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O10 Healthy HIV-1-seropositive individuals have impaired alveolar immunity despite highly active antiretroviral therapy

Paul Collini

University of Sheffield

BHIVA April 2016

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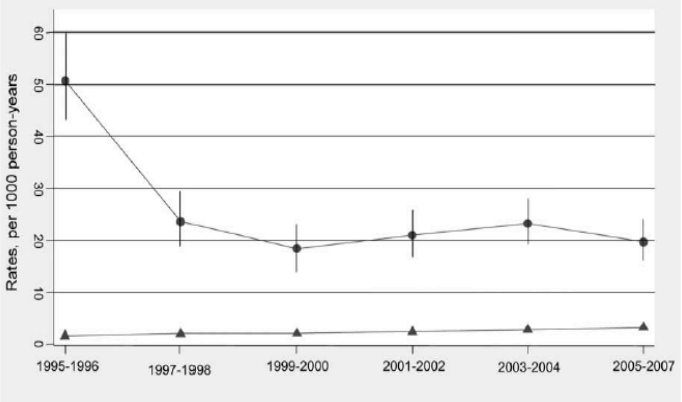
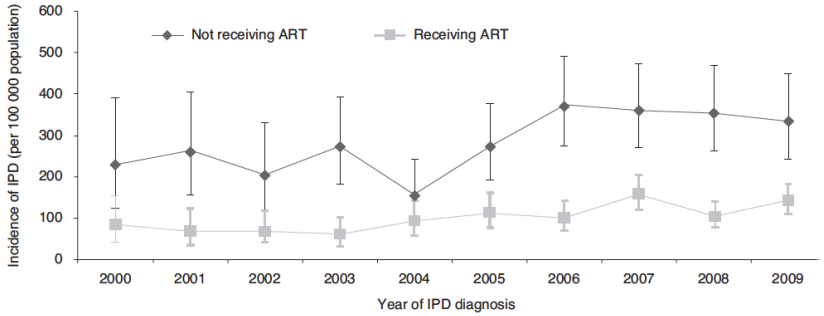
HIV+ individuals risk pneumococcal infection and chronic lung disease in the HAART era

Clinical Infectious Diseases

Hospitalization for Pneumonia among Individuals With and Without HIV Infection, 1995–2007: A Danish Population-Based, Nationwide Cohort Study

Ole S. Sogaard,[1] Nicolai Lohse,[2] Jan Gerstoft,[3] Gitte Kronborg,[4] Lars Ostergaard,[1] Court Pedersen,[5] Gitte Pedersen,[6] Henrik Toft Sørensen,[2] and Niels Obel[3]





AIDS
OFFICIAL JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

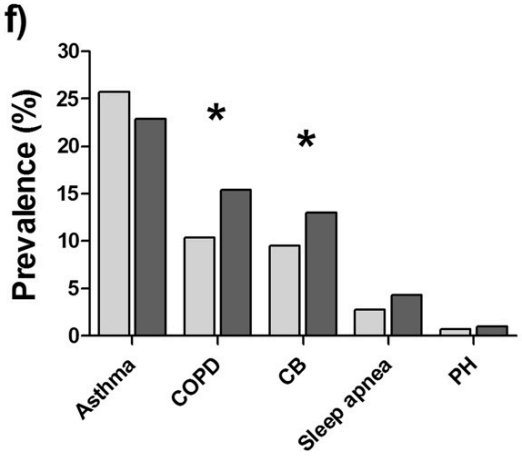
Invasive pneumococcal disease among HIV-positive individuals, 2000–2009

Zheng Yin[a], Brian D. Rice[a], Pauline Waight[b], Elizabeth Miller[b],

BMC Pulmonary Medicine

Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts

Matthew R Gingo[1*], Goundappa K Balasubramani[2], Thomas B Rice[1], Lawrence Kingsley[2,3], Eric C Kleerup[4],



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Sogard (2009) CID; **Yin, Z** (2012) AIDS, 26:87-94, **Gingo M.R.** (2014) BMC Pulm Med 14: p. 75.

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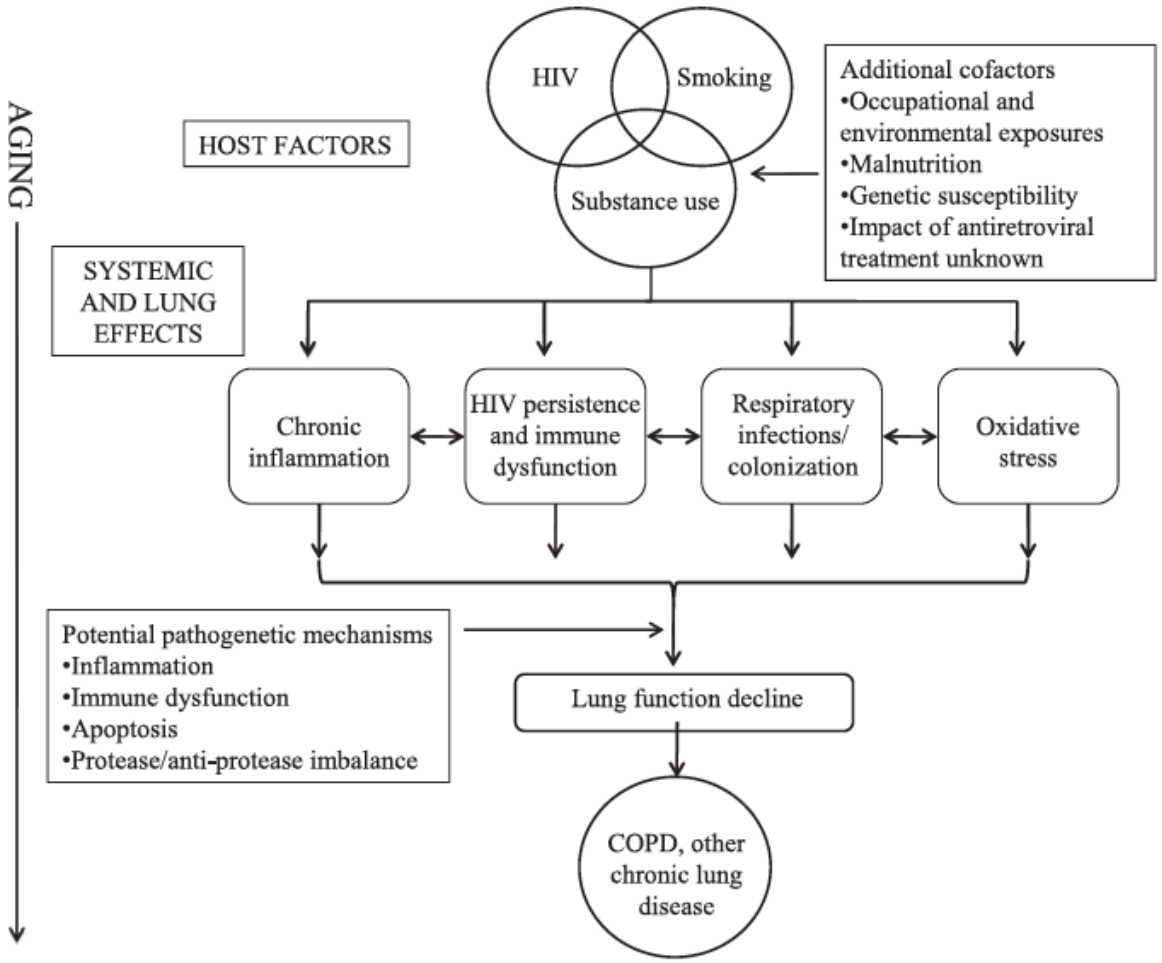
Driven by host factors, systemic and lung effects of chronic HIV



Crothers, K. (2011) Am J Respir Crit Care Med,.

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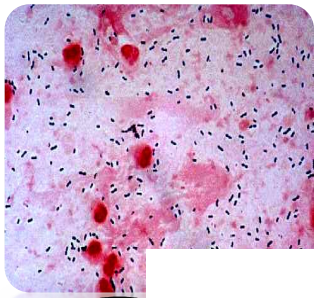
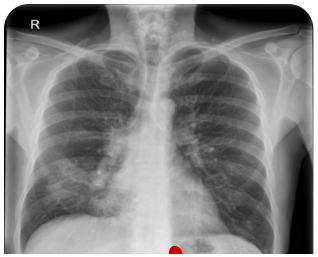
Alveolar macrophages (AM) play a pivotal role in the control of bacteria in the lung



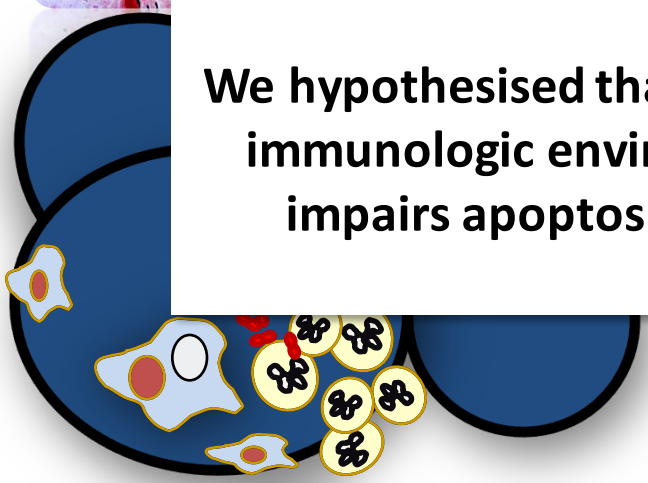


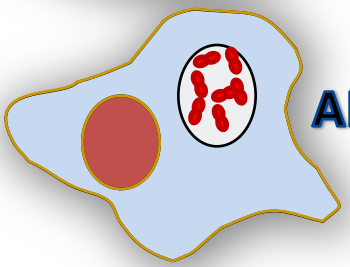
HIV-1 promotes resistance to apoptosis in macrophages which contributes to these cells acting as a viral reservoir for HIV-1

The Journal of Immunology

Circulating Monocytes in HIV-1-Infected Viremic Subjects Exhibit an Antiapoptosis Gene Signature and Virus- and Host-Mediated Apoptosis Resistance[1]

We hypothesised that there is a persistently altered virologic and immunologic environment in the HIV lung during HAART that impairs apoptosis-associated pneumococcal killing by AM





APOPTOSIS

BioMed Central

Research

Open Access

Apoptosis resistance in HIV-1 persistently-infected cells is independent of active viral replication and involves modulation of the apoptotic mitochondrial pathway

Pablo N Fernández Larrosa*[1], Diego O Croci[2], Diego A Riva[3], Mariel Bibini[1], Renata Luzzi[1], Mónica Saracco[1], Susana E Mersich[3], Gabriel A Rabinovich[2] and Liliana Martínez Peralta[1]

Blumenthal RL J Allergy Clin Immunol. 2001; Dockrell J Infect Dis 2001;. Dockrell J Immunol. 2003; Marriott J Clin Invest. 2005; Guillemard, E. Virology 2004; Olivetta, E. Exp Cell Res 2006; Giri, M.S. Journal of Immunology 2009

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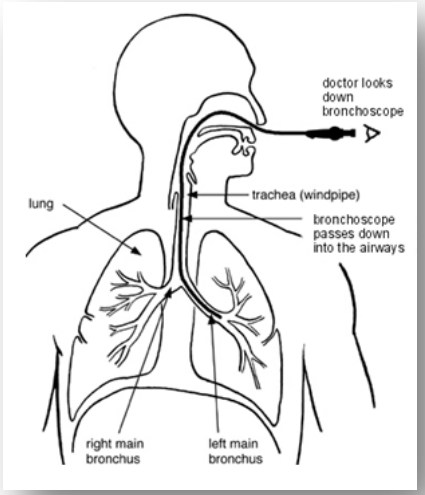
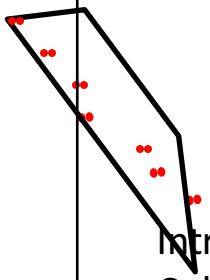
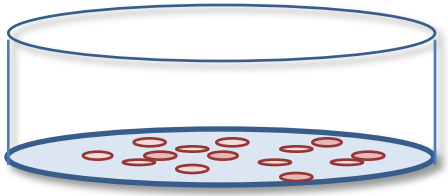
	HIV ARV (n = 14)	HIV NAÏVE (n = 3)	CONTROL (n = 12)
Age (years)	42.4 ± 2.4	41.7 ± 5.3	40.8 ± 2.7
Male Sex	8, 57%	3, 100%	8, 67%
Ethnicity			
White	9	3	9
Black African	4	0	3
other ethnicity	1	0	0
Nadir CD4 (cells/mm3)	213 ± 26	587 ± 105	n/a
CD4 (cells/mm3)	643 ± 51	672 ± 176	n/a
CD4:CD8	0.83 ± 0.07	0.66 ± 0.003	n/a
HIV RNA (log10 copies/mL)	all undetectable	4.43 ± 3.84	n/a
ART		n/a	n/a
Protease Inhibitor	6		
NNRTI	7		
Mixed or other	1		
Duration (months)	87.2 ± 14.5*		

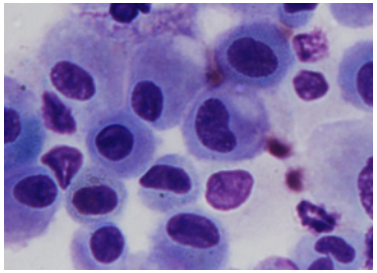
data expressed as mean ± SEM

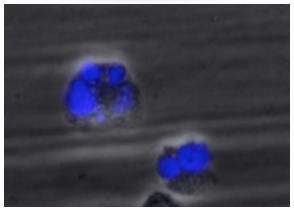




Intracellular Bacterial killing
Cell death and apoptosis







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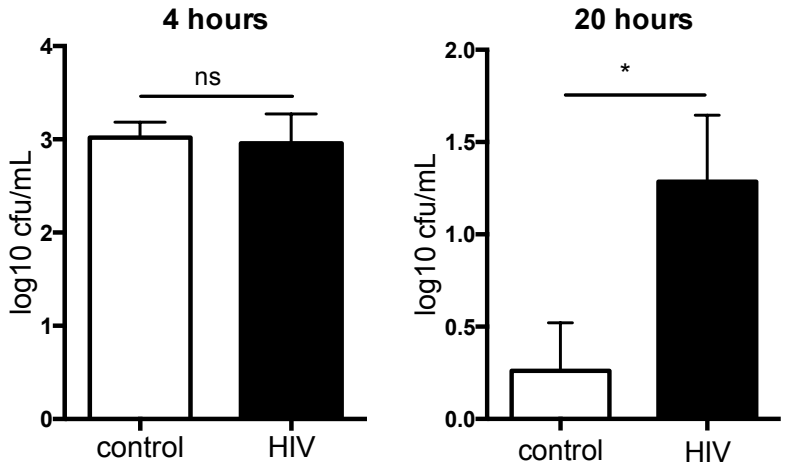
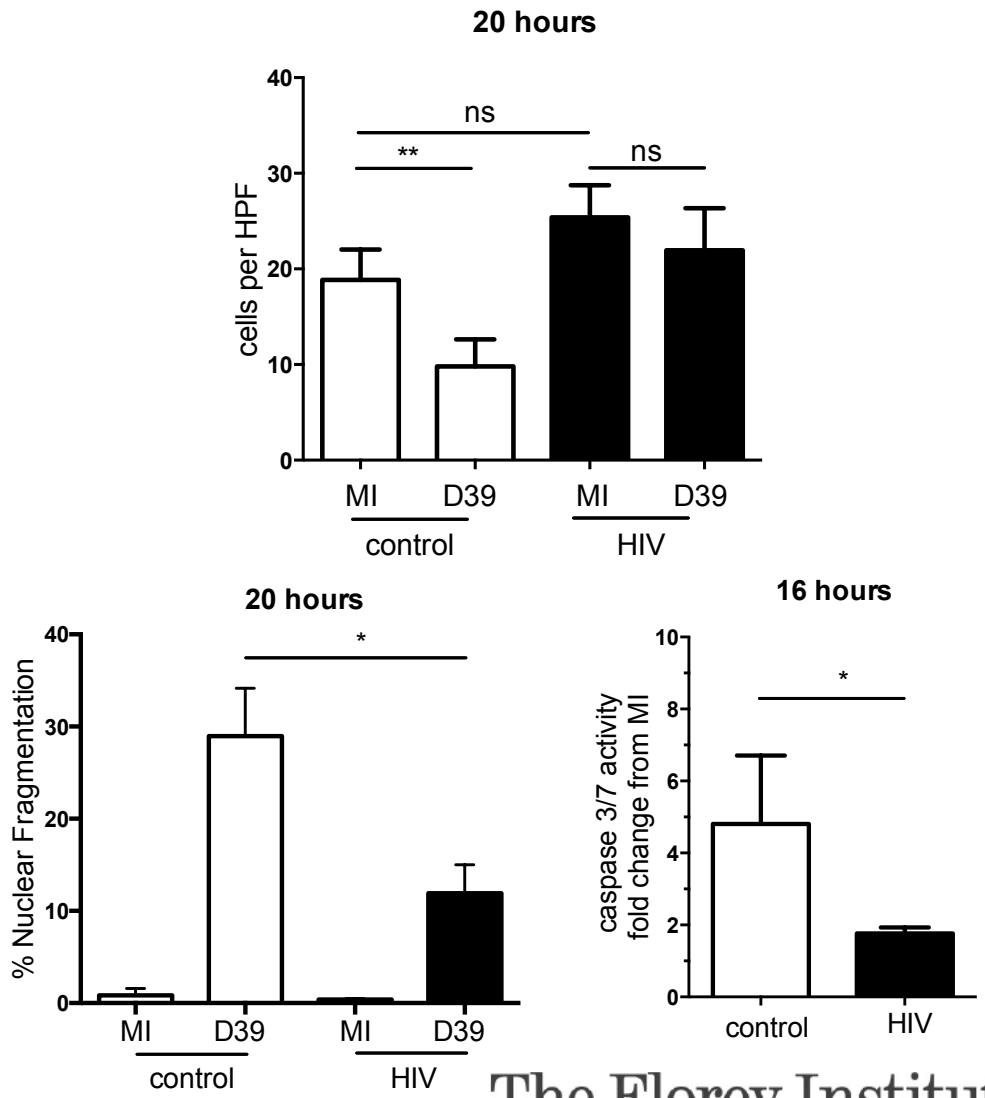
HIV+ AM demonstrated impaired intracellular killing of pneumococci



Associated with reduced apoptosis



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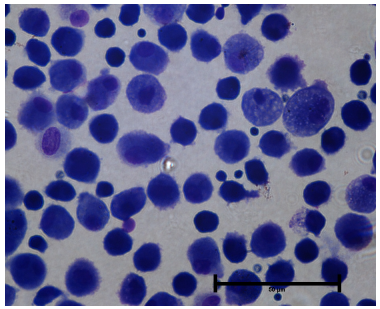
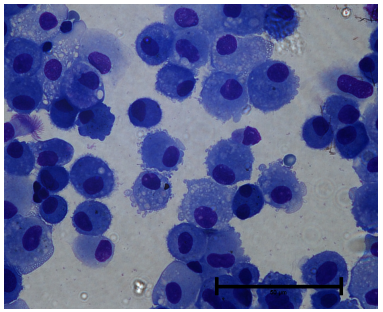
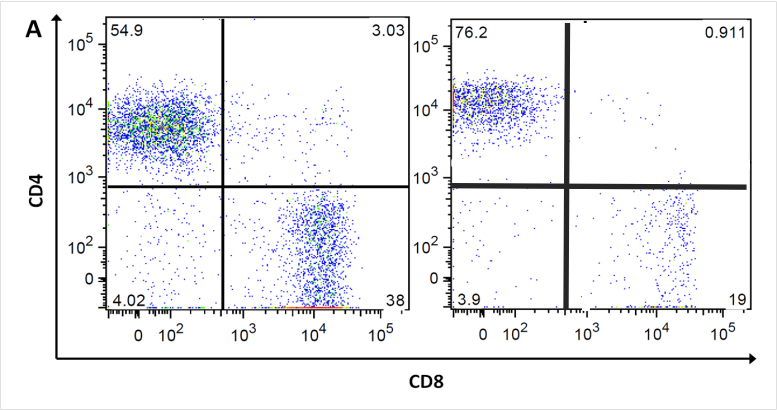
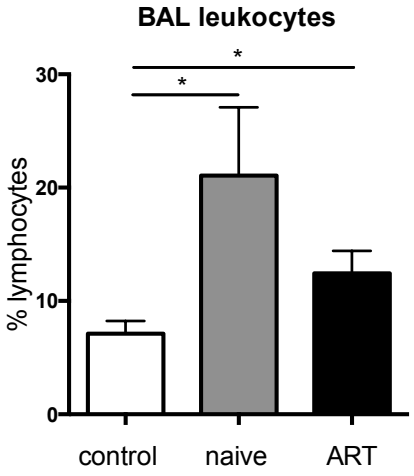
HIV+ on ART have a BAL lymphocytosis

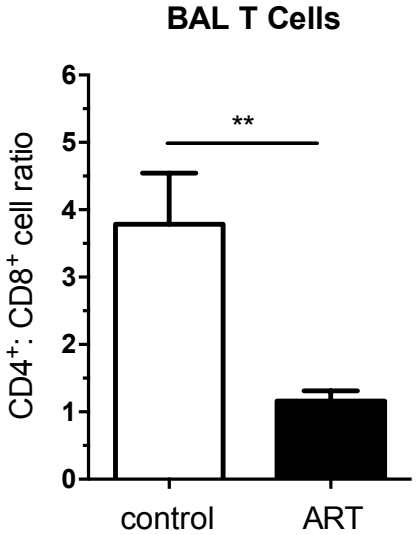


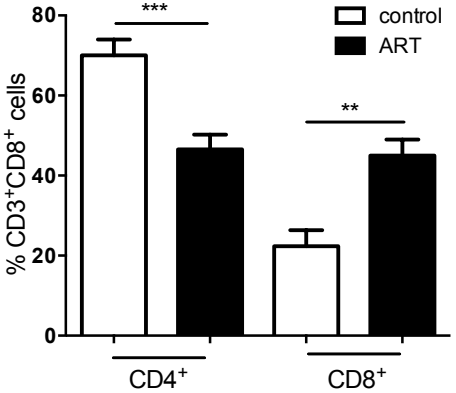


….with a CD8+ predominance of T cells









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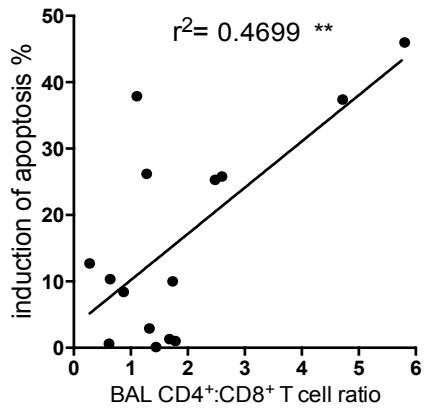
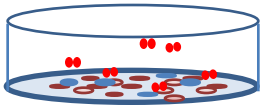
<<10% AM infected with HIV in vivo - indirect mechanism?

OPEN ACCESS Freely available online PLOS | PATHOGENS

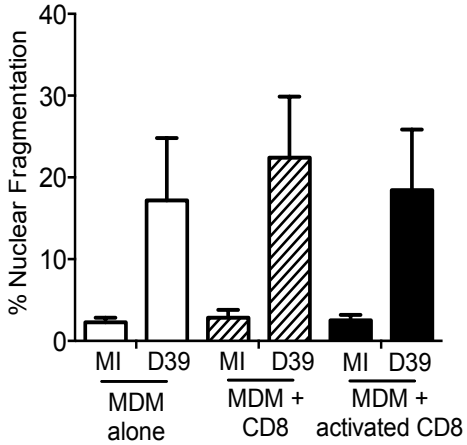
HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality

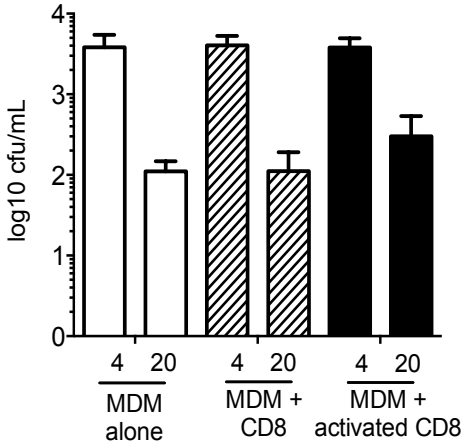
Sergio Serrano-Villar[1]*, Talia Sainz[2], Sulggi A. Lee[3], Peter W. Hunt[3], Elizabeth Sinclair[3], Barbara L. Shacklett[4], April L. Ferre[4], Timothy L. Hayes[4], Ma Somsouk[3], Priscilla Y. Hsue[3], Mark L. Van Natta[5], Curtis L. Meinert[5], Michael M. Lederman[6], Hiroyu Hatano[3], Vivek Jain[3], Yong Huang[7], Frederick M. Hecht[3], Jeffrey N. Martin[8], Joseph M. McCune[3], Santiago Moreno[1], Steven G. Deeks[3]





Human monocyte derived macrophage





Jambo, K.C. Mucosal Immunity 2014; Lewin, S.R. AIDS 1998; Sierra-Madero, J.G. JID 1994; Serrano-Villar, S. PLoS Pathog. 2014;

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Apoptotic Killing of HIV-1–Infected Macrophages Is Subverted by the Viral Envelope Glycoprotein

Simon Swingler, Angela M. Mann, Jin Zhou, Catherine Swingler, Mario Stevenson*

Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, United States of America

Is gp120 present in the alveolar space?

Is gp120 mediating the pneumococcus associated anti apoptotic effect on AM?

Swingler PLoS Pathogens 2007 Gundavarapu, S. PLoS One 2011,3; Sanosuosso, M. JID 2009;

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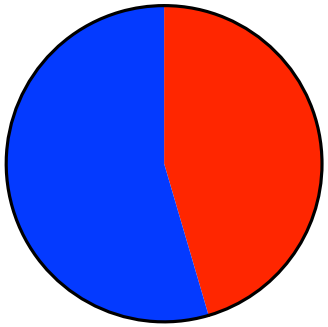
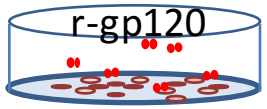
gp120 detectable in BAL fluid despite HAART

BAL fluid gp120

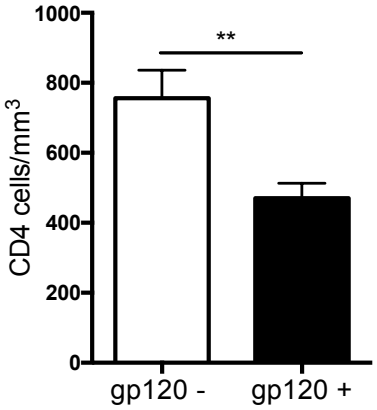


n = 11

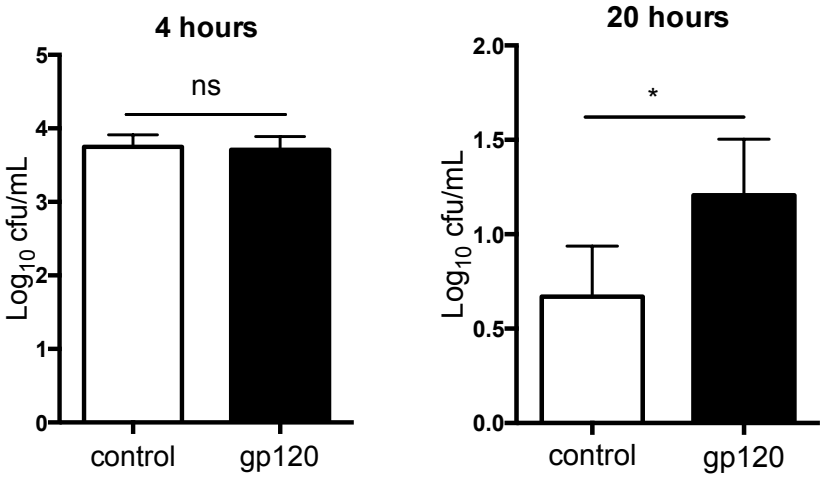
sandwich ELISA with anti-gp120 monoclonal Ab: 14E,17B, EH21

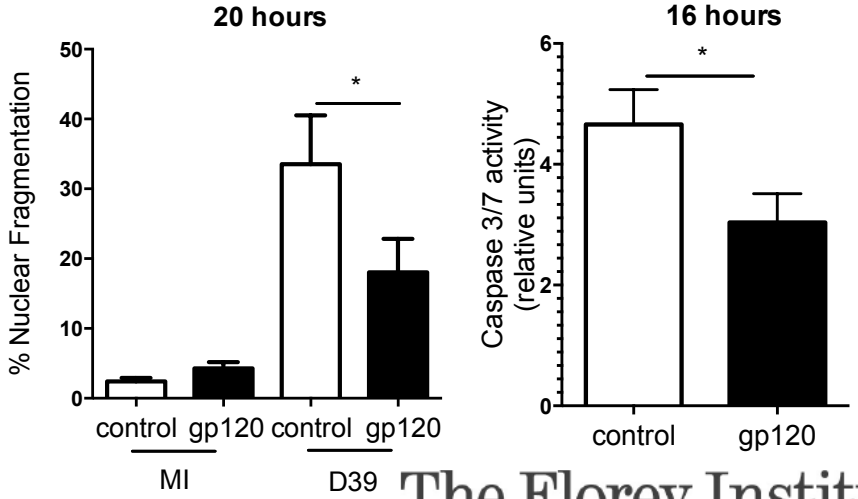


Human monocyte derived macrophage



gp120 treatment of MDM impairs apoptosis associated killing of pneumococci





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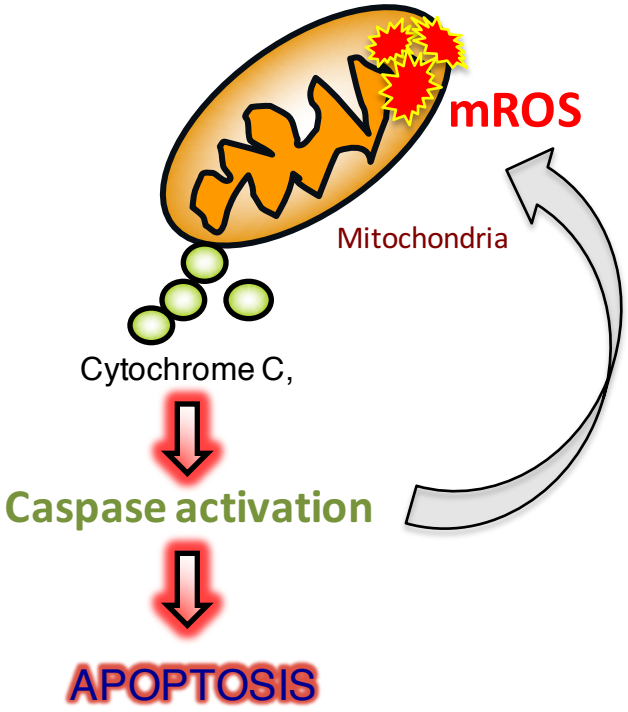
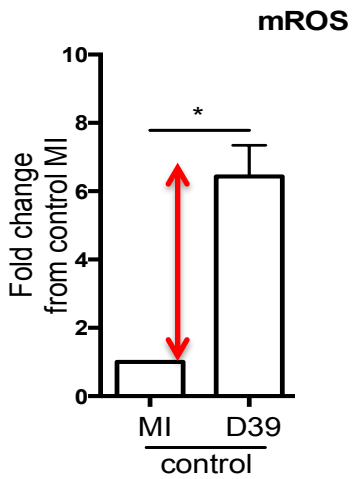
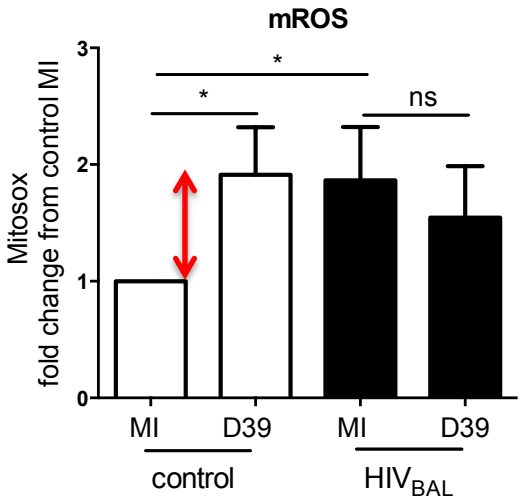
gp120 impairs apoptosis associated Mitochondrial ROS generation which may impair killing







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Conclusions

In HIV seropositive individuals

- A CD8 lymphocytosis persists and gp120 remains detectable in the lung despite HAART.
- Alveolar macrophages have an impaired apoptotic response to pneumococci which limits their killing capacity
- gp120 causes macrophage oxidative stress and impairs apoptosis-associated killing of pneumococci.

Thus, the immune environment of the lung fails to correct with HAART and may play a role in HIV associated lung disease.

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Acknowledgements

wellcome trust

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Ian Geary
Jonathan Kilby
Sarah Moll

Moira Whyte

Patients & Volunteers

Tulane University, New Orleans
James E Robinson

UCL, London
Maddy Noursadeghi

LSTM, Liverpool
Steve Gordon

Sheffield Teaching Hospitals
Endoscopy Unit
Clinical Research Facility

MRC Medical Research Council

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