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# HIV in the lung: virological and immunological findings in long-term ART

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Department of Infection, Immunity and Cardiovascular Diseases  
The University of Sheffield

# HIV+ individuals still at risk of 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,<sup>1</sup> Nicolai Lohse,<sup>2</sup> Jan Gerstoft,<sup>2</sup> Gitte Kronborg,<sup>4</sup> Lars Ostergaard,<sup>1</sup> Court Pedersen,<sup>5</sup> Gitte Pedersen,<sup>6</sup> Henrik Toft Sorensen,<sup>2</sup> and Niels Obel<sup>1</sup>



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

Zheng Yin<sup>a</sup>, Brian D. Rice<sup>a</sup>, Pauline Waight<sup>b</sup>, Elizabeth Miller<sup>b</sup>,



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

Matthew R Gingo<sup>1\*</sup>, Goundappa K Balasubramani<sup>2</sup>, Thomas B Rice<sup>1</sup>, Lawrence Kingsley<sup>2,3</sup>, Eric C Kleerup<sup>4</sup>,



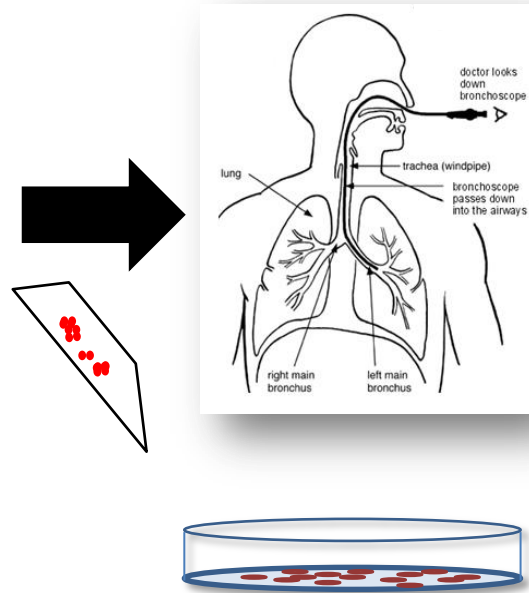
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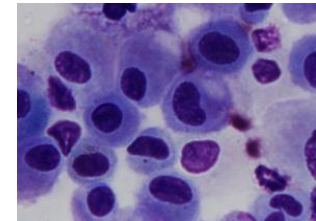
## Driven by host factors and systemic and lung effects of chronic HIV

14 HIV+ patients  
With UDE VL and Normal  
CD4 on HAART  
Vs  
3 HIV+ not on HAART  
Vs  
12 HIV-ve controls

ALL  
Non smokers  
No HBV/HCV  
No Acute lung pathology

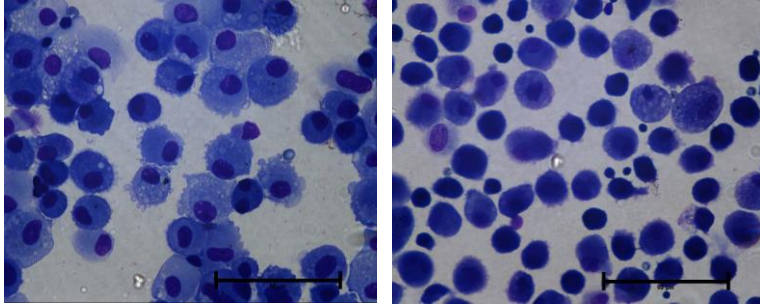


HIV+ AM demonstrated  
impaired intracellular  
killing of pneumococci



HIV+ on ART have a BAL lymphocytosis

....with a CD8+ predominance of T cells



The Journal of Infectious Diseases 2008; 197:109–16

## Effect of Highly Active Antiretroviral Therapy on Viral Burden in the Lungs of HIV-Infected Subjects

Homer L. Twigg III,<sup>1</sup> Michael Weiden,<sup>2</sup> Fred Valentine,<sup>2</sup> Carol T. Schnitzlein-Bick,<sup>1</sup> Roland Bassett,<sup>3</sup> Lu Zheng,<sup>2</sup>

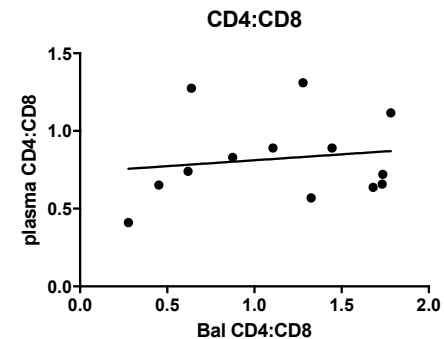
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PLOS PATHOGENS

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

Knox S. et al. 2010 J. Virol. 2010, 84(18):9010.



# HIV-1 in the lung?

p24 in AM cultures from  
2/2 ART-naïve and 3/10  
ART-treated HIV-1-  
seropositive donors

Sample ID	HIV status
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive
	Positive (ART naïve)
	Seronegative
	Seronegative
	Seronegative

BAL analysed for HIV-1 RNA

- 14 HIV-positive  
13/14 on ART; 1/13 ART naïve
- 3 HIV-negative

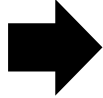
All volunteers were

- non-smoking adults
- no active or chronic lung disease
- No active viral hepatitis.

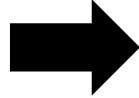
# HIV-1 in the lung?



6 -12 ml of  
acellular BAL



Ultracentrifuged  
240,000g  
x 20 min at 4°C



Abbott  
m2000rt  
platform

## Tested for inhibition and sensitivity

Plasma & BAL obtained from HIV-negative volunteers spiked with WHO 3<sup>rd</sup> International HIV-1 RNA Standard & BAL from HIV-positive ART naive

Standard Input (log <sub>10</sub> cps/ml)	Plasma detection (log <sub>10</sub> cps/ml)	BAL detection (log <sub>10</sub> cps/ml)
	Mean of 2	Mean of 2
2.0	1.8	1.8
2.7	2.5	2.5
3.0	2.7	2.8
3.7	3.5	3.5
4.0	3.8	3.9
RP2003 (ART Naive)		1.9 log <sub>10</sub> cps/ml

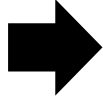
Input Vol.	LLD
12 mL	ND < 1 cp/ml
6 mL	ND < 2cps/mL



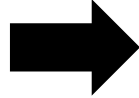
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Sample	Volume (ml)	HIV-1 RNA cps/ml	
		Replicate 1	Replicate 2
ZP2303	12	< 1 cp/ml	< 1 cp/ml
WP2102	12	< 1 cp/ml	< 1 cp/ml
UP2307	12	4 cps/ml	2 cps/ml
AP1109	12	< 1 cp/ml	< 1 cp/ml
VP0910	12	< 1 cp/ml	1 cp/ml
TP2401	12	< 1 cp/ml	< 1 cp/ml
SP1501	11	< 1-2cps/ml	< 1-2cps/ml
MP2802	6	< 2cps/mL	
HP1402	11	< 1-2cps/ml	
EP1101	9.5	< 1-2cps/ml	
OP1604	9.5	< 1-2cps/ml	
QP2310	12	< 1 cp/ml	
XP3007	12	< 1 cp/ml	

# HIV-1 in the lung?

The Journal of Infectious Diseases 2008; 197:109–16

MAJOR ARTICLE

AIDS RESEARCH AND HUMAN RETROVIRUSES  
Volume 31, Number 1, 2015  
© Mary Ann Liebert, Inc.  
DOI: 10.1089/aid.2014.0133

IMMUNOLOGY

## Effect of Highly Active Antiretroviral Therapy on Viral Burden in the Lungs of HIV-Infected Subjects

Homer L. Twigg III,<sup>1</sup> Michael Weiden,<sup>2</sup> Fred Valentine,<sup>2</sup> Carol T. Schinzel-Bick,<sup>1</sup> Roland Bassett,<sup>2</sup> Lu Zheng,<sup>2</sup>

## Healthy HIV-1-Infected Individuals on Highly Active Antiretroviral Therapy Harbor HIV-1 in Their Alveolar Macrophages

Sushma K. Cribbs,<sup>1,2</sup> Jeffrey Lennox,<sup>3</sup> Angela M. Caliendo,<sup>4</sup> Lou Ann Brown,<sup>5</sup> and David M. Guidot<sup>1,2</sup>



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PLOS ONE | www.plosone.org | October 2013 | Volume 8 | Issue 10 | e77160



## HIV gp120 Induces Mucus Formation in Human Bronchial Epithelial Cells through CXCR4/ $\alpha$ 7-Nicotinic Acetylcholine Receptors

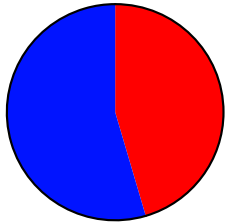
Sravanthi Gundavarapu<sup>1</sup>, Neerad C. Mishra<sup>1</sup>, Shashi P. Singh<sup>1</sup>, Raymond J. Langley<sup>1</sup>, Ali Imran Saeed<sup>2</sup>, Carol A. Feghali-Bostwick<sup>3</sup>, J. Michael McIntosh<sup>4,5</sup>, Julie Hutt<sup>1</sup>, Ramakrishna Hegde<sup>6</sup>, Shilpa Buch<sup>7</sup>, Mohan L. Sopori<sup>1\*</sup>

<sup>1</sup>Respiratory Immunology Division, Lovelace Respiratory Research Institute, Albuquerque, New Mexico, United States of America, <sup>2</sup>Pulmonary and Critical Care Medicine, University of

# does gp120 mediate lung pathology?

gp120 detectable in BAL  
fluid despite HAART

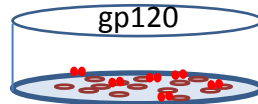
BAL fluid gp120



■ not detected    ■ detected  
n = 11

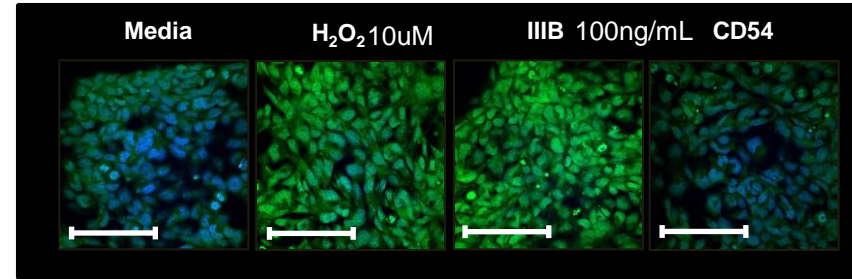
sandwich ELISA monoclonal  
anti-gp120 1.4E,1.7B, EH21

gp120 treatment of MDM  
impairs apoptosis associated  
killing of pneumococci

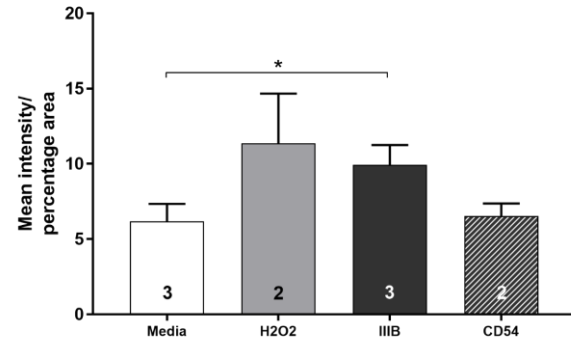


Human MDM

gp120 induces oxidative stress in  
bronchial-epithelial cells



BEAS-2Bs + CellROX stain 30mins



n=15, \*p<0.05, paired s t-test

n=3, \*p < 0.05, Paired t test. Submitted to AJRCCM August 2018

## Conclusions

- There remains elevated risk of pneumococcal infection and chronic lung disease risk despite suppressive ART
- Evidence of persistent lower respiratory tract T cell population imbalance and macrophage dysfunction
- Detectable HIV-1 RNA and gp120
- gp120 may macrophage dysfunction and damage bronchial epithelium

# Acknowledgements

## University of Sheffield

**David Dockrell**

MD Mohasin

Martin Bewley

Katie Cook, Ian Geary

Jonathan Kilby

Sue Clark

**Robert Read**

## Sheffield Teaching Hospitals

Endoscopy Unit

Clinical Research Facility

Sarah Moll

## University of Liverpool

Anna Maria Geretti

Thanos Papadimitropoulos,

Apostolos Beloukas,

## LSTM, Liverpool

Steve Gordon

## Tulane University, New Orleans

James E Robinson

## UCL, London

Maddy Noursadeghi

## Patients & Volunteers

