Dr Laura Waters

University College London Medical School

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Laura Waters	None
Date	**22 September 2012**

Dr Mark Atkins

Imperial College Healthcare NHS Trust, London

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Mark Atkins	Acts in a consultancy capacity fo The Doctors Laboratory, London.
Date	**22 September 2012**

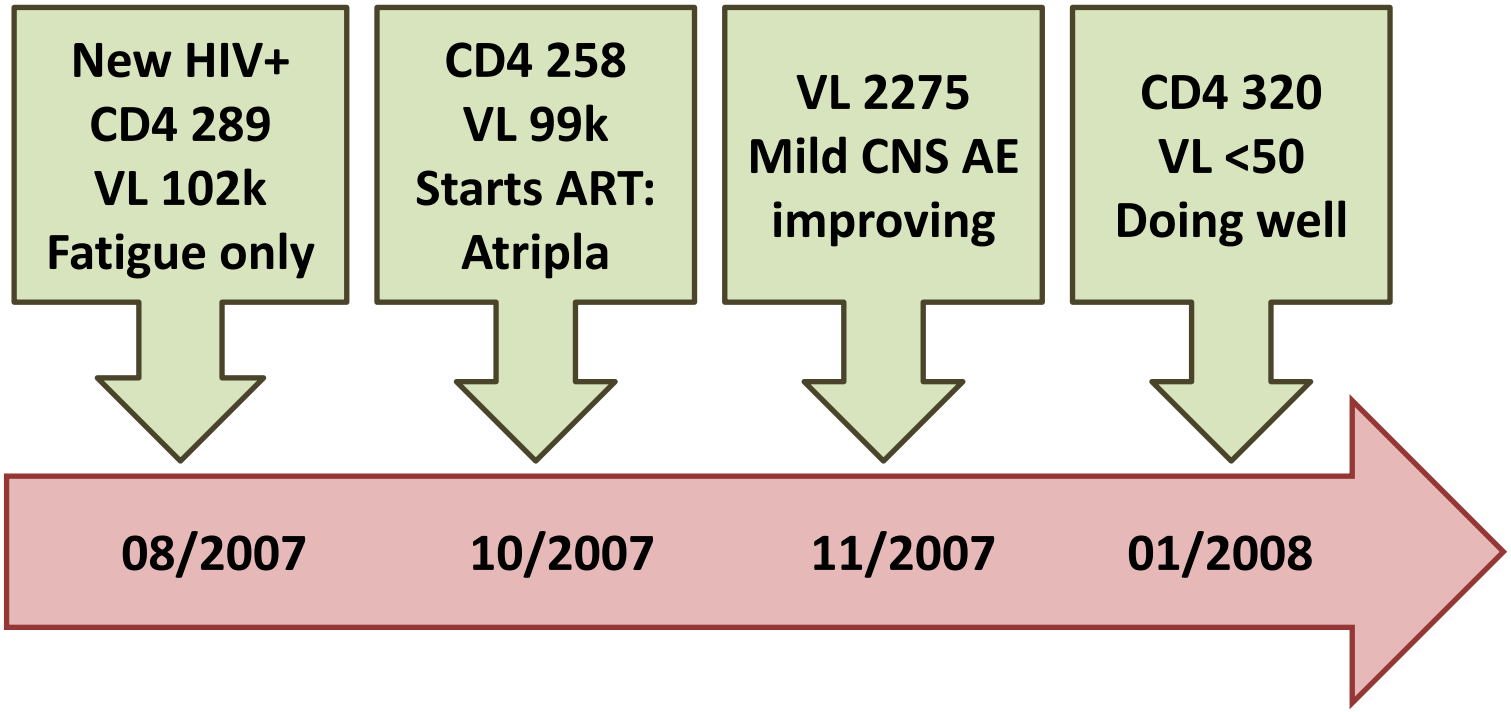
Low-level Viraemia Case & Discussion

Dr Mark Atkins &

Dr Laura Waters

Mr X

- 37 year old Caucasian MSM



Results

Date	HIV-RNA
05/05/2008	55
01/06/2008	<50
19/08/2008	127
30/08/2008	<50
28/10/2008	<50
07/01/2009	76
01/02/2009	84

Is this blipping?

1. Yes
2. No

Blip definitions

- **BHIVA Treatment Guidelines 2012**
  - Blip = detectable VL <400, preceded & followed by an undetectable, without change of therapy
  - Single VL >400 should be investigated further
  - If repeated blips, attempt resistance testing

- **BHIVA Monitoring Guidelines 2011**
  - Blip = single VL 50–1000 preceded and followed by a measurement of <50

Low-level viraemia (LLV)

- **BHIVA Treatment Guidelines 2012**
  - Sustained detectable VL <400
  - Some patients have VL up to 1000 without resistance development & therapeutic drug levels

Key points

- Definitions of blips and low level viraemia (LLV) vary significantly.
- It is important to use a single assay. Results may not be interchangeable especially at low levels. (Garrett et al, J Clin Virol 2012).
- Confirm with second sample.
- Risk of failure;- fully suppressed << Blippers << persistent LLV (Geretti et al Antiviral Ther 2008)
- The size and frequency of blips predicts failure. (Grennan et al J Infect Dis 2012)

What next?

1. Switch regimen
2. Continue to monitor
3. Resistance test
4. Something else

Mr X

- Excellent adherence:
  - No missed doses
  - All doses within a 1 hour window
- Antacids prn, no other medication

Results

Date	HIV-RNA
27/02/2009	105*
16/03/2009	<50
01/05/2009	140*

***Resistance test sent**

Resistance tests

- **First test:**
  - Did not amplify
- **Second test:**
  - Wild type

Are resistance tests at low VL reliable?

1. Yes
2. No
3. Don’t know
4. Don’t send them

Standard genotyping in LLV
(50-1000 copies/ml)

No. samples	Success rate
144	89% overall 84% with VL 50-300 95% with VL >300-100
112	69% with VL 50-200 90% with VL 200-600 95% with VL 600-1000
78	78% overall (cf 95% for >1000) >1000, 87% with VL 201-1000 69% with VL 50-200

1: Mackie *et al*. *J. Virol. Methods* 2004; **2:** Waters *et al*. *AIDS*; **3:** Elgalib *et al. J Clin Microbiol*. 2010

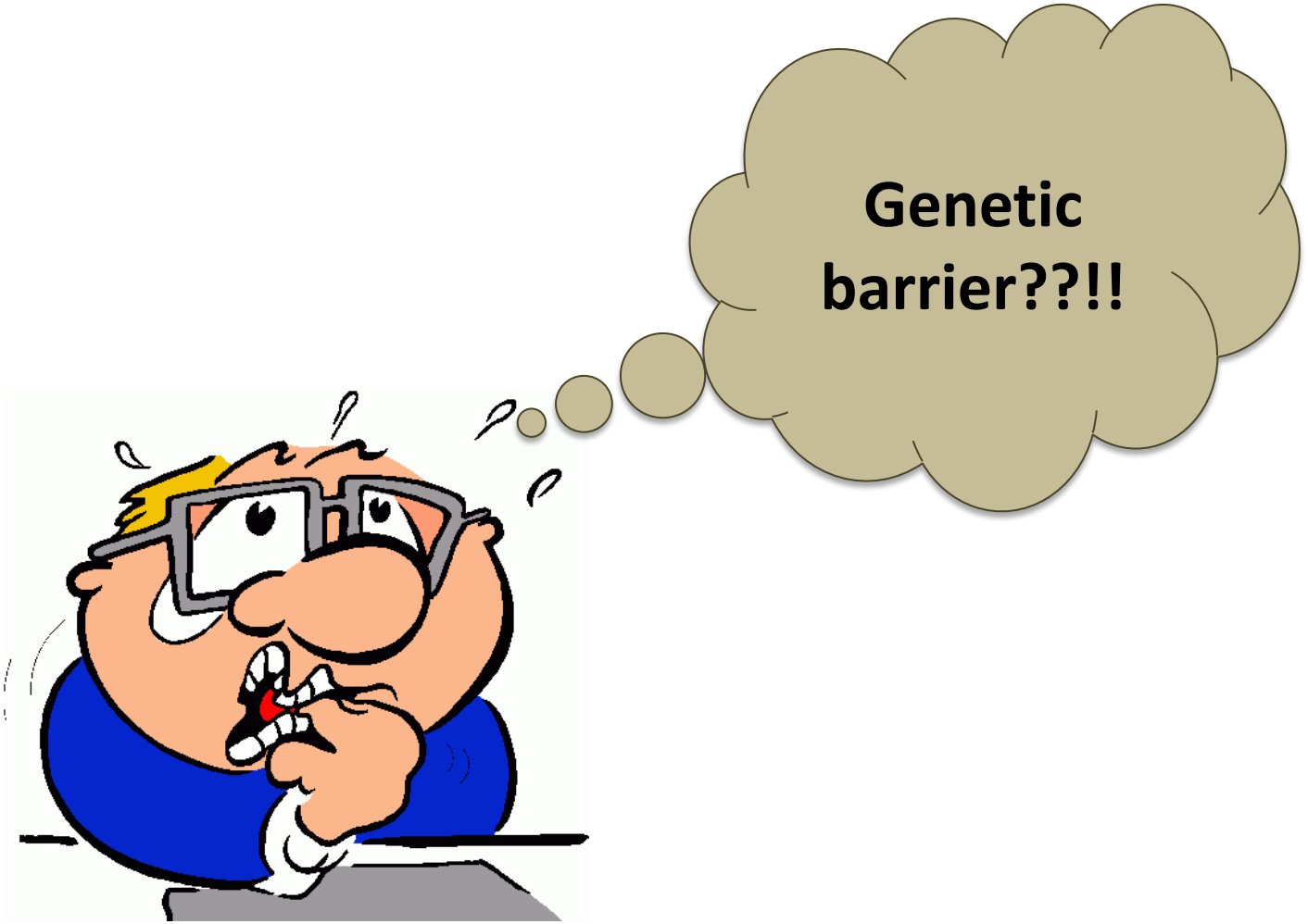
Key points

- DNA genotyping may detect significantly fewer resistance mutations than cumulative RNA testing on previous samples.
- Cellular DNA pools are more stable than plasma RNA in which resistance mutations are enhanced at the time of treatment failure.

  - Delaugerre et al HIV Medicine 2012
  - Garcia et al Antiviral Ther 2011
  - Winden et al J Antimicrbial Chemother 2011

What next for Mr X?

1. Continue NNRTI
2. Intensify regimen with 1 drug
3. Intensify regimen with 2 drugs
4. Change to boosted PI
5. Something else


Genetic barrier??!!

BHIVA 2012

“LLV on a low genetic barrier regimen warrants prompt regimen change”

Evidence

- ATHENA Cohort[1]
  - 4447 patients, 21.2% episodes of LLV (50-1000 copies/ml)
  - During 29 (1.7%) episodes LLV, a sequence was obtained. RAMs were found in 22 (76%). 12/29 (41%) LLV episodes followed or preceded by high-level viremia

- Mackie *et al*[2]
  - Analysis of UK resistance database
  - 1001/7861 (12.7%) resistance tests on VL <1000
  - VL <300 on an NNRTI, 61/126 (48%) had NNRTI resistance

1: Van Sighem *et al*. JAIDS 2008.**2:** Mackie *et al*.

Mr X

- June 2009: switched to Truvada/darunavir/ritonavir (once daily)

Antiretroviral Drug Resistance in HIV-1–Infected Patients Experiencing Persistent Low-Level Viremia During First-Line Therapy

Babafemi Taiwo,[1,a] Sebastien Gallien,[2,a] Evgenia Aga,[3] Heather Ribaudo,[3] Richard Haubrich,[4] Daniel R. Kuritzkes,[2] and Joseph J. Eron Jr[5]

- Subjects were identified retrospectively from two ACTG clinical trials
  - A5142 and EFV arms of A5095
- NTVS cases were defined as subjects with HIV-1 RNA levels between 50 and 1000 c/mL on at least 2 occasions during a 6-month period or longer while on randomized ART
- **NTVS was observed in 5% of the trial population**
- Length of NTVS period (weeks): 38 (24 - 48)
- HIV-1 RNA during NTVS period (copies/ml)
  - First value 97 (59 – 368)
  - Minimum 25 (25 – 115)
  - Maximum 260 (79 – 1,333)
  - Time adjusted AUC 77 (49 – 470)

J Infect Dis. 2011 Aug 15;204(4):515-20

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- Resistance mutations emergence in 20/54 **(37%)** of patients

- Mutations RT gene
  M184VI (n=14),
  K103N (n=9),
  M230L (n=3)

- No mutations in protease gene

- Risk factors
  - Race/ethnicity
  - Level of pVL

		New Resistance		P
		No (N=31)	Yes (N=23)	
Length of NTVS period*		33 (24 – 56)	25 (23 – 48)	1.0
# of HIV-1 RNA determinations*		5 (4 – 8)	5 (3 – 7)	0.12
# of Outliers ≤50 c/ml	*1* *2*	61% 3%	30% 4%	0.05
# of Outliers ≥1,000 c/ml	*1*	6%	30%	0.03
HIV-1 RNA during NTVS period (c/ml)	*Min.** *Max.** *T-AUC**	25 (25 – 70) 143 (86 – 592) 69 (52 – 135)	62 (25 – 244) 368 (120 – 6,856) 137 (63 – 758)	0.003 0.008 <0.001

J Infect Dis. 2011 Aug 15;204(4):515-20

Results

Date	HIV-RNA
11/07/2009	58
13/08/2009	<40
01/10/2009	<40
03/01/2010	51
14/02/2010	48
31/03/2010	72

What next for Mr X?

1. Check adherence
2. Resistance test
3. Intensify regimen
4. Change regimen
5. Something else

Mr X

- **Adherence**
  - Adamant nil missed and never late
  - Uses telephone for adherence reminders
- **Resistance** test
  - Fails to amplify
- **TDM**
  - Trough [DRV] 658 ng/ml

Results

Date	HIV-RNA
02/05/2010	<40
08/07/2010	65
29/09/2010	90

What next?

- Should we intensify?
- Should we try a different VL assay?
- Should we do nothing?

Guidelines

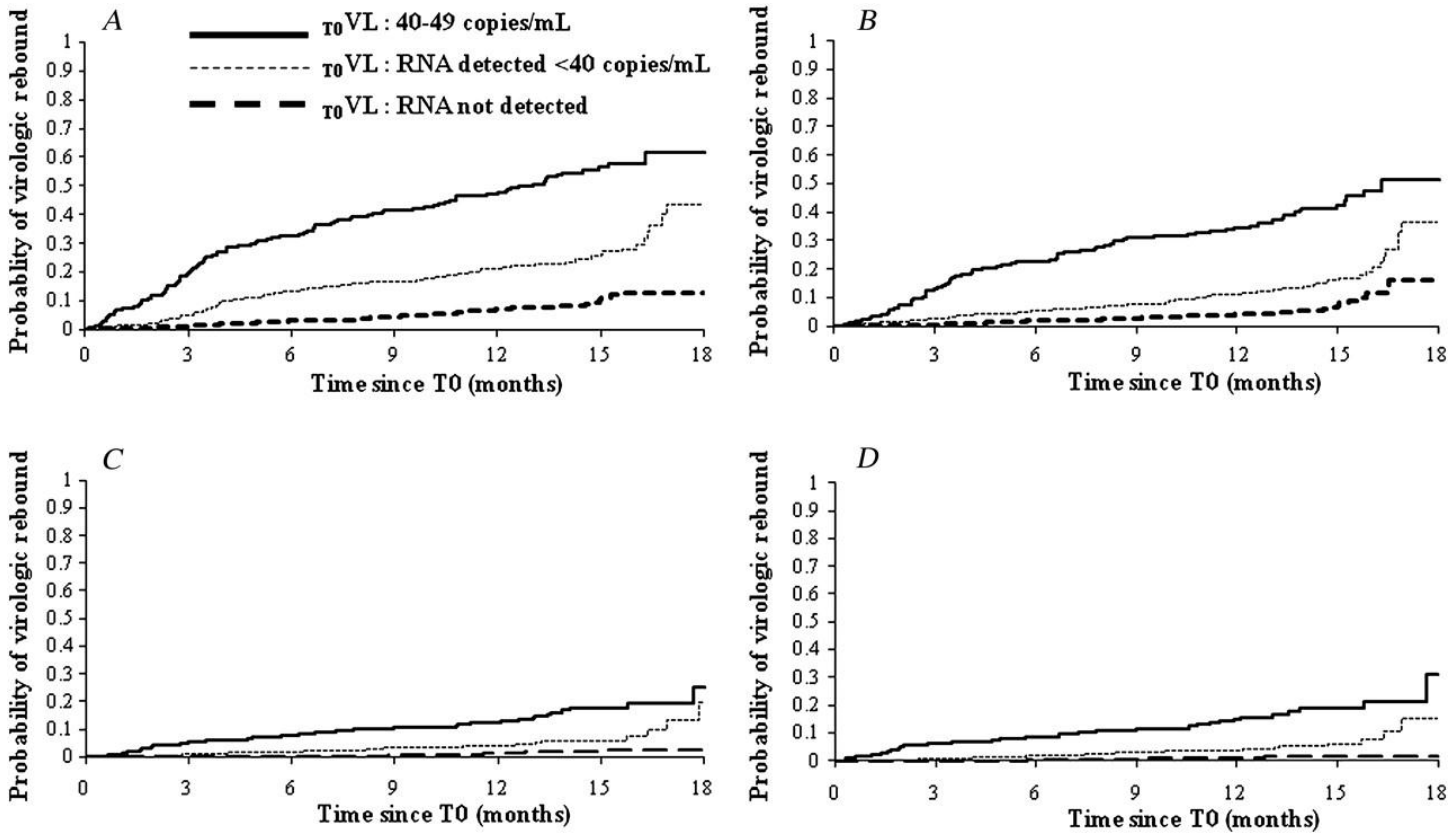
BHIVA 2012	EACS v6	DHHS 2012	IAS 2012
Prompt switch of LLV on NNRTI regimen	If plasma VL >50 and <500-1000 check adherence and repeat VL in 1-2M. Consider changing ART based on current/past R and ART history	VF defined by ACTG as VL >200 based on assay variability Consider R testing if VL 500-1000	Lack of consensus on on VL 50-200 Evaluate factors associated with VF and consider ART switch

Mr X – what we did

- We discussed his options
- Elected to continue to monitor
- Annual resistance tests
- Review plan if VL > 500

How low is low enough?

Time to virologic rebound according to the T0 viral load (VL) and 4 definitions (A–D) of rebound.



Doyle T et al. Clin Infect Dis. 2012;54:724-732

Clinical Infectious Diseases

Issues

- Resistance evolution over time.
- Impact of LLV on immune activation and inflammation
- Impact of persistent LLV on compartmental resistance evolution
- How do we manage residual low-level vireamia?

Thank you