GRAVE**
- ☐ DECESSO
- ☐ OSPEDALIZZAZIONE O PROLUNGAMENTO OSPED.
- ☐ INVALIDITA' GRAVE O PERMANENTE
- ☐ HA MESSO IN PERICOLO DI VITA
- ☐ ANOMALIE CONGENITE/ DEFICIT NEL NEONATO

◊ **NON GRAVE**

8. EVENTUALI ESAMI DI LABORATORIO RILEVANTI PER ADR: *riportare risultati e date in cui gli accertamenti sono stati eseguiti*

9. ESITO
- ◊ RISOLUZIONE COMPLETA ADR IL __/__/__
- ◊ RISOLUZIONE CON POSTUMI
- ◊ MIGLIORAMENTO
- ◊ REAZIONE INVARIATA O PEGGIORATA
- ◊ DECESSO IL __/__/__
  - ☐ dovuto alla reazione avversa
  - ☐ il farmaco può avere contribuito
  - ☐ non dovuto al farmaco
  - ☐ causa sconosciuta
- ◊ NON DISPONIBILE

10. AZIONI INTRAPRESE: *specificare*

In caso di sospensione compilare i campi da 16 a 19

INFORMAZIONI SUL FARMACO