Paolo Maggi

Minority Report

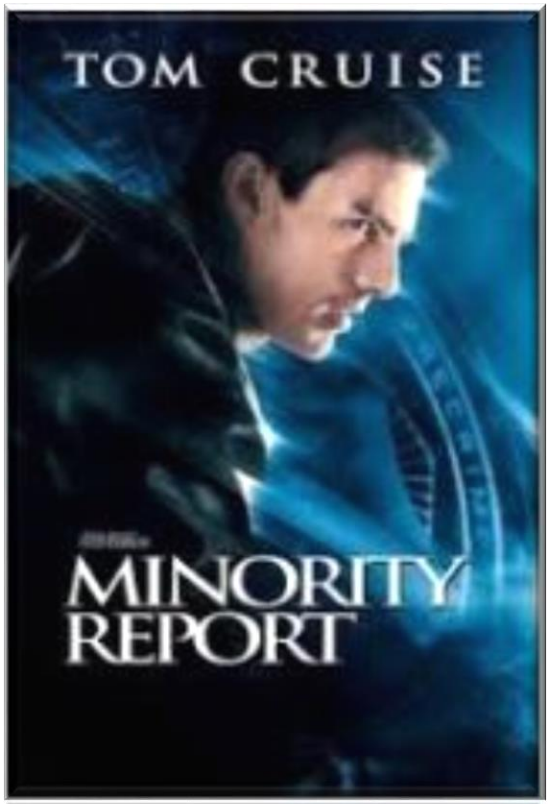
Indizi dalla letteratura: ciò che potrà riservarci il futuro

8° WORKSHOP NAZIONALE CISAI
PERUGIA, 30 - 31 MARZO 2017
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

Minority Report

may refer to:

"a committee report written by one or more members of a committee to officially state a position counter to the committee's majority" (From Wikipedia)



Minority reports:

- BMI: un grande ritorno
- Bilirubina: la vera protezione cardiovascolare?
- INI: davvero così CV friendly?
- Le relazioni pericolose: Statine e vitamina D
- I biologici risolveranno tutti i nostri problemi?

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OBESITY AND FATTY LIVER DISEASE

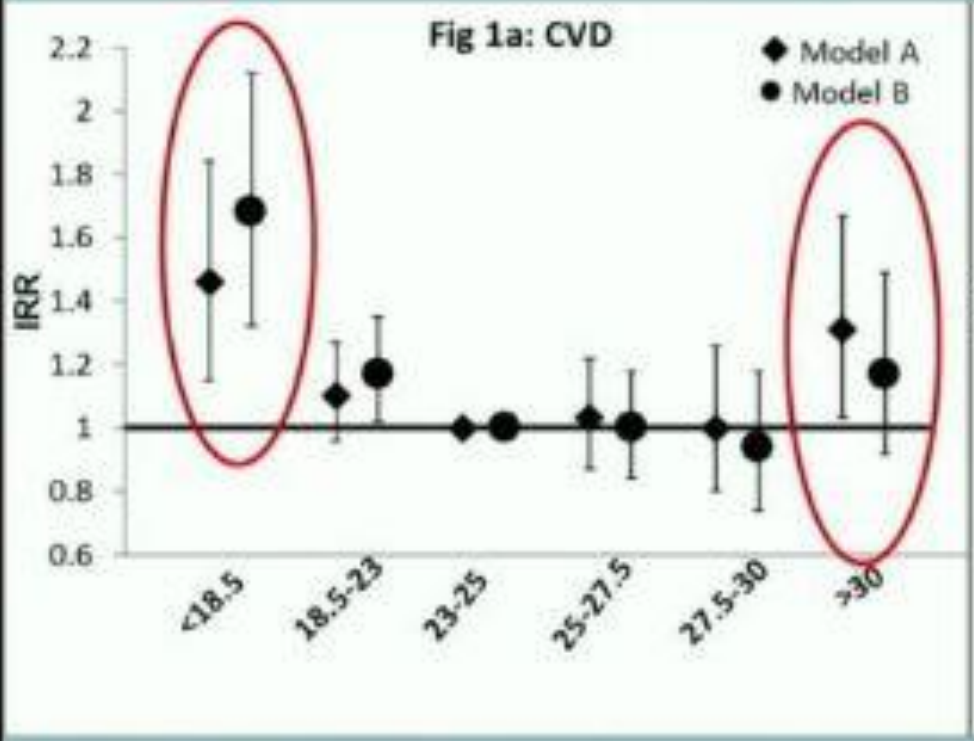
BODY MASS INDEX AND THE RISK OF SERIOUS NON-AIDS EVENTS: THE D:A:D STUDY

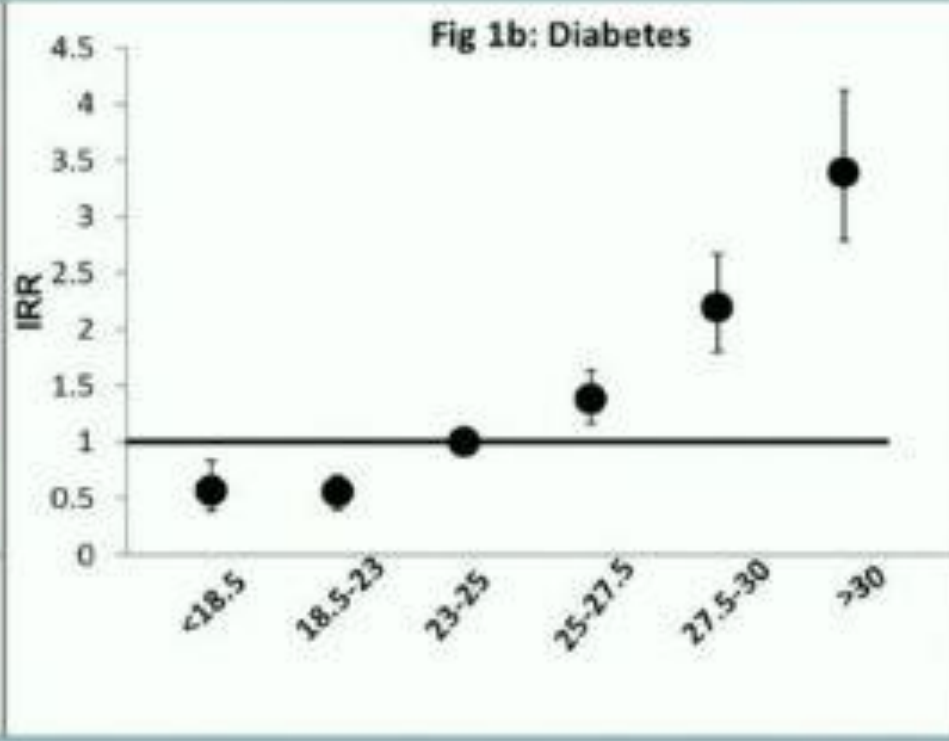
Amit C Achhra

Kirby Institute, UNSW Australia; & NCB Hosp and JJP VA Med Ctr, New York, USA

Results

Relative risk of each SNAE according to BMI





*Model B additionally adjusted for time-updated lipids, blood pressure and incident diabetes

Results

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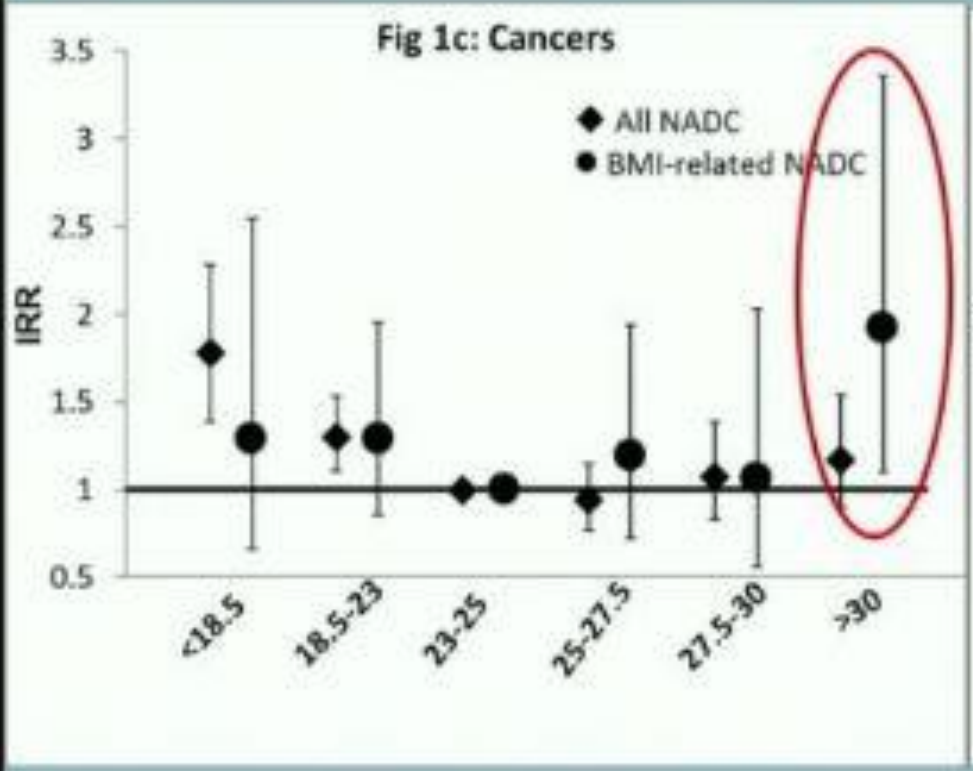

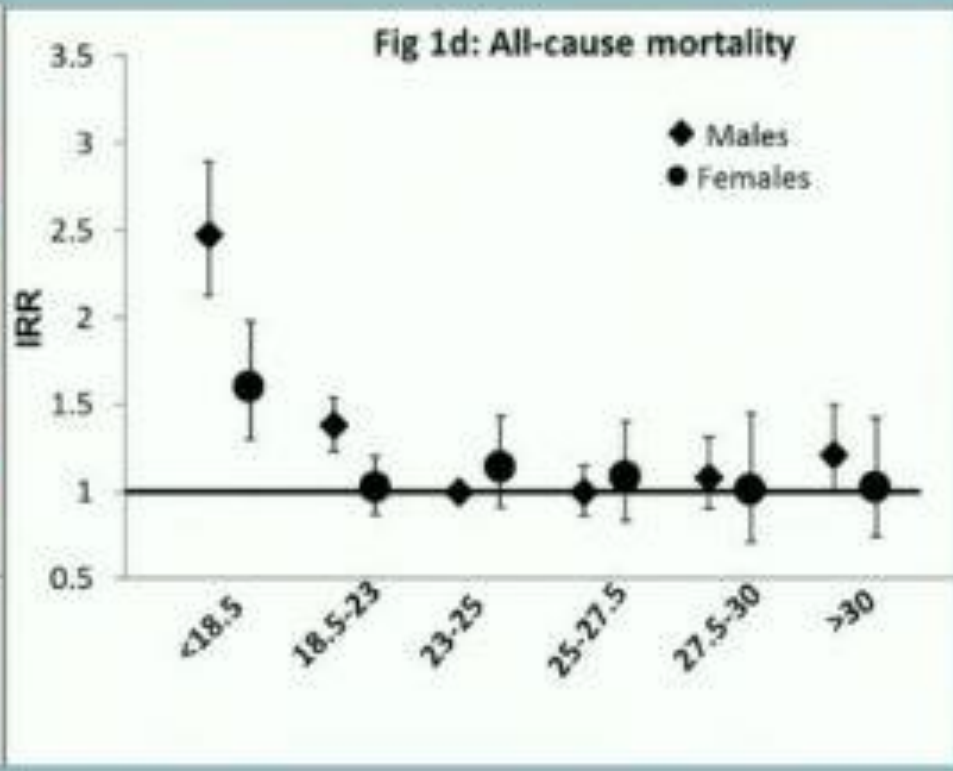

Conclusions

- Low BMI preceding an event by at least 1-2 years was associated with an increased risk of CVD, cancers and all-cause mortality.
  - Residual confounding by smoking can not be excluded
- Risk of SNAEs (except diabetes) only start to increase at very high levels of BMI (>30), with minimal increased risk even at BMIs of 25-30.
- Data are limited by fewer study participants at extreme BMI levels, especially >30. Also limitations of BMI as a marker of body weight/fat.
- Future work should evaluate optimum BMI in the HIV-positive population and assess how short term and long term changes in BMI relate to the risk of SNAEs.

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BODY-MASS INDEX AND ADJUDICATED HEART FAILURE IN A LARGE ELECTRONIC HIV COHORT

Matthew J . Feinstein

Heart failure is significantly more common among underweight and low-normal weight HIV+ patients and somewhat more common among obese HIV+ patients when compared with mildly overweight HIV+ patients. This **“reverse J-shaped”** association may reflect diverse pathophysiologies of HF in HIV, including chronic disease-related wasting for HIV+ patients with low-normal BMI versus traditional cardiovascular risk factor burden among obese HIV+ patients.

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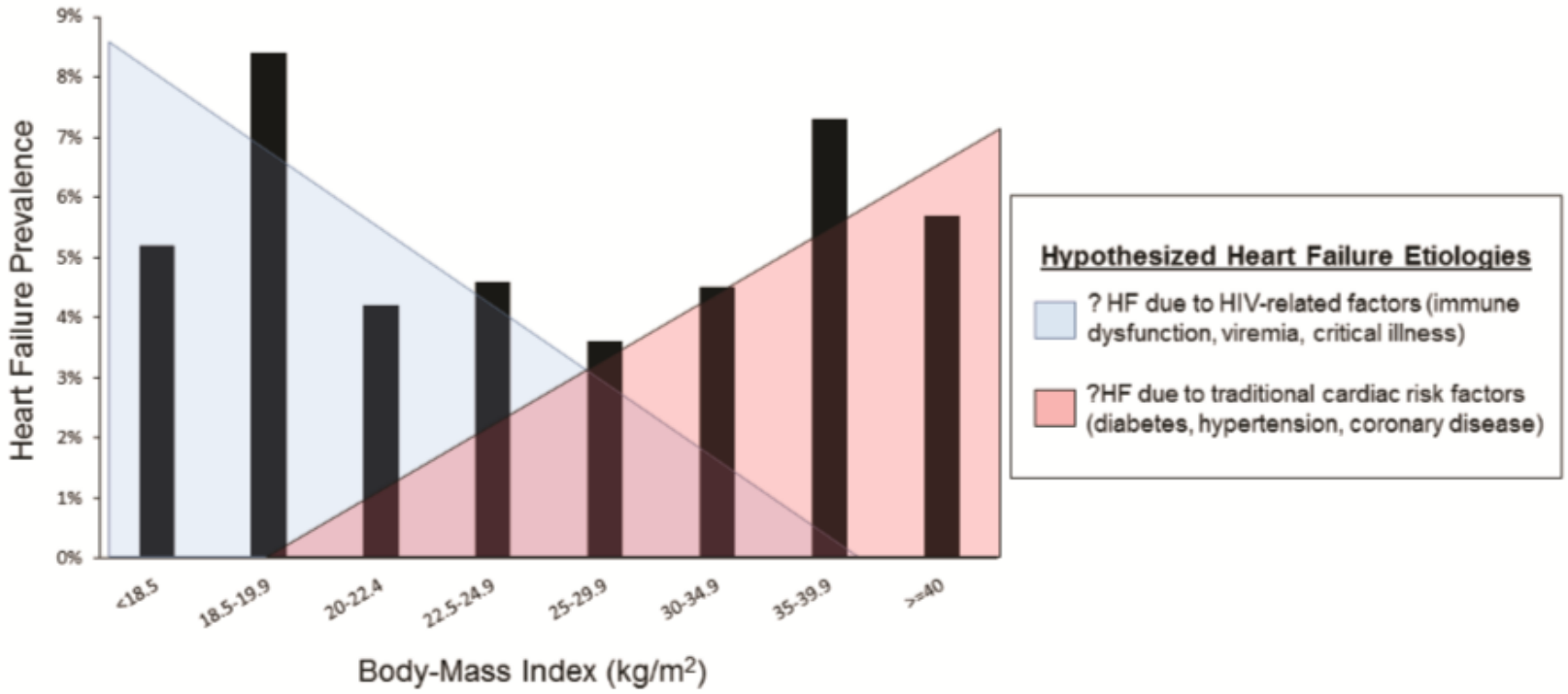
Matthew J . Feinstein

Figure. Heart Failure Prevalence among HIV-Infected Persons by Body-Mass Index



SIMIT
Società Italiana
di Malattie Infettive
e Tropicali

In collaborazione con:

Ministero della Salute

Sezioni L e M del Comitato Tecnico Sanitario

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

22 Novembre 2016

La prevenzione

Lo screening per le patologie non infettive HIV correlate è parte integrante della valutazione infettivologica [AII] [7], deve essere periodico e comunque va eseguito (o aggiornato) prima dell'inizio o di ogni cambiamento di terapia antiretrovirale [AIII] [17,18].

ANAMNESI		
VALUTAZIONI (*)	**FREQUENZA DEL FOLLOW-UP CON cART**	**COMMENTI**
Patologie non infettive pregresse e presenti	Alla presa in carico del paziente	Valutazione da ripetere in caso di trasferimento del paziente ad altro centro di cura.
Familiarità (es. per malattia cardiovascolare precoce: si intendono eventi cardiovascolari, diabete, ipertensione, insufficienza renale cronica).	Alla presa in carico del paziente	Malattia cardiovascolare precoce – eventi cardiovascolari in parenti di primo grado: uomini < 55 anni, donne < 65 anni.
Terapie farmacologiche concomitanti.	A ogni visita	
Stile di vita attuale e cattive abitudini per la salute: - Uso di sostanze ricreazionali (alcol, fumo, sostanze stupefacenti) - Dieta - Attività fisica	Ogni 6-12 mesi	Il danno tossico da alcol si esprime per un introito maggiore di 30 grammi al giorno nel maschio e 20 grammi nella femmina. Mezzo litro di vino: 50 grammi; Mezzo litro di birra: 20 grammi; Un superalcolico: 20 grammi.
(*) = Sempre alla diagnosi di HIV e prima di iniziare la cART.		

ANTROPOMETRIA		
VALUTAZIONI (*)	**FREQUENZA DEL FOLLOW-UP CON cART**	**COMMENTI**
Misurazione indice di massa corporea e circonferenza vita.	Una volta l'anno	L'esame obiettivo per la lipodistrofia deve essere segmentale, utilizzando, dove possibile, griglie di valutazione dell'entità della lipoatrofia e della lipoipertrofia separatamente.
Valutazione clinica della distribuzione del grasso corporeo..	Una volta l'anno, riservata a centri di riferimento	Gli strumenti della misura oggettiva della lipoatrofia e della lipoipertrofia comprendono la DXA (con misurazione della percentuale della massa grassa agli arti), la TC addome (con misurazione del grasso sottocutaneo viscerale).
(*) = Sempre alla diagnosi di HIV e prima di iniziare la cART.		

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Cumulative CVD Events and Hazard Ratios of UGT1A1*28 Genotype and Bilirubin Levels*

	Cumulative CVD Events , n (Events per 1000 Person-years			Hazard Ratio (95% Confidence Interval)		
	6/6 (820)	6/7 (769)	7/7 (191)	For 7/7 vs 6/6+6/7	For 0.1 mg/dL Bilirubin	For 7/7 vs 6/6/+6/7 Adjusted for Bilirubin
CVD cases	79 (4.24)	69 (3.93)	8 (1.78)	0.36 (0.18-0.74), *P*=0.006	0.90 (0.84-0.96), *P*=0.003	0.53 (0.25-1.15), *P*=0.108
CHD cases	60 (3.18)	52 (2.92)	5 (1.11)	0.30 (0.12-0.74), *P*=0.009	0.87 (0.81-0.96), *P*=0.001	0.50 (0.19-1.29), *P*=0.152
MI cases	26 (1.34)	29 (1.6)	4 (0.88)	0.52 (0.19-1.43), *P*=0.202	0.87 (0.78-0.97), *P*=0.013	0.96 (0.32-2.83), *P*=0.927

*At 24 years of Follow-up

- Significant associations between the UGT1A1*28 allele and decreased risk of CVD were found using the Cox proportional hazards model
- Individuals with genotype 7/7 (population frequency of 11%) had approximately one third the risk for CVD and CHD as carriers of the 6 allele, which resulted in a hazard ratio (95% CI) of 0.36 (0.18 to 0.74) and 0.30 (0.12 to 0.74), respectively

Lin J-P, et al. Circulation. 2006;114:1476-1481.

New approaches?

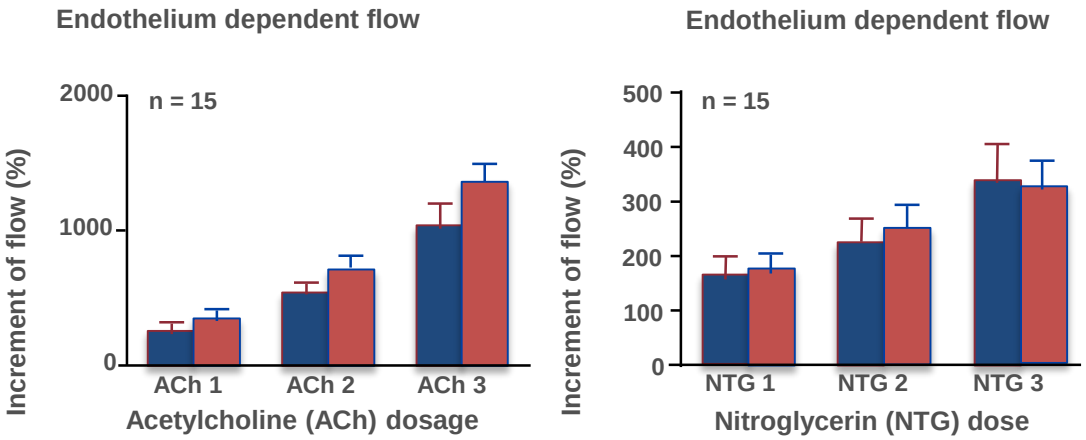
Heme oxygenase–carbon monoxide signalling pathway in atherosclerosis: anti-atherogenic actions of bilirubin and carbon monoxide?

Richard C.M. Siow, Hideyo Sato[1], Giovanni E. Mann*

Vascular Biology Research Centre, School of Biomedical Sciences, King's College London, Campden Hill Road, London W8 7AH, UK

Siow C.M. et al., Cardiovascular Research 1999; 41:385-394

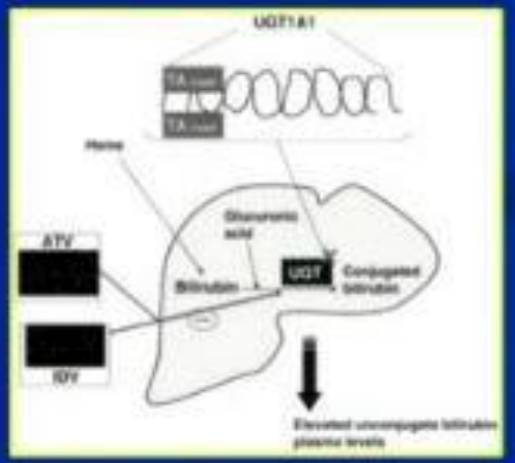
The bilirubin-increasing drug ATV improves endothelial function in patients with Type 2 Diabetes Mellitus (T2DM)



Dekker D et al.Arterioscler Thromb Vasc Biol 2011; 31:458–463

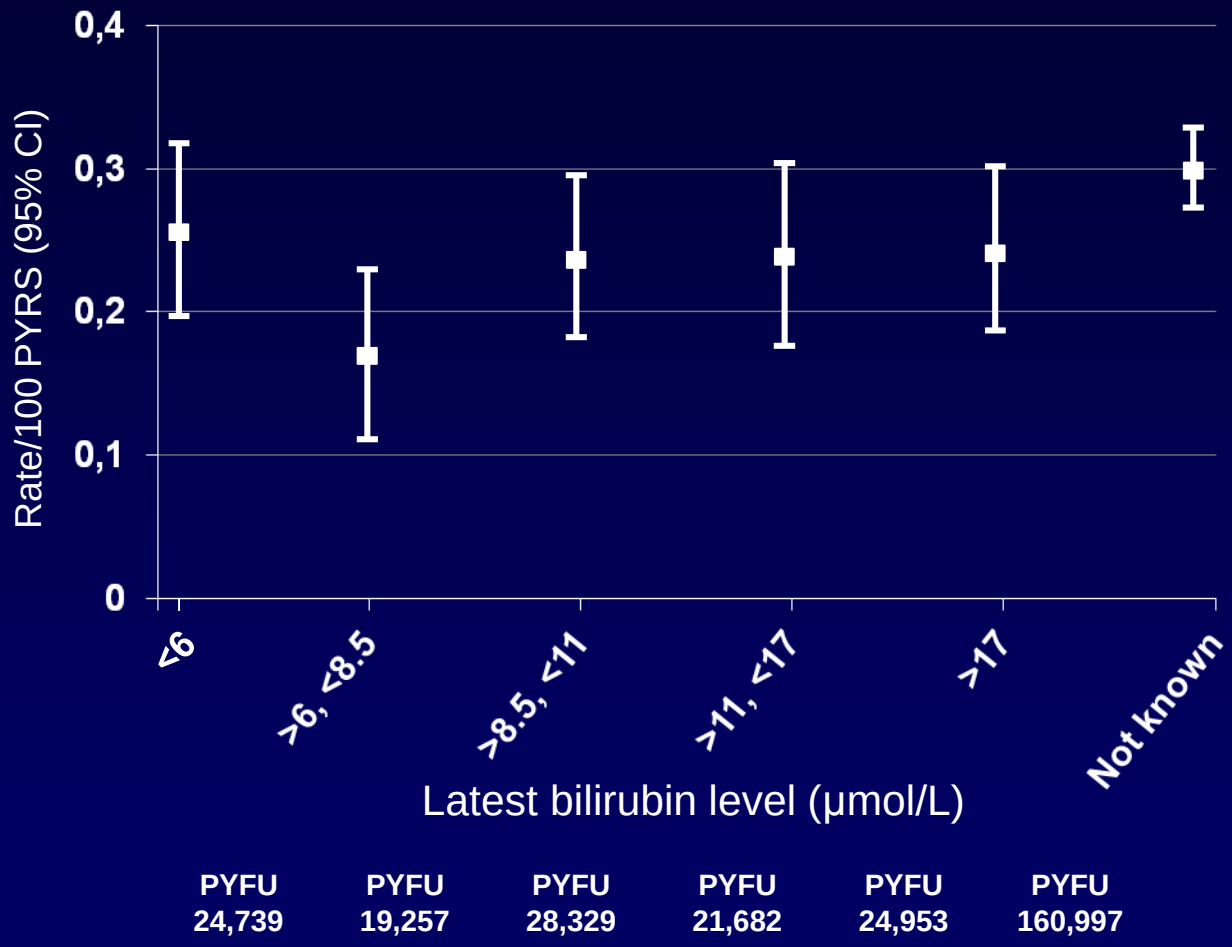
Bilirubin

- Elevated levels associated with anti-atherogenic properties[1]:
  - Lower lipid levels
  - Reduced oxidative stress
  - Inhibit platelet activity
- Atazanavir (ATV) causes hyperbilirubinemia[2]



[1]Perlstein *ATVB/AJM* 2008; Bulmer *Prog Lipid Res* 2013; Kundar *Athero* 2015
[2]Rodriguez-Novoa *Pharmacogenomics J* 2006

D:A:D: MI event rate stratified by latest bilirubin level



- Further adjustment for the latest bilirubin level, in the subgroup of cohorts that provide these data, had no impact on the size of the association with either MI or stroke

Monforte et al. CROI 2012, poster 823.

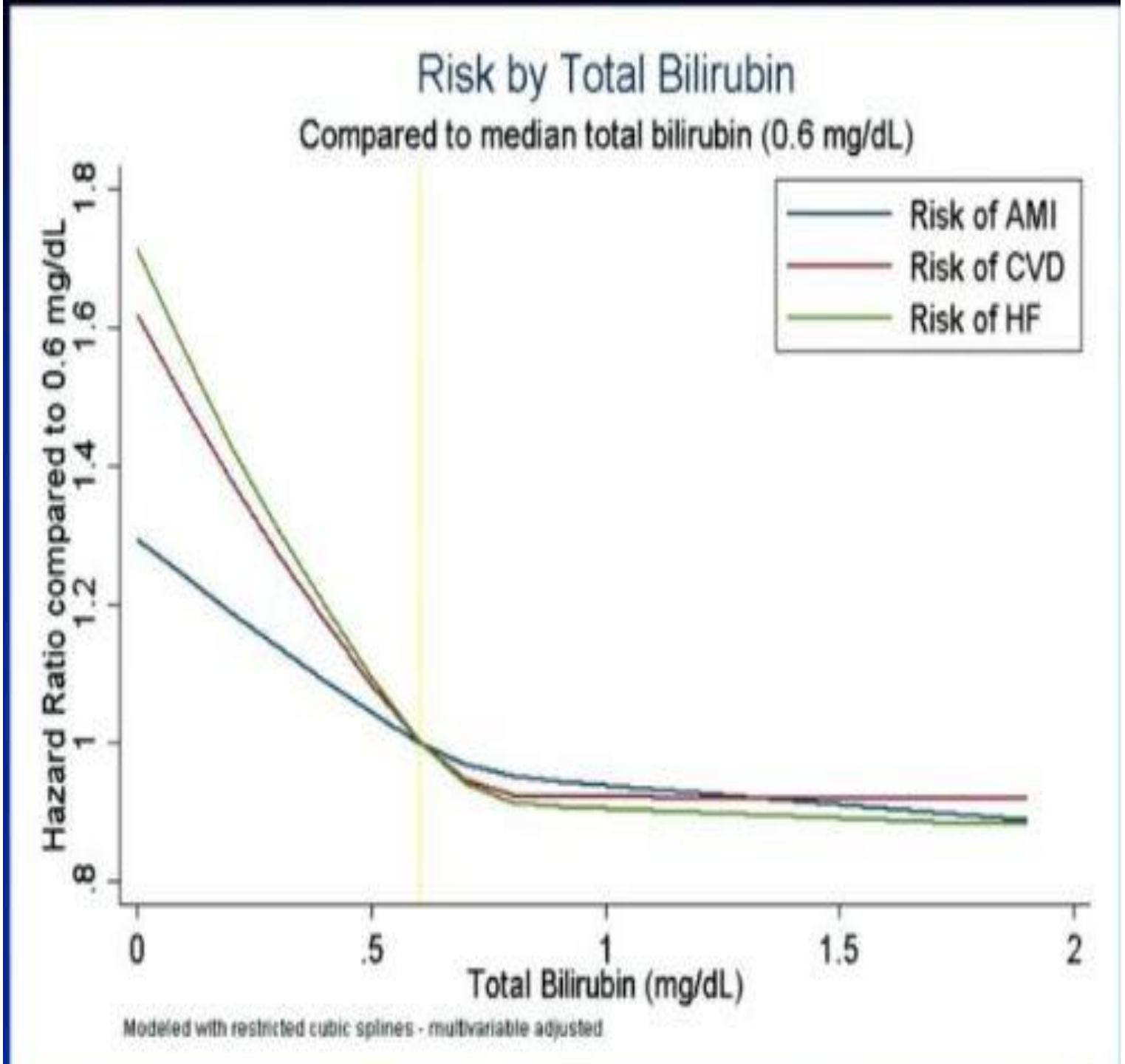
PYFU, person-years of follow-up

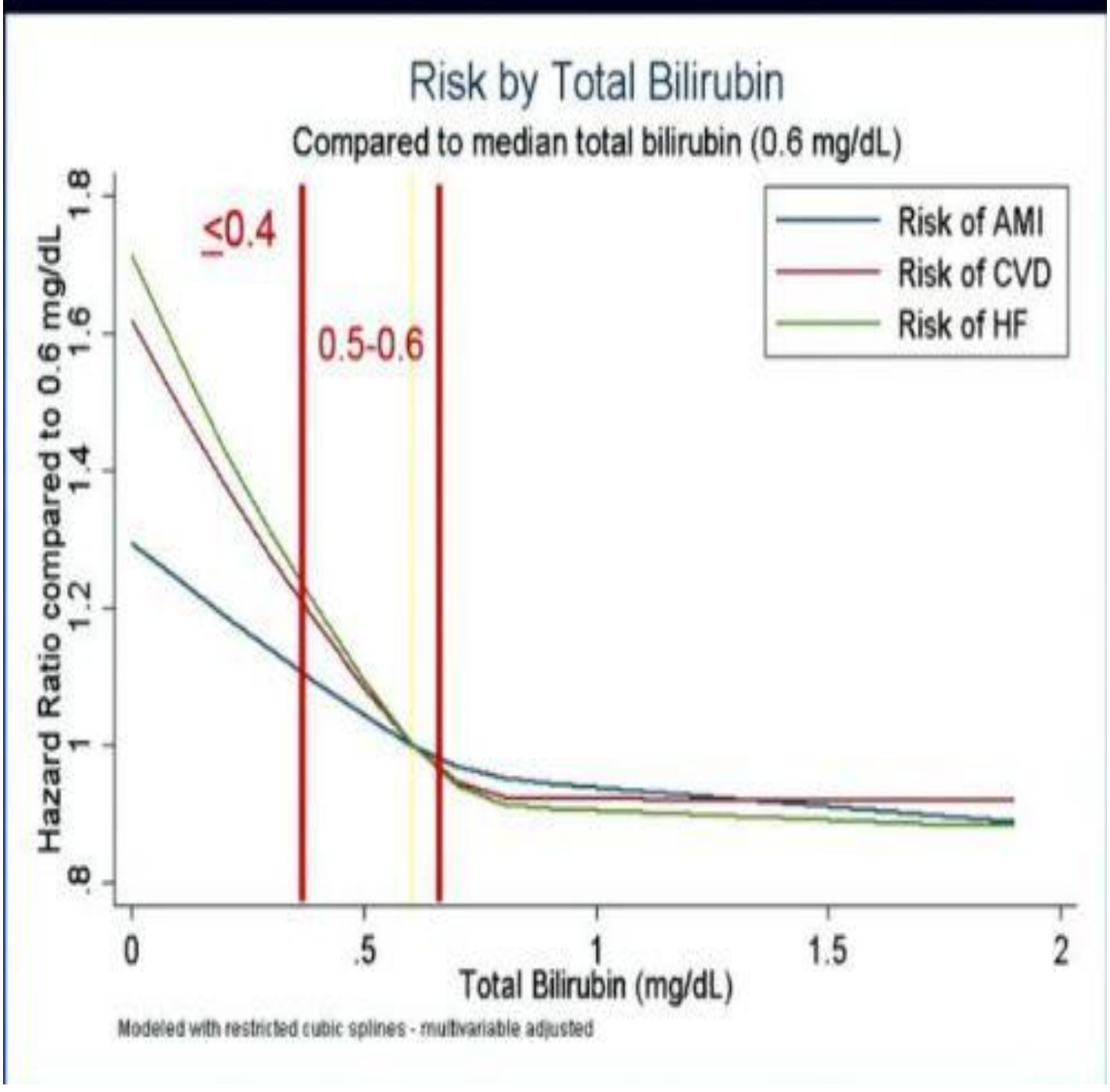
INFLAMMATION AND AGE-RELATED COMPLICATIONS

HYPERBILIRUBINEMIA PREVENTS CARDIOVASCULAR DISEASE FOR HIV+ AND HIV- INDIVIDUALS

Vincent C. Marconi

School of Medicine, Emory University, Atlanta, GA, USA


Risk by Total Bilirubin
Compared to median total bilirubin (0.6 mg/dL)
Risk of AMI
Risk of CVD
Risk of HF
Hazard Ratio compared to 0.6 mg/dL
.8
1
1.2
1.4
1.6
1.8
0
.5
1
1.5
2
Total Bilirubin (mg/dL)
Modeled with restricted cubic splines - multivariable adjusted


Risk by Total Bilirubin
Compared to median total bilirubin (0.6 mg/dL)
≤0.4
0.5-0.6
Risk of AMI
Risk of CVD
Risk of HF
Hazard Ratio compared to 0.6 mg/dL
.8
1
1.2
1.4
1.6
1.8
0
.5
1
1.5
2
Total Bilirubin (mg/dL)
Modeled with restricted cubic splines - multivariable adjusted

CVD by HIV and Atazanavir

Group	N	CVD Events	Rate (95%CI)
Uninfected	62,739	4248	10.21 (9.91-10.53)
HIV+, no ART	8,477	541	11.95 (10.99-13.01)
HIV+, ART with ATV	1,260	67	13.02 (10.24-16.54)
HIV+, ART no ATV	19,326	1747	13.33 (12.72-13.97)

Incidence rate is per 1000 person-years
CVD= cardiovascular disease (HF + AMI + Ischemic Stroke)

Conclusion

- Higher bilirubin is associated with decreased CVD:
  - Among HIV+ and uninfected veterans
  - Before and after adjusting for confounders
  - Among veterans without liver disease
- Future analyses

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Inibitori dell'integrasi: gli effetti favorevoli inattesi
Integrase Inhibitors: the unexpected favorable effects
Paolo Maggi
Clinica delle Malattie Infettive, Università degli Studi di Bari
antiretrovirale
sulla densità minerale ossea
| Paolo Bagella
Pag 57 | Sistemi informatici per favorire la gestione degli eventi avversi ai farmaci
| Mauro Giacomini
Pag 62 | Inibitori dell'integrasi: gli effetti favorevoli inattesi
| Paolo Maggi
Rivista Scientifica Trimestrale
2016 settembre
www.jhamagazine.net
3

- Lake J; Currier JS; Koteff J et al. Cardiovascular biomarkers after switching to ABC/DTG/3TC: the STRIIVING study. CROI 2016 Boston, abstract #660.

- Lichtenstein KA, Armon C, Nagabhushanam V et al. A pilot study to assess inflammatory biomarker changes when **raltegravir is added to a virologically suppressive HAART regimen** in HIV-1-infected patients with limited immunological responses. Antivir Ther. 2012;17(7):1301-9.

- Silva EF, Charreau I, Gourmel B. et al. Decreases in inflammatory and coagulation biomarkers levels in HIV-infected patients **switching from enfuvirtide to raltegravir**: ANRS 138 substudy. J Infect Dis. 2013 Sep;208(6):892-7.

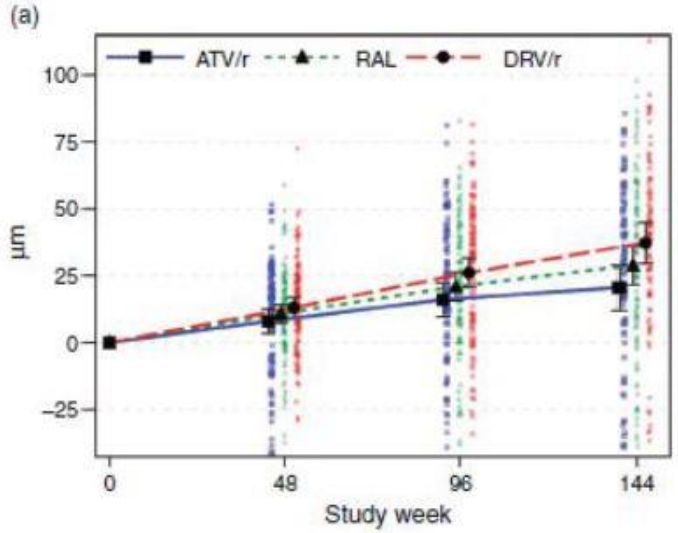
- McCausland MR, Juchnowski SM, Zidar DA, et al. Altered Monocyte Phenotype in HIV-1 Infection Tends to Normalize with Integrase-Inhibitor-Based Antiretroviral Therapy. PLoS One. 2015 Oct 2;10(10):e0139474.

- Funderburg NT, Andrade A, Chan ES et al. Dynamics of immune reconstitution and activation markers in HIV+ treatment-naïve patients treated with **raltegravir, tenofovir disoproxil fumarate and emtricitabine**. PLoS One. 2013 Dec 18;8(12):e83514.

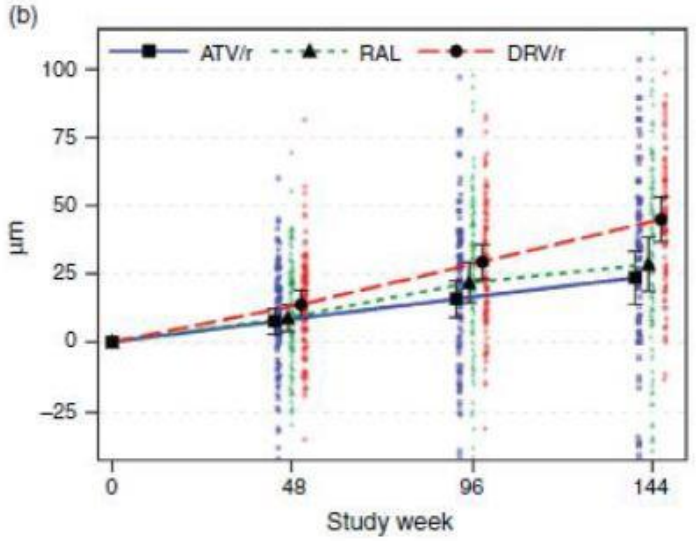
- Taiwo B, Matining RM, Zheng L et al. Associations of T cell activation and inflammatory biomarkers with virological response to **darunavir/ritonavir plus raltegravir** therapy. J Antimicrob Chemother. 2013 Aug;68(8):1857-61.

- Hileman CO, Kinley B, Scharen-Guivel V, et al. Differential Reduction in Monocyte Activation and Vascular Inflammation With Integrase Inhibitor-Based Initial Antiretroviral Therapy Among HIV-Infected Individuals. J Infect Dis. 2015 Aug 1;212(3):345-54.

ARDENT: Effects of initiating three contemporary ART regimens on progression of IMT over 3 years



Change in common carotid artery intima–media thickness progression



Change in carotid artery bifurcation intima–media thickness progression

Conclusion: In ART-naive HIV-infected individuals at low cardiovascular disease risk, carotid IMT progressed more slowly in participants initiating ATV/r than those initiating DRV/r, with intermediate changes associated with RAL. This effect may be due, in part, to hyperbilirubinemia.

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Stein JH et al. AIDS Sep2015

Raltegravir is Associated with Greater Abdominal Fat Increases after Antiretroviral Therapy Initiation Compared to Protease Inhibitors

P Bhagwat, I Ofotokun, GA McComsey, TT Brown, C Moser,
CA Sugar, JS Currier

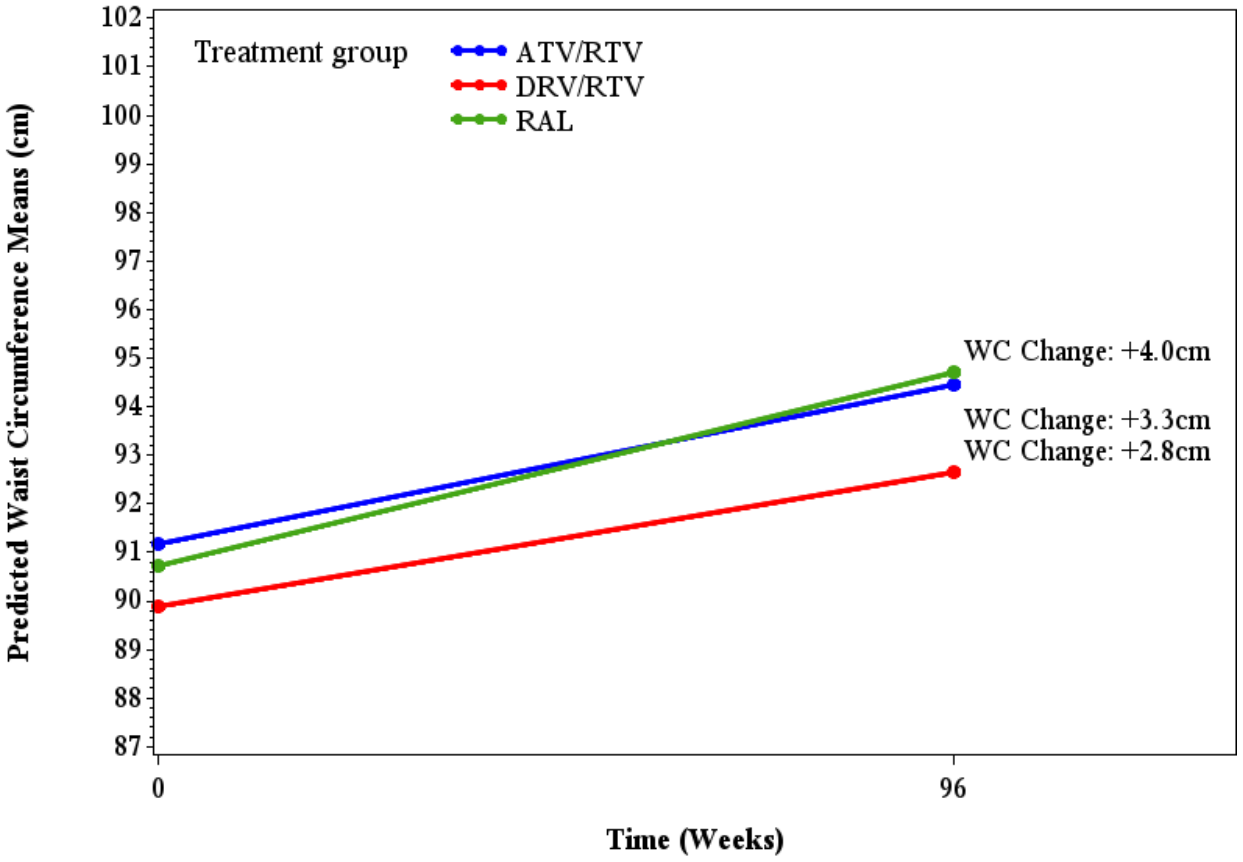
September 12, 2016
18th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV

Study Data: ACTG A5257

- Phase III randomized clinical trial from May 2009 to June 2013
- Subjects were randomized in a 1:1:1 ratio to each regimen
  - Raltegravir (RAL)
  - Darunavir/Ritonavir (DRV/r)
  - Atazanavir/Ritonavir (ATV/r)
    - Each in combination with Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)
- 1,814 subjects enrolled
  - Treatment-naïve HIV-infected men and women aged 18 or older

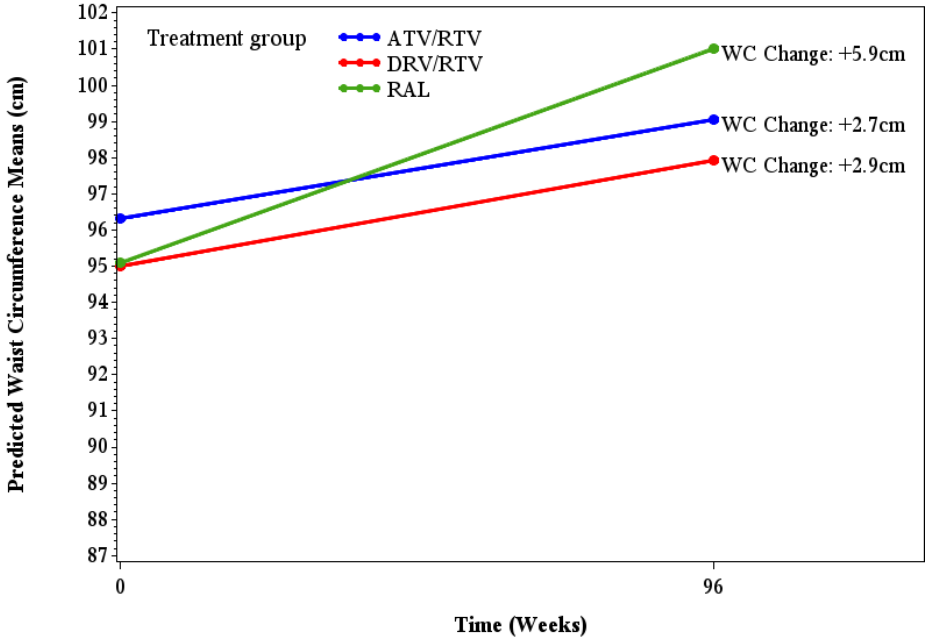
Results: Overall Treatment Differences

Overall:
WC Over 96 Weeks by Treatment Group

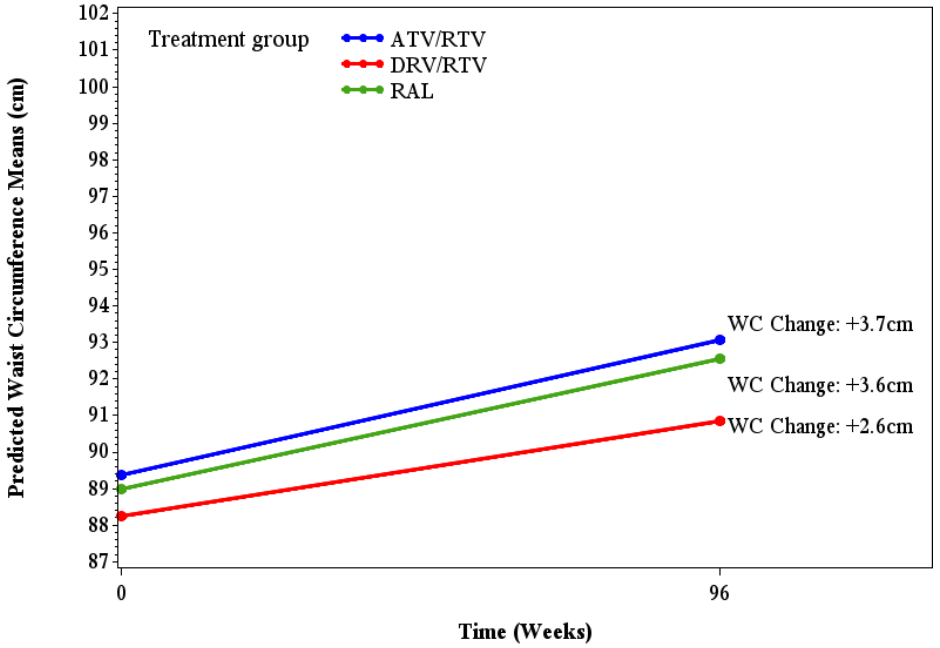


Results: Modification by Sex

Females:
WC Over 96 Weeks by Treatment Group

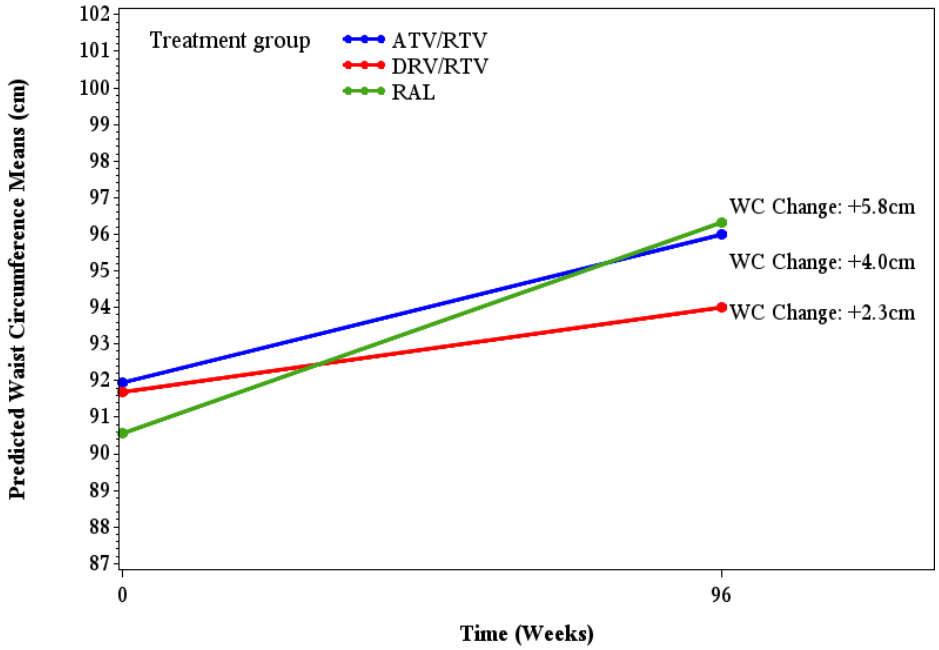


Males:
WC Over 96 Weeks by Treatment Group

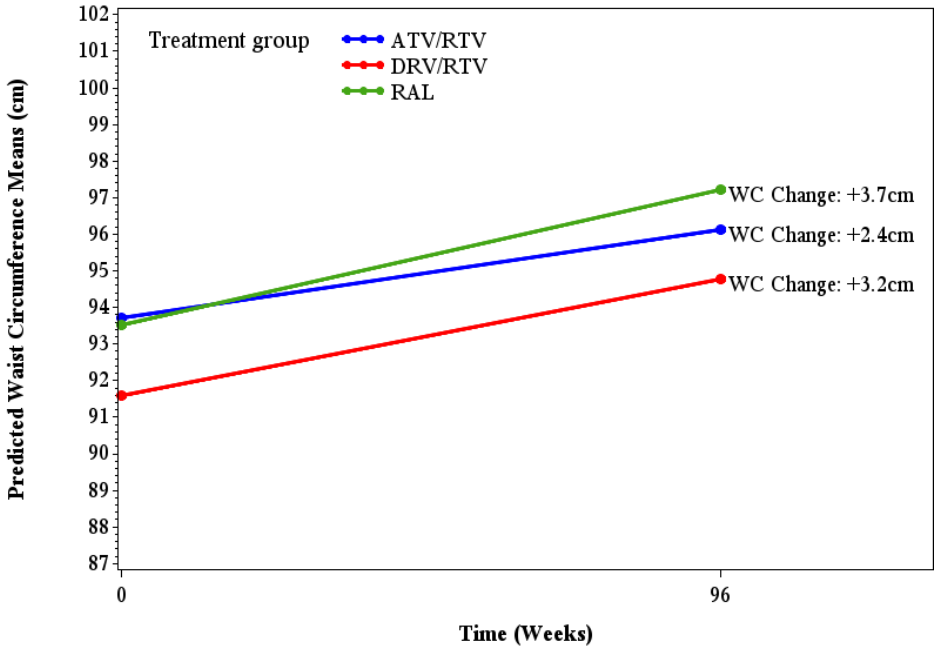


Results: Modification by Race/Ethnicity

Black Non-Hispanic:
WC Over 96 Weeks by Treatment Group



Other Race/Ethnicity:
WC Over 96 Weeks by Treatment Group



Results: Model including all predictors

Covariate	Complete Case Analysis: Differential Mean Change (95% CI)	Complete Case Analysis: p-value	Imputed Data: Repeated Model: Differential Mean Change (95% CI)	Imputed Data: Repeated Model: p-value	Imputed Data: Change Score Model: Differential Mean Change (95% CI)	Imputed Data: Change Score Model: p-value
Treatment						
RAL	--	--	--	--	--	--
ATV/r	-0.34 (-1.39, 0.71)	0.5210	-0.74 (-1.68, 0.21)	0.1253	-0.65 (-1.58, 0.29)	0.1749
DRV/r	-0.70 (-1.75, 0.36)	0.1951	-1.22 (-2.17, -0.28)	0.0114	-1.07 (-2.00, -0.13)	0.0255
PIs	-0.52 (-1.43, 0.39)	0.2643	-0.98 (-1.80, -0.16)	0.0188	--	--
Sex						
Males	--	--	--	--	--	--
Females	0.62 (-0.51, 1.74)	0.2833	0.90 (-0.11, 1.91)	0.0822	0.74 (-0.26, 1.74)	0.1467
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.05 -0.03, 2.12)	0.0565	0.70 (-0.29, 1.69)	0.1672	0.61 (-0.38, 1.59)	0.2262
Hispanic	-0.10 (-1.40, 1.20)	0.8772	-0.22 (-1.37, 0.94)	0.7128	-0.17 (-1.32, 0.98)	0.7678
Other	-1.18 (-3.83, 1.46)	0.3804	-1.92 (-4.41, 0.58)	0.1328	-1.94 (-4.39, 0.50)	0.1191
Age (years)	0.0084 (-0.032, 0.049)	0.6854	0.020 (-0.017, 0.057)	0.2877	0.023 (-0.013, 0.060)	0.2096
Baseline BMI (kg/m^2)	0.026 (-0.053, 0.10)	0.5195	0.015 (-0.056, 0.086)	0.6817	0.0044 (-0.066, 0.075)	0.9031
Baseline HIV-1 RNA (log_{10} copies/mL)	1.83 (1.13, 2.54)	<.0001	1.86 (1.23, 2.49)	<.0001	1.70 (1.07, 2.33)	<.0001
Baseline CD4+ (100 cells/mm^3)	-0.65 (-0.91, -0.39)	<.0001	-0.74 (-0.98, -0.50)	<.0001	-0.75 (-0.98, -0.51)	<.0001

Discussion

- Raltegravir associated with larger WC increases compared to protease inhibitors
  - Difference between treatment arms not found in metabolic substudy (A5260s)
- Results indicated that the treatment effect on WC gains varied by sex and race/ethnicity
  - Not been extensively examined previously
  - Prior research has shown that metabolic effects of treatment may be modified by patient characteristics
  - Treatment may be affecting fat accumulation in individuals differently after initiation

OBESITY AND FATTY LIVER DISEASE

Predictors of Severe Weight/Body Mass Index Gain Following Antiretroviral Initiation

Priya Bhagwat

University of California, Los Angeles, Los Angeles, CA, USA

Discussion

- Protease inhibitors may be associated with less severe weight increases compared to integrase inhibitor raltegravir
- Black non-Hispanic compared to white non-Hispanic individuals may have higher odds of severe weight/BMI gain
- Baseline disease state was strongly associated with severe weight/BMI gain over 96 weeks
  - May be due to increased inflammation in adipose tissue, leading to its expansion
  - Supports early treatment initiation to prevent severe disease state and adverse weight outcomes from occurring

Results: Adjusted model predicting severe weight gain

Covariate	Adjusted Imputed Data Model	
	Odds Ratio (95% CI)	p-value
Treatment		
RAL	--	--
ATV/r	0.72 (0.53, 0.99)	0.0427
DRV/r	0.74 (0.54, 1.01)	0.0555
Sex		
Males	--	--
Females	1.35 (0.97, 1.89)	0.0742
Race/Ethnicity		
White Non-Hispanic	--	--
Black Non-Hispanic	1.55 (1.10, 2.20)	0.0129
Hispanic	0.99 (0.67, 1.48)	0.9757
Other	0.50 (0.17, 1.45)	0.2021
Age (years)	1.01 (0.99, 1.02)	0.2859
Baseline BMI (kg/m^2)	0.98 (0.96, 1.01)	0.1767
Baseline HIV-1 RNA (log_{10} copies/mL)	2.52 (2.00, 3.16)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.78 (0.72, 0.85)	<.0001

Results: Adjusted model predicting severe BMI gain

Covariate	Adjusted Imputed Data Model	
	Odds Ratio (95% CI)	p-value
Treatment		
RAL	--	--
ATV/r	0.83 (0.62, 1.13)	0.2381
DRV/r	0.73 (0.53, 0.99)	0.0414
Sex		
Males	--	--
Females	1.14 (0.83, 1.58)	0.4085
Race/Ethnicity		
White Non-Hispanic	--	--
Black Non-Hispanic	1.48 (1.06, 2.08)	0.0217
Hispanic	1.44 (0.99, 2.10)	0.0555
Other	0.48 (0.16, 1.43)	0.1851
Age (years)	1.01 (0.995, 1.02)	0.2407
Baseline BMI (kg/m^2)	1.03 (1.00, 1.05)	0.0375
Baseline HIV-1 RNA (log_{10} copies/mL)	1.79 (1.44, 2.22)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.79 (0.73, 0.86)	<.0001

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A SWITCH TO RALTEGRAVIR DOES NOT LOWER PLATELET REACTIVITY IN HIV-INFECTED ADULTS

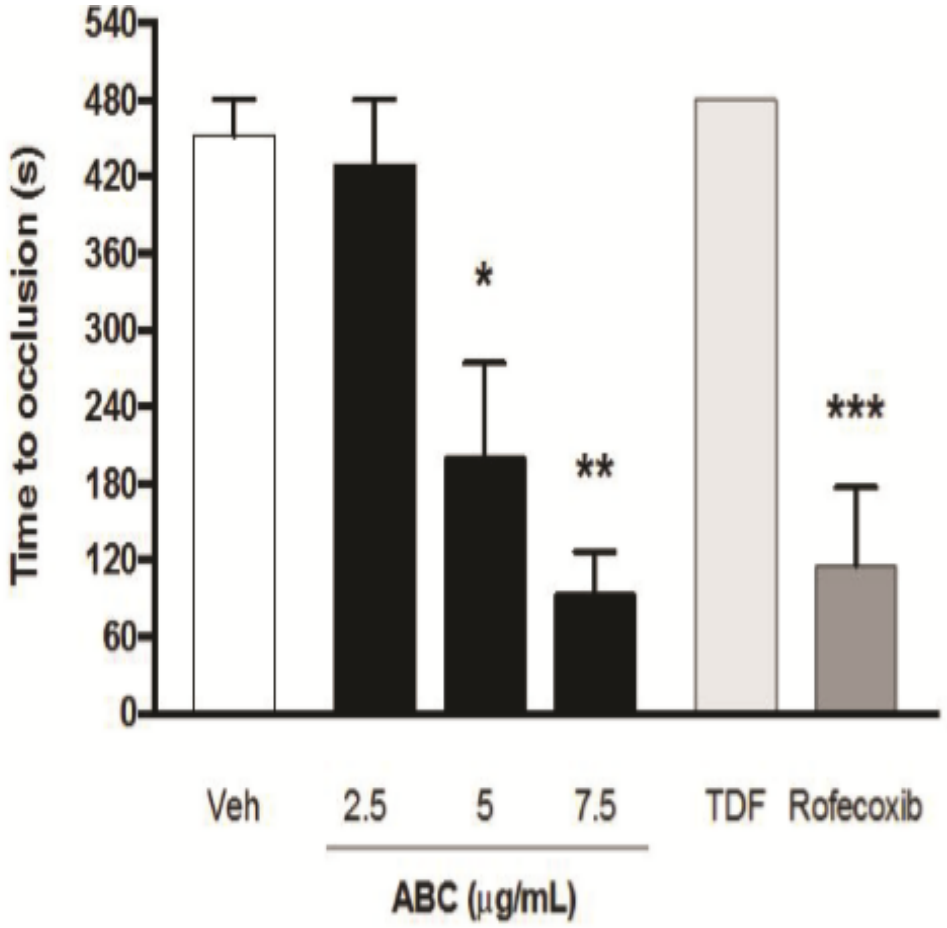
Wouter A . van der Heijden

- A switch to a raltegravir-based regimen in virally suppressed HIV-infected individuals reduces neither platelet reactivity nor platelet-monocyte aggregation.

609

PROTHROMBOTIC EFFECTS OF ABACAVIR IN AN IN VIVO MODEL

Isabel Andujar



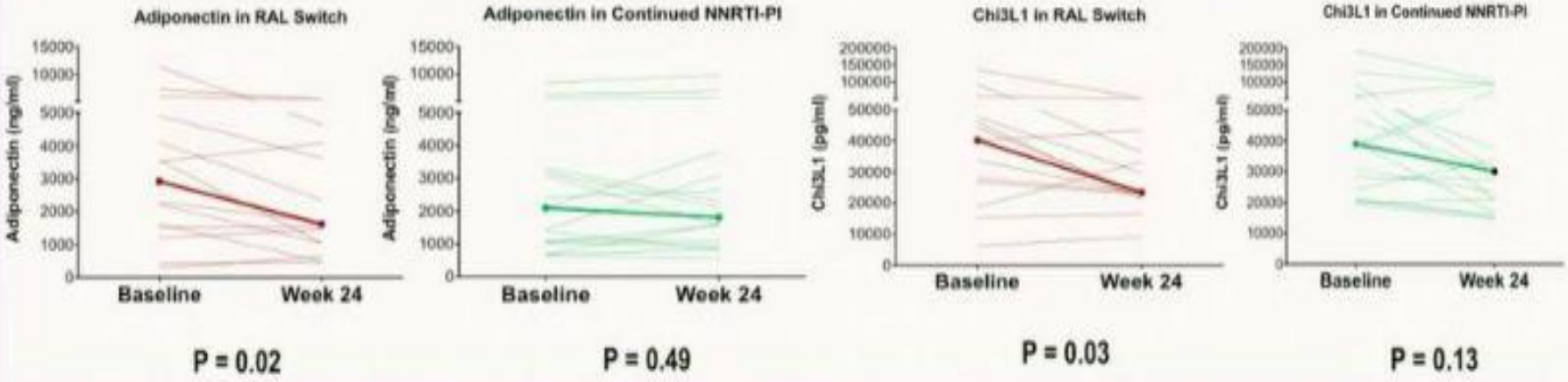
OBESITY AND FATTY LIVER DISEASE

RALTEGRAVIR SWITCH AND BIOMARKERS OF LIVER STEATOSIS AND METABOLIC SYNDROME IN WOMEN

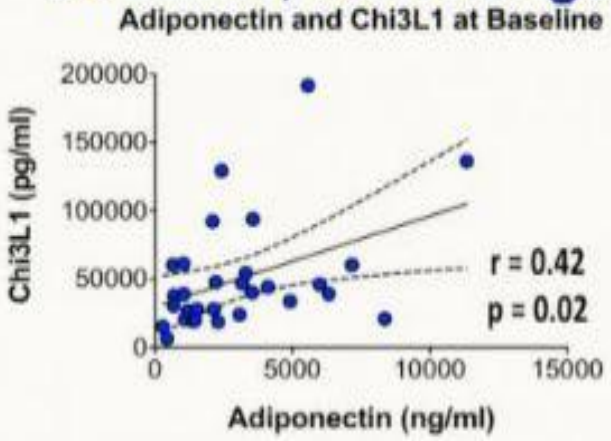
Jordan E Lake

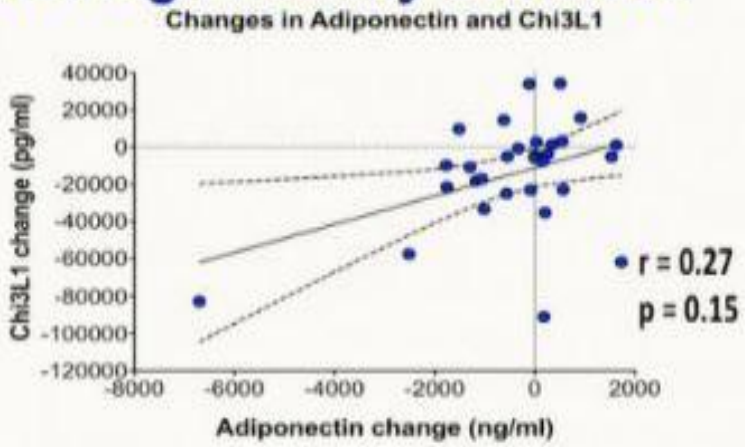
University Texas Houston, Houston, USA

Adiponectin and Chi3L1 decreased significantly 24 weeks after switch to RAL, but not with continued PI/NNRTI

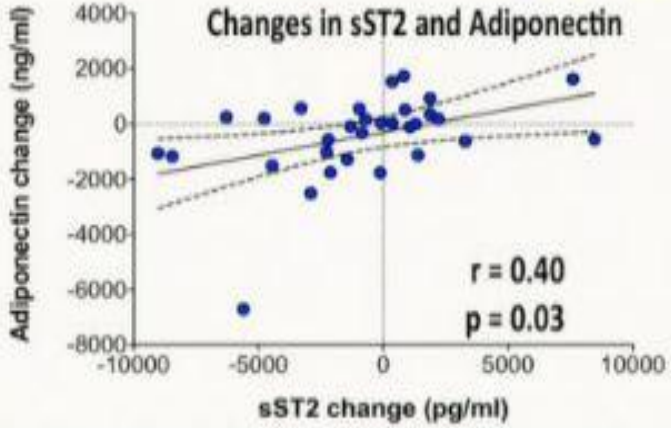


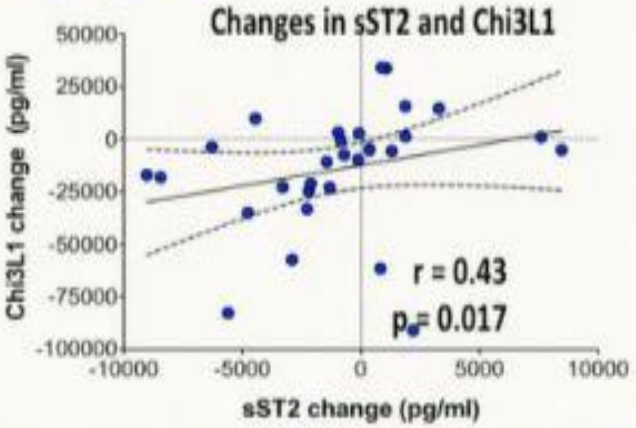
Higher adiponectin levels correlate with higher Chi3L1 levels at baseline, but changes do not significantly correlate



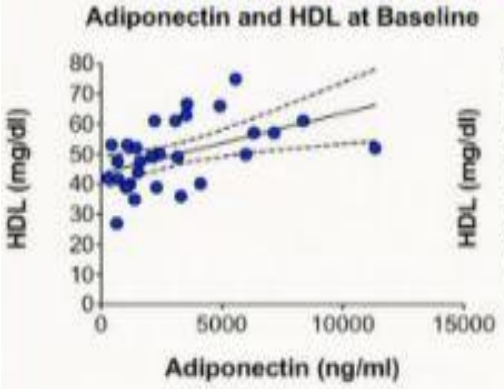


Decreases in adiponectin and Chi3L1 correlate with decreases in the fibrosis marker sST2

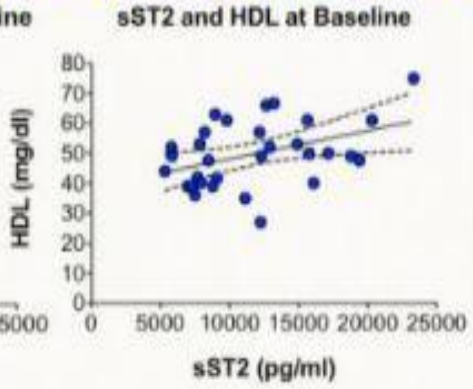




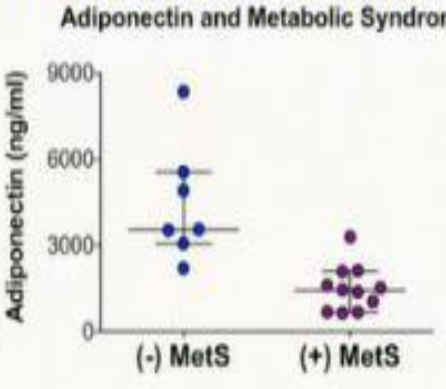
Higher baseline adiponectin and sST2 levels correlate with higher baseline HDL levels, and were lower in women with metabolic syndrome



r = 0.55
p = 0.001

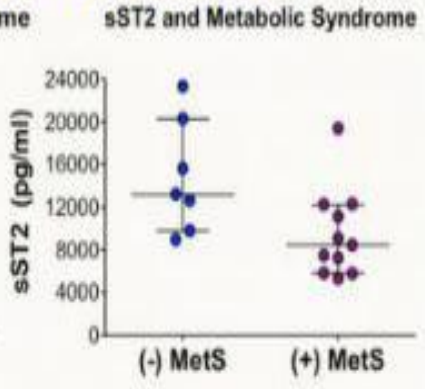


r = 0.38
p = 0.03



3558 vs 1453 ng/mL

P=0.0003



13206 vs 8473 pg/mL

P=0.02

Summary and Conclusions

- In HIV+ women with central obesity, the adipocytokine adiponectin and the biomarker of liver steatosis and metabolic syndrome Chi3L1 decreased following switch to RAL.
- Decreases in adiponectin and Chi3L1 correlated with decreases in the fibrosis marker sST2.
- These changes did not correlate with changes in body composition or fat quantity, and may reflect a dynamic metabolic and inflammatory environment following switch to RAL.
- These exploratory analyses are limited by small sample size and lack of clinical endpoints for comparison.
- Further research is needed to determine whether switching from NNRTI/PI-based regimens to RAL will improve hepatic steatosis and/or dysmetabolism.

Minority reports:

- BMI: un grande ritorno
- Bilirubina: la vera protezione cardiovascolare?
- INI: davvero così CV friendly?
- Le relazioni pericolose: Statine e vitamina D
- I biologici risolveranno tutti i nostri problemi?

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VITAMIN D DEFICIENCY IMPAIRS THE BENEFICIAL EFFECTS OF STATIN IN TREATED HIV

Corrilynn O . Hileman

SATURN-HIV study

While levels of 25(OH)D did not change with rosuvastatin, **baseline vitamin D deficiency decreased the effectiveness of rosuvastatin**. Vitamin D supplementation may be warranted for deficient patients initiating statin therapy.

Effetti favorevoli della terapia con statine a dosaggio elevato sulla concentrazione plasmatica della vitamina D nei pazienti con infezione da HIV-1 in terapia antiretrovirale.

Calza L, Magistrelli E, Rosselli Del Turco E, Colangeli V, Borderi M, Bon I, Re MC, Viale P.

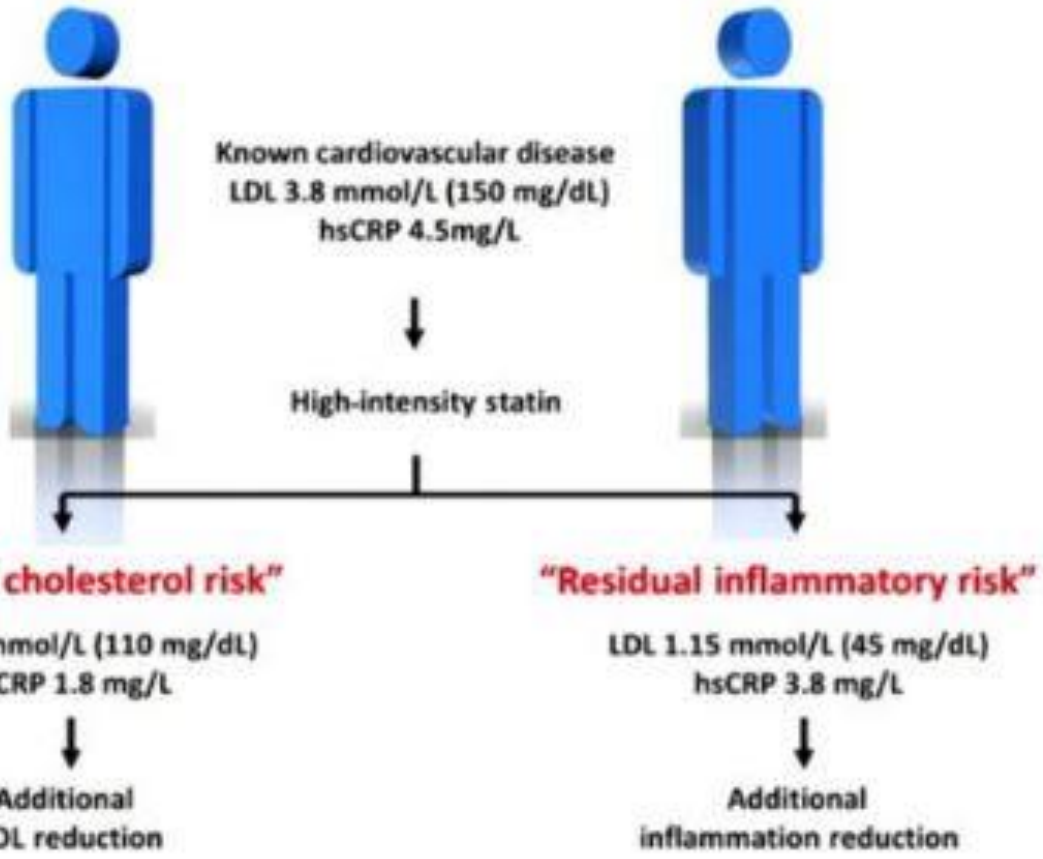
Conclusioni

La terapia con rosuvastatina o atorvastatina a dosaggio elevato per 12 mesi nei pazienti in cART con ipercolesterolemia ha prodotto, oltre alla riduzione attesa dei parametri lipidici, un significativo incremento della concentrazione plasmatica media di vitamina D. Questo dato richiede ovviamente una conferma da più ampi studi randomizzati, ma suggerisce una correlazione tra l'effetto pleiotropo delle statine e quello antiinfiammatorio della vitamina D anche nei pazienti HIV-positivi.

Minority reports:

- BMI: un grande ritorno
- Bilirubina: la vera protezione cardiovascolare?
- INI: davvero così CV friendly?
- Le relazioni pericolose: Statine e vitamina D
- I biologici risolveranno tutti i nostri problemi?

Residual inflammatory risk: what are options after statin treatment?



Ridker PM European Heart Journal 2016

INFLAMMATION AND AGE-RELATED COMPLICATIONS

IL-1β INHIBITION SIGNIFICANTLY REDUCES ATHEROSCLEROTIC INFLAMMATION IN TREATED HIV

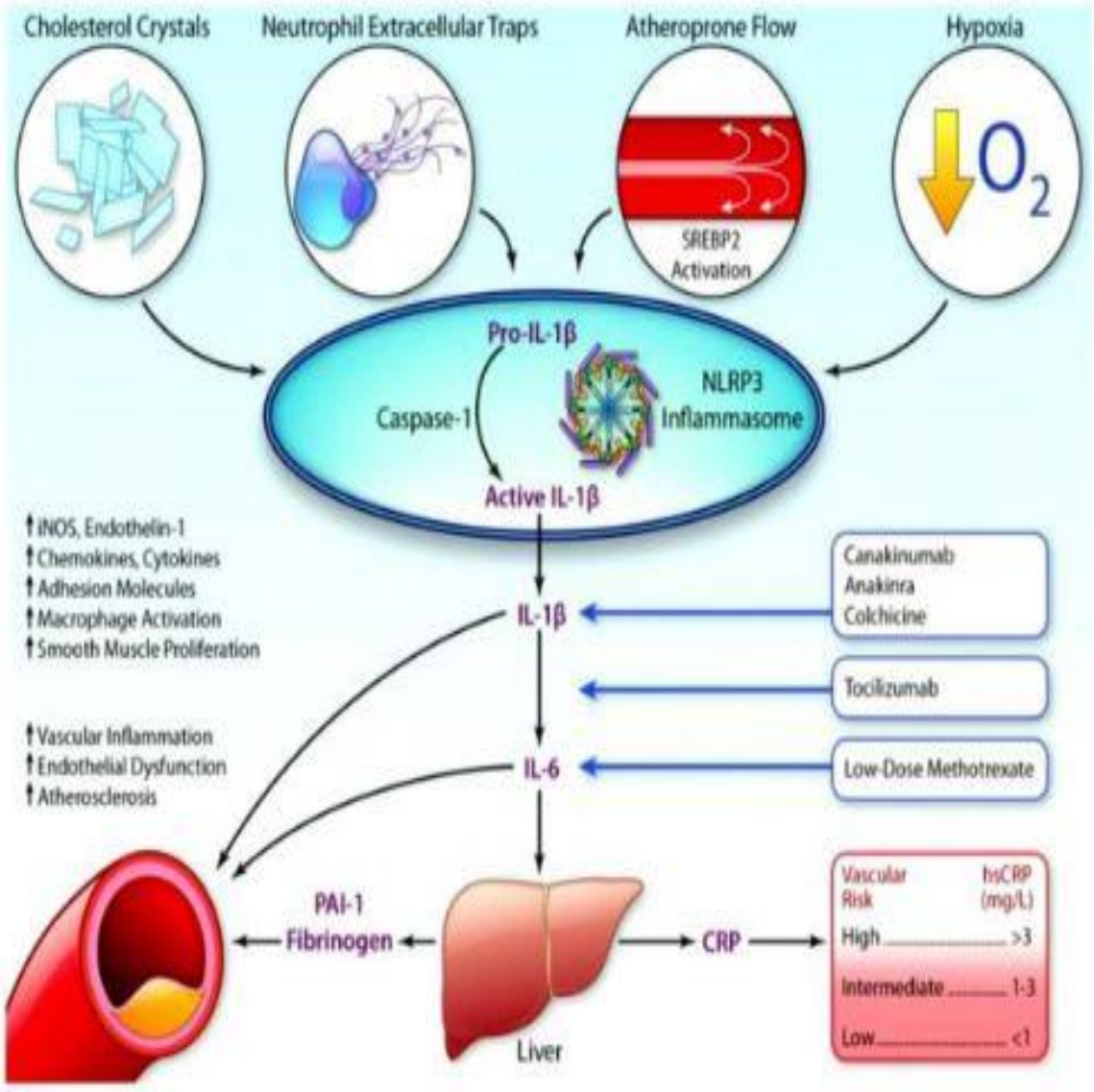
Priscilla Hsue

University of California, San Francisco, San Francisco, CA, USA

IL-1β inhibition using canakinumab

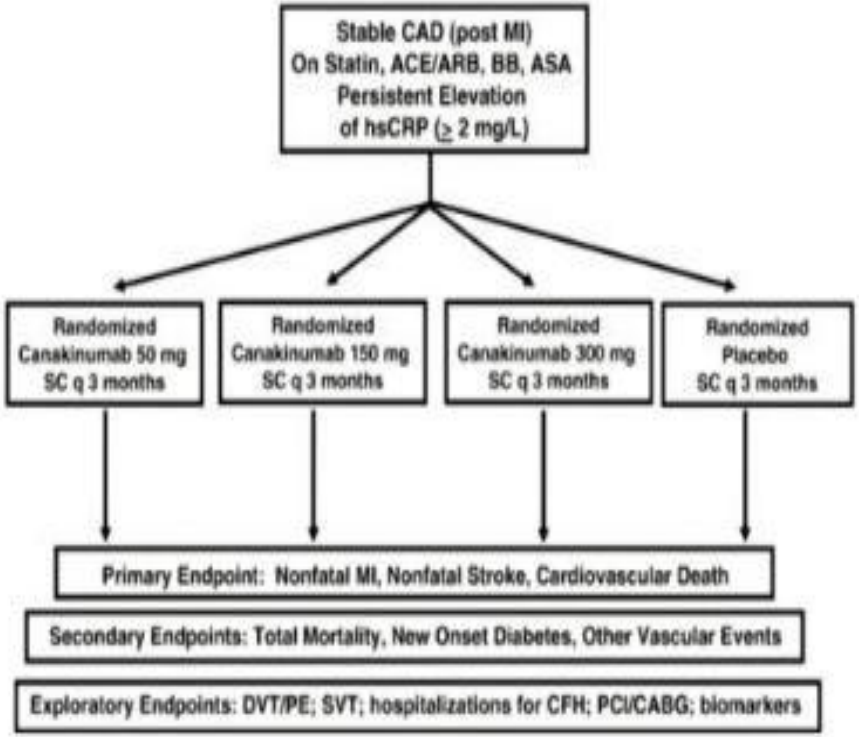
- Canakinumab is a human monoclonal IL-1β antibody indicated for treatment inflammatory disorders such as CAPS and Muckle-Wells syndrome
  - Dosing is quarterly subcutaneous injection
- Binds IL-1β and blocks interaction of cytokine with type I and II receptors
- Produces a rapid and sustained inhibition of inflammation with only minimal effects on lipids

Targeting inflammation: Moving upstream



Ridker P Circulation Research 2016

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

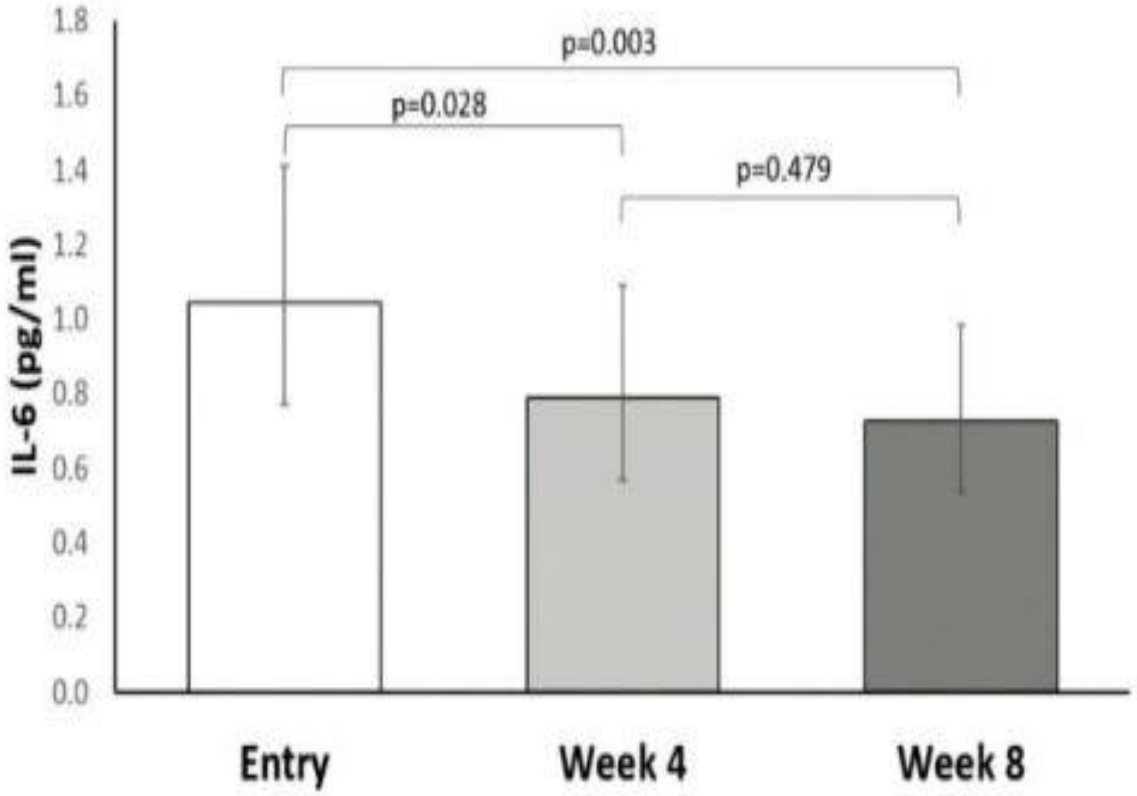


- 10,000 adults with known CAD
- HIV-infected individuals are excluded

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

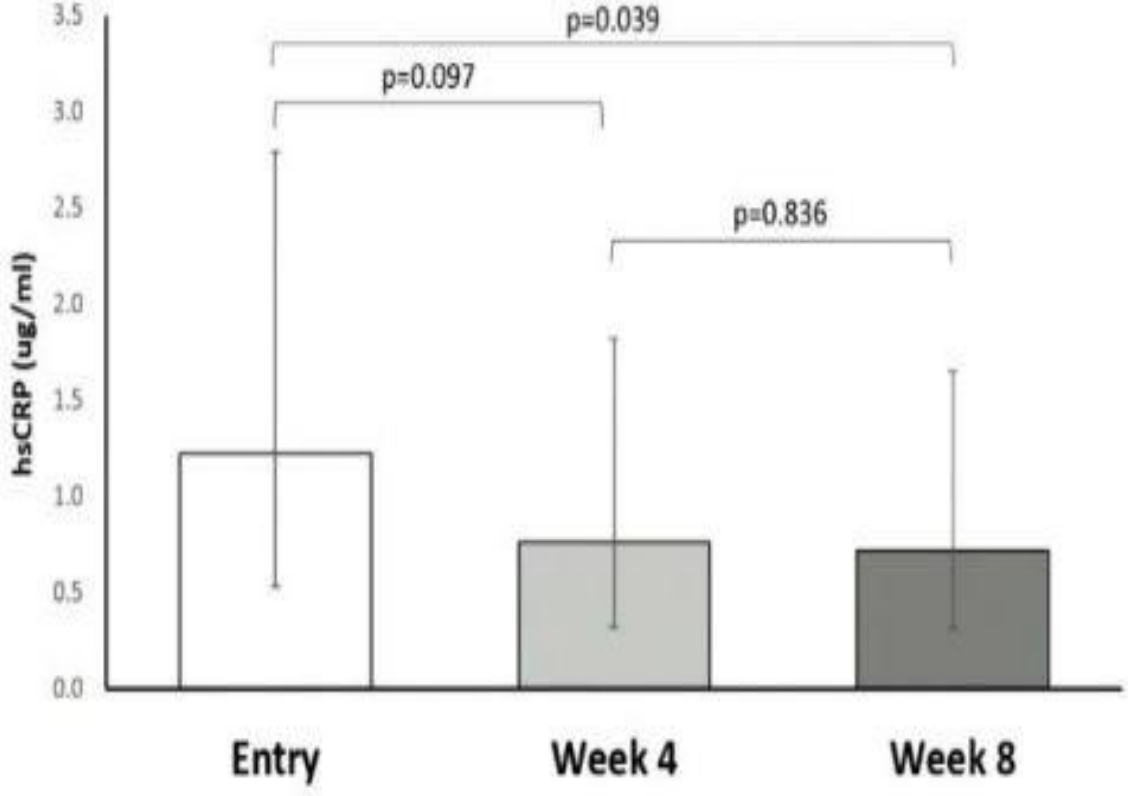
Ridker P AHJ 2011

Interleukin -6



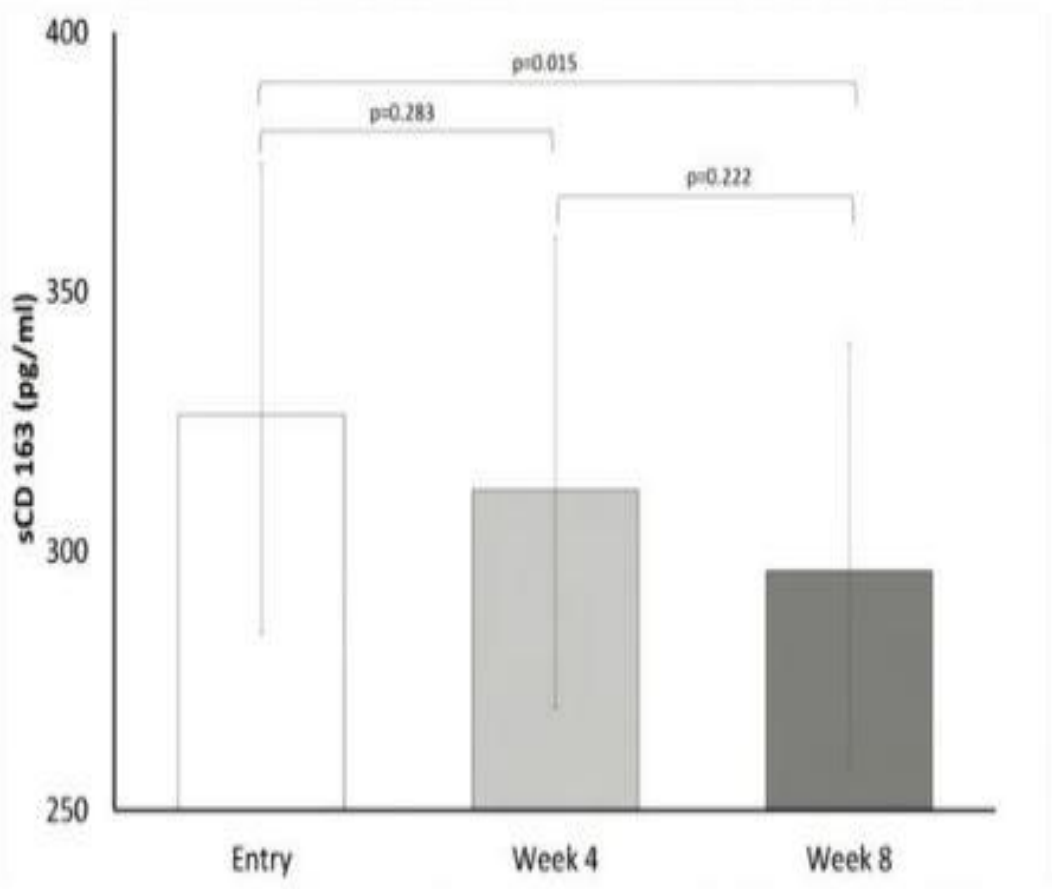
Canakinumab significantly reduced IL-6 by 24% from BL to week 4 (p=0.028) and by 30% from BL to week 8 (p=0.003)

High sensitivity CRP



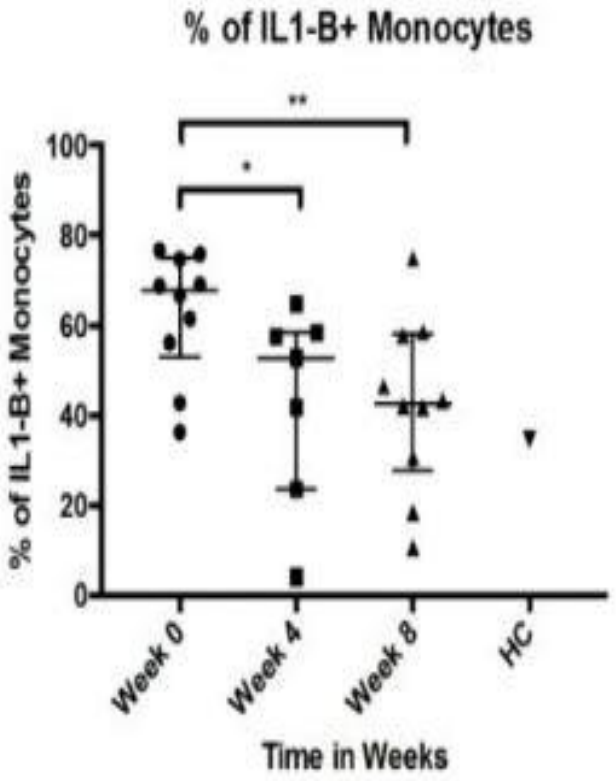
hsCRP reduced by 41% (p=0.039) from baseline to week 8

Soluble CD163



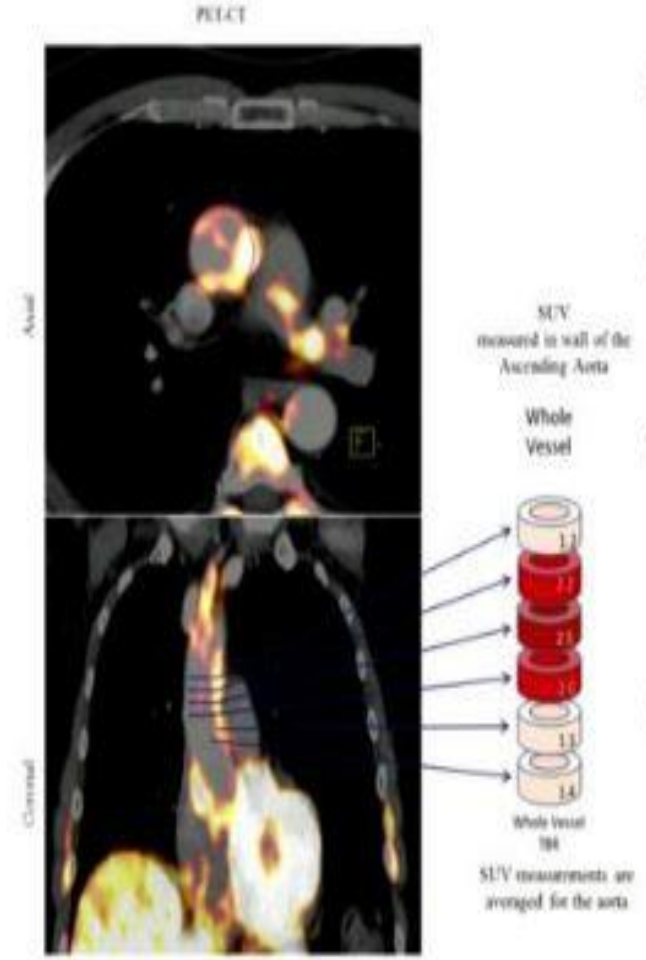
Il-1β inhibition with canakinumab was associated with a reduction in sCD163 by 9% (p=0.015, baseline vs. week 8).

Monocyte function: Response to LPS



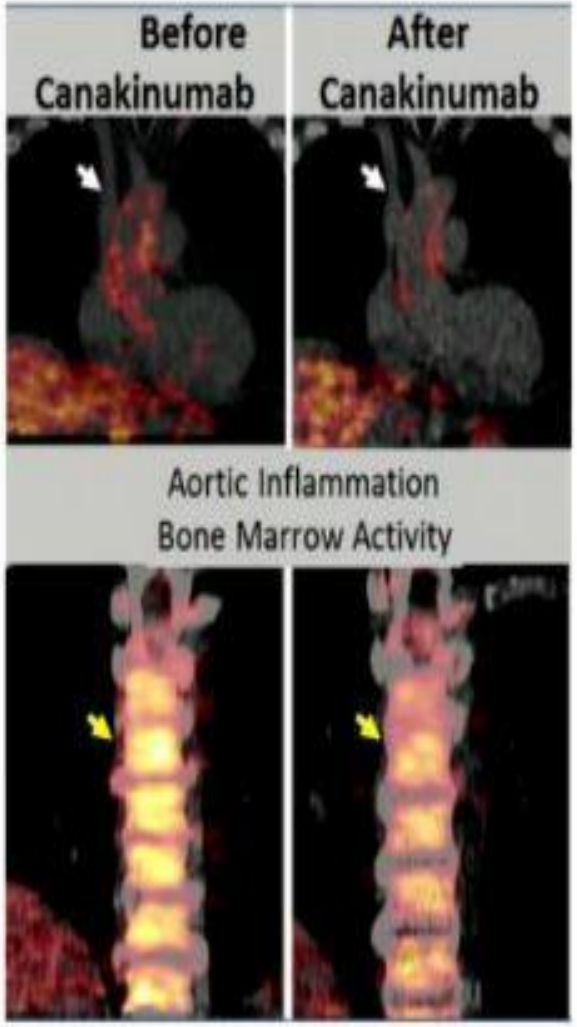
Less production of IL-1β and IL-6 after LPS stimulation (baseline to week 4, p=0.03, baseline to week 8, p=0.006)

Imaging: FDG-PET/CT

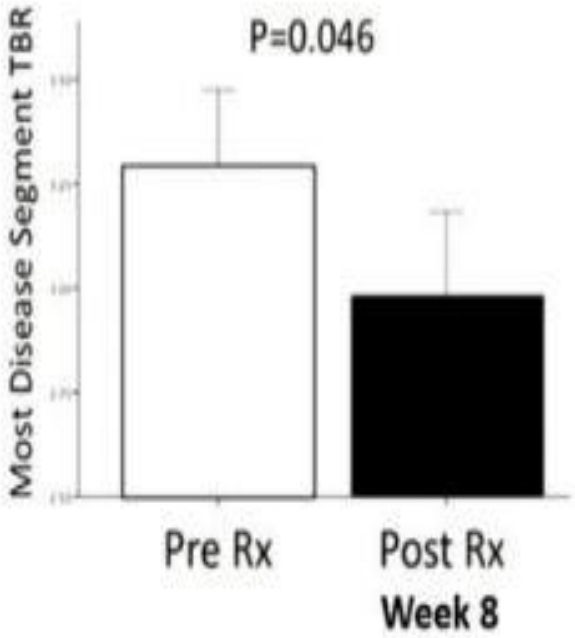


- Measures metabolic activity (glucose uptake)
- Established measure of vascular inflammation
- Image analysis performed by radiologist blinded to clinical/temporal data
- Tissues of interest: aorta, carotid arteries, axillary lymph nodes, bone marrow

IL-1β inhibition with canakinumab reduces both arterial and bone marrow activity



Arterial Inflammation



10% reduction in arterial inflammation (mean index MDS 3.29±0.57 vs. 2.98±0.64, p=0.046)

Conclusions

- In this pilot study (n=10), a single dose of canakinumab was well-tolerated in treated HIV-infected individuals
- Canakinumab significantly reduced inflammatory markers (IL-6, hsCRP, and sCD163)
- A single dose of canakinumab did not impact T cell activation or monocyte phenotypes (with exception of CCR5+ monocytes)
- Monocyte function was reduced which is consistent with inflammatory marker findings
- Canakinumab significantly reduced arterial inflammation and bone marrow activity

1992 – 2012

United Nations Declaration on MINORITY RIGHTS