

HIV and CVD

Do we really understand the risk?

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UCD School of Medicine & Medical Science



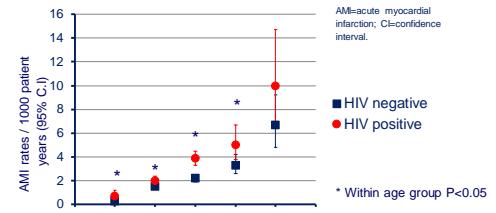
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HIV and CVD – incidence of MI



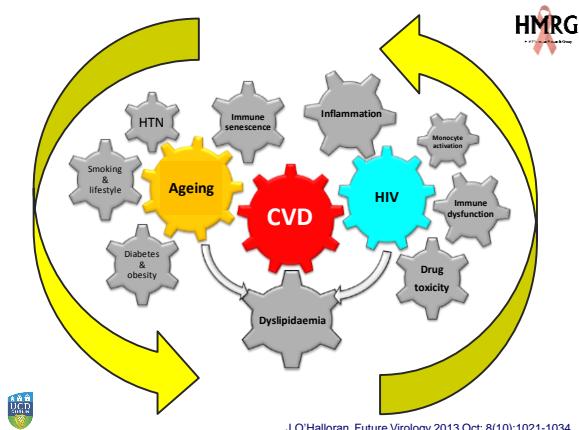
- AMI commonest cause of death in ART-treated patients¹
- Rates of MI higher in HIV-positive versus HIV-negative²



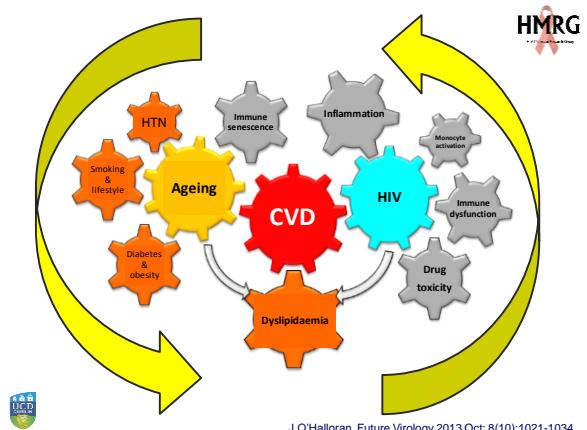
- RR of MI with age not different between HIV and the general population risk estimates³

1. Rodger A et al. AIDS. 2013 Mar 27;27(6):973-9. 2. Freiberg MS, et al. JAMA Int Med. 2013; 173(8):614-22.

3. Petoumenos K et al. HIV Med 2014. May 19.



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

CVD – assessing risk



National Heart, Lung, and Blood Institute

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Heart Attack

Do you know how many risk factors affect your heart attack risk? Take our quick quiz to find out!

• smoking

• high blood pressure

• being overweight

• being on certain medications

Australian absolute cardiovascular disease risk calculator

Enter Age: []

Gender: []

Smoking Status: []

Total Chol: []

HDL: []

LDL: []

Triglycerides: []

BP: []

Diabetes: []

Chronic Kidney Disease Tool

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HIV PHARMACO-VIGILANCE

INFECTIONS • SIDE EFFECTS • TREATMENT • TOOLS

Tools

RISK EVALUATION TOOLS

D:A:D and ASCVD lower risk profile than FHS-CVD¹



http://www.heart.org/HEARTORG/Conditions/HeartAttack/HeartAttackToolsResources/Heart-Attack-Risk-Assessment_UCM_303944_Article.jsp
<http://www.cvdcheck.org/>

<http://hpv.org/Home/Tools/tabid/91/cid/ExamView/mid/500/ed/0/d/0/Defarit.aspx>, 1. Krimme M et al. HIV Med 2015 [Epub ahead of print]

HIV and MI



Characteristics of those with MI in D:A:D

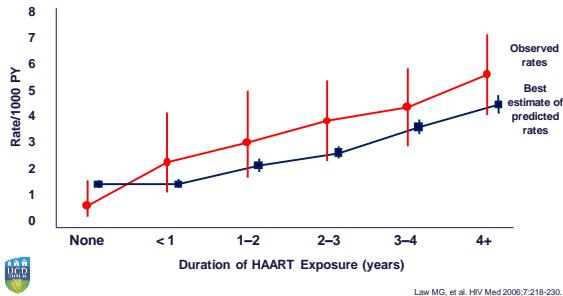
	Year of MI				
	99-02	03-04	05-06	07-08	09-11
Number of MIs	212	194	157	171	110
Male (%)	91.0	92.8	90.5	89.5	92.7
Age (yrs)	48	49	49	51	51
CD4 (cells/mm ³)	398	444	454	436	546
Smokers (%)	49.5	46.9	55.4	57.3	58.2
Family history (%)	14.2	13.9	14.7	15.2	13.6
High risk (%)	28.8	23.2	22.3	26.9	32.7
1 mth mortality (%)	26.4	24.7	19.8	16.4	8.2



Sabin CA et al. Abstract 748, 20th CROI, Atlanta, 2013.

HIV and MI – role of traditional risk factors

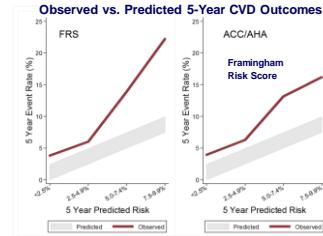
Framingham risk assessment may underestimate MI risk in HIV
Observed and predicted MI rates according to ART exposure (D:A:D Study)



HIV and CVD – incidence of MI

CVD risk prediction equations consistently underestimate CVD risk in HIV+ subjects

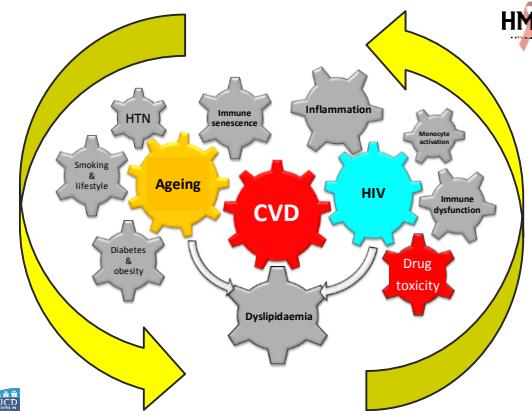
- Partners Healthcare System HIV longitudinal cohort (n=2270)¹
- HIV Outpatient Study cohort (n=2392)²



- Regan S, et al. CROI 2015, Seattle, WA. #751
- Thompson-Paul A, et al. CROI 2015; Seattle, WA. #747

HIV & CVD

What are the unmeasured risks?

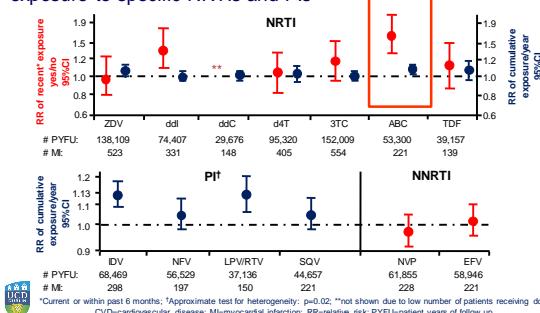


J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

Cardiovascular events: Do drugs matter?



D.A.D: MI risk is associated with recent and/or cumulative exposure to specific NRTIs and PIs

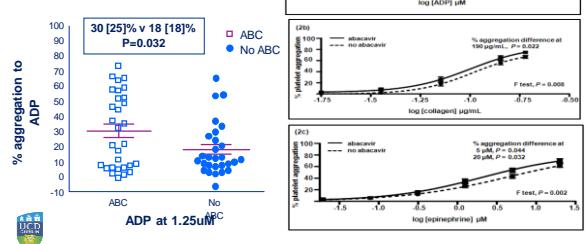


Platelet dysfunction



May explain reversible increased risk of MI with ABC

Increased platelet reactivity in HIV-infected patients on abacavir-containing ART



Satchell CS et al. JID 2011;204:1202-10

Switching from Lamivudine/Abacavir (3TC/ABC) to Emtricitabine/Tenofovir DF (FTC/TDF) Based Regimen (SWIFT) Study

Platelet Biology Sub-study

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¹HIV Molecular Research Group, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland, ² Cardiovascular Biology Group, Royal College of Surgeons in Ireland, Dublin, Ireland

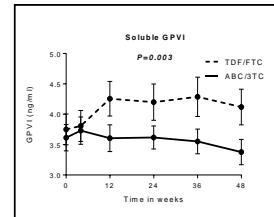


SWIFT Study - results

Characteristic	TDF/FTC n=156	ABC/3TC n=156
Age, years [mean (SD)]	46.0 (9)	46.7 (9.7)
Male [N (%)]	130 (83.3)	134 (85.9)
Caucasian ethnicity [N (%)]	97 (62.2)	106 (67.9)
History of dyslipidaemia [N (%)]	88 (56.4)	102 (65.4)
History of hypertension [N (%)]	49 (31.4)	50 (32.1)
Current smoker [N (%)]	39 (25.0)	42 (26.9)
Protease inhibitor at baseline [N (%)]		
LPV/r	47 (30.1)	52 (33.3)
ATV/r	62 (39.7)	61 (39.1)
FPV/r	35 (22.4)	30 (19.2)
DRV/r	8 (5.1)	9 (5.8)
Other	4 (2.6)	4 (2.6)
Concomitant medication		
Lipid lowering therapy	97 (62.2)	107 (68.6)
NSAIDS	45 (28.8)	40 (25.9)



SWIFT Study - results

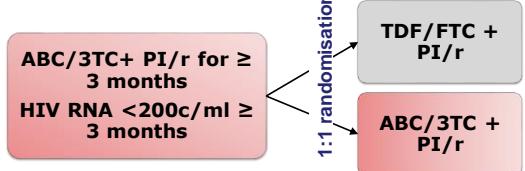


- Significant increase in sGPVI in the TDF/FTC group
- (+0.57 ng/ml, 95% CI; 0.2 - 0.94), p=0.003
- Persisted when corrected for age, gender ethnicity, smoking status, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and creatinine and change from baseline to week 48 in creatinine



J O'Halloran, et al. CROI 2014. Abstract 749LB

SWIFT Study design



Aim of SWIFT platelet biology sub- study

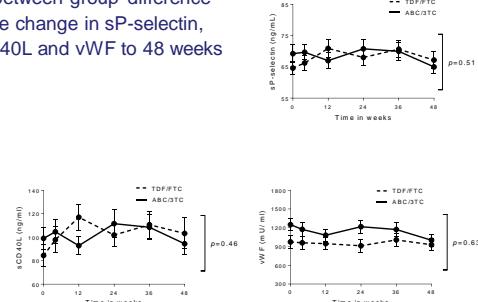
To examine changes in markers of platelet function as a sub-study of the SWIFT trial

O'Halloran J et al. CROI 2014. Abstract LB749

SWIFT Study - results

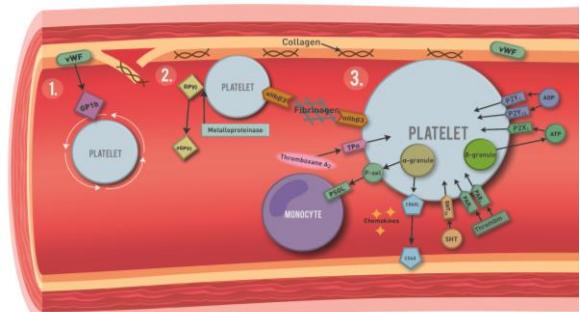


No between-group difference in the change in sP-selectin, sCD40L and vWF to 48 weeks



J O'Halloran, et al. CROI 2014. Abstract 749LB

SWIFT Study design

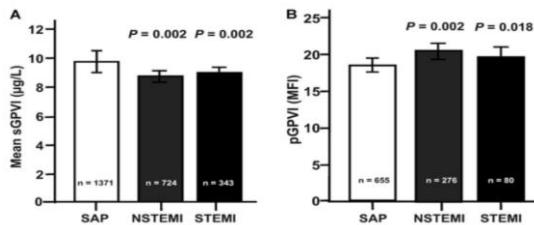


J O'Halloran, Personal Communication May 2015

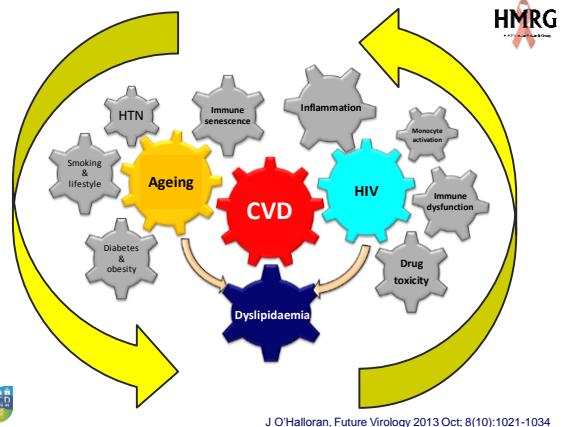
GPVI and CVD



Imbalance in soluble versus platelet-bound GPVI in both ACS¹ and stroke^{2,3}



1 Bigalke et al. *Clin Chem* 2011;57:898-904. 2 Wurster T *Platelets* 2013;24:560-565. 3 Al-Tamami et al. *Stroke* 2011;42:498-500.

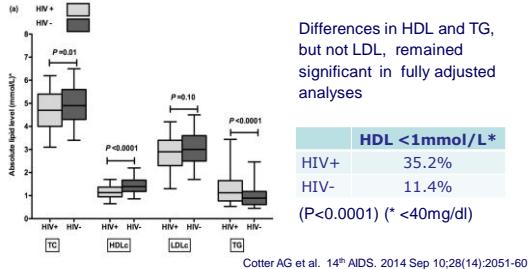


J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

Dyslipidaemia in HIV UPBEAT

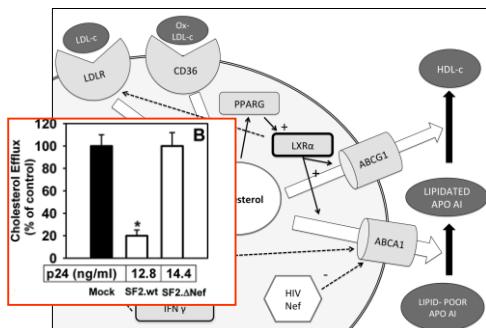


	HIV- (N=259)	HIV+ (N=190)	P
Age	41 (34, 48)	38 (33, 46)	0.08
Male gender	42.9%	61.6%	<0.0001
Smokers	36.3%	16.2%	0.0001



Cotter AG et al. 14th AIDS. 2014 Sep 10;28(14):2051-60

HIV, HDL and monocytes

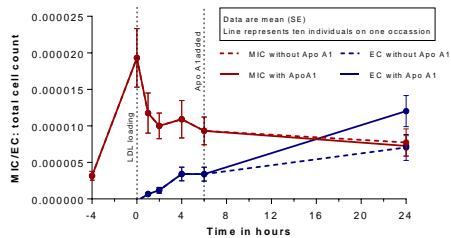


Feeney ER et al. JID 2013 Feb 15;207(4):628-37 Mujawar et al. Plos Biol 2006;4:e365. .

Monocyte Cholesterol Efflux (MCE) assay



Quantification of MIC/ EC standardised for total cell count in HIV neg subjects



MCE = ratio of extracellular to intracellular cholesterol ($EC_T : MIC_T$)

Additional 24 hr measure with ApoA1 ($EC_A : MIC_A$).



Monocyte Cholesterol Efflux (MCE) assay



- Monocyte Intracellular Cholesterol (MONIC) Study
- Cross-sectional, HIV+ (N=50) ART naïve and HIV- (N=50)
- Matched for age, gender, ethnicity, smoking status, hep C

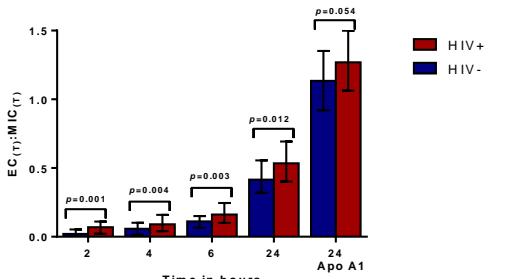
	HIV negative (n=50)	HIV positive (n=50)	P=
Age (years)	34.5 (30, 43)	35 (29, 41)	0.99
Male gender (n, %)	39 (78)	40 (80)	0.81
Caucasian (n, %)	38 (76)	38 (76)	1.0
Current smoker (n, %)	14 (28)	12 (24)	0.65
Cholesterol (mg/dL)	5.0 (4.6, 5.7)	4.3 (3.5, 4.7)	0.000
HDL (mg/dL)	1.29 (1.15, 1.52)	0.96 (0.82, 1.21)	0.000
LDL (mg/dL)	3.2 (2.6, 3.8)	2.5 (2.1, 3.0)	0.000
Triglycerides (mg/dL)	1.08 (0.78, 1.33)	1.25 (0.87, 1.70)	0.09
Total: HDL ratio	3.8 (3.3, 4.4)	4.4 (3.6, 5.3)	0.01



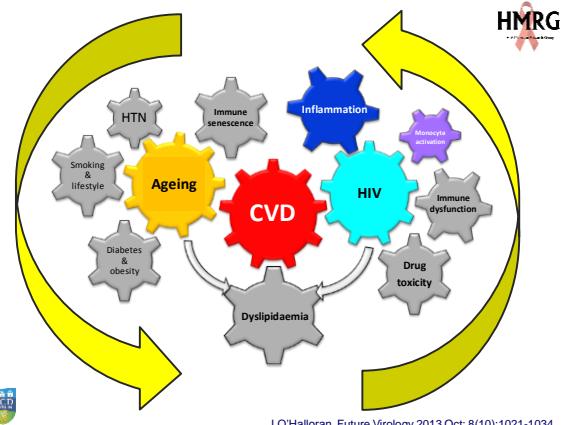
O'Halloran J et al. CROI 2015; abstract 732

Monocyte Cholesterol Efflux (MCE) assay HMRG

Untreated HIV associated with *enhanced*, not inhibited, MCE!

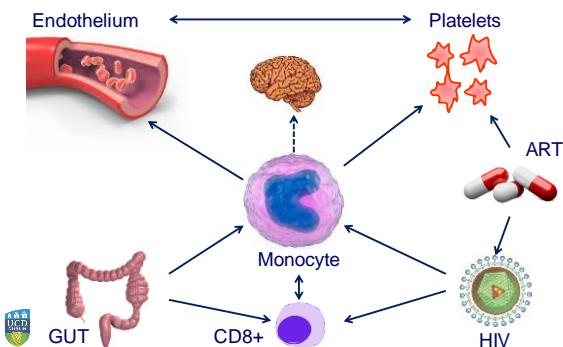


O'Halloran J et al. CROI 2015; abstract 732



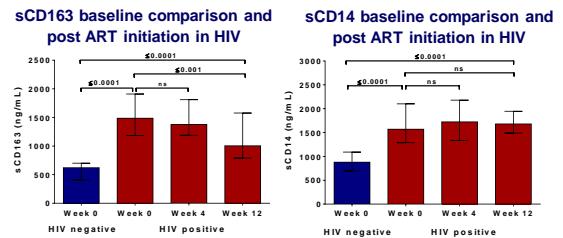
J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

HIV, CVD and inflammation



Markers of monocyte activation

- Both sCD14 & sCD163 were significantly higher in untreated HIV+ subjects compared to HIV- controls
- ART initiation resulted in significant reductions in sCD163
- No effect on sCD14 with ART initiation



O'Halloran J et al. HIV Med. 2015 Jun 25. doi: 10.1111/hiv.12270



Effect of initiating antiretroviral therapy on markers of monocyte activation, endothelial dysfunction and platelet activation in HIV-1 infection

JA O'Halloran^{1,2}, E Dunne³, MMP Gurwith¹, JS Lambert^{1,2}, GJ Sheehan², ER Feeney¹, A Pozniak⁴, P Reiss⁵, D Kenny³, PWG Mallon^{1,2}

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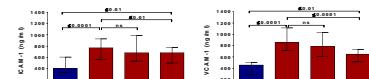
O'Halloran J et al. HIV Med. 2015 Jun 25. doi: 10.1111/hiv.12270



Markers of endothelial dysfunction

- Pre-ART, higher ICAM-1, VCAM-1 and vWF versus controls
- Significant reductions in all endothelial markers post ART initiation
- Remained higher than control values at week 12

ICAM-1 / VCAM-1



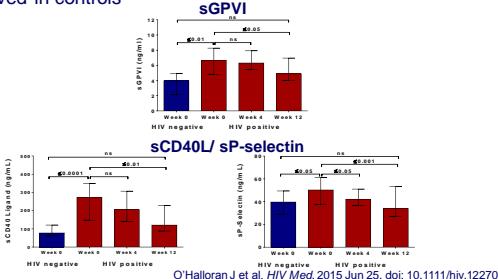
O'Halloran J et al. HIV Med. 2015 Jun 25. doi: 10.1111/hiv.12270



Markers of platelet function



- Pre-ART sGPVI, sCD40L and sP-selectin higher in HIV+ subjects compared with HIV- controls
- All platelet markers significantly reduced with ART, to levels observed in controls



HIV and CVD summary

- Excess risk of CVD in those with HIV, despite effective therapy
- Traditional risk factors do not fully explain excess CV risk
- Drug and HIV-specific effects on vascular function and thrombosis among the potential contributory mechanisms
- Complex interactions between gut, immune activation, coagulation and endothelial dysfunction
- Improve risk assessment – systems biology



Future research to understand risk



Randomized Trial to Prevent Vascular Events in HIV

'Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults'

- NHLBI / NIAID 'A5332'
- Pitavastatin 4mg vs placebo
- N=6,500, HIV+ on ART, age >40 yrs, ASCVD risk <7.5%
- 1^o endpoint time to CVD event
- 2^o endpoints include non-calcified plaque, inflammation (sCD163)



<http://reprievetrial.org/overview/> <https://clinicaltrials.gov/ct2/show/NCT02344290>

Accessed Sept 2015



Future research to understand risk

'Pharmacokinetic and Clinical Observations in People over Fifty'



POPPY
Pharmacokinetic and clinical observations in people over 50

UK and Ireland



The Netherlands



Acknowledgements



HIV Molecular Research Group:

- Dr Eoin Feeney
- Dr Tara McGinty
- Dr Jane O'Halloran
- Dr Elena Alvarez-Barco
- Robert Maughan
- Willard Tinago
- Alan Macken
- Albhe Flaherty
- Sadhbh Tennant
- Aoife Lacey
- Joanne Maher
- Maria Byrne

Infectious Diseases MMUH

- Dr Jack Lambert
- Dr Gerard Sheehan

