

# Professor Anna Maria Geretti

University of Liverpool

# HIV Persistence During Long-Term Suppressive Antiretroviral Therapy

---

*Anna Maria Geretti<sup>1</sup>, Paola Vitiello<sup>2</sup>, Stacey King<sup>1</sup>, Andrew Owen<sup>1</sup>, Alessandro Cozzi-Lepri<sup>3</sup>, and Andrew Phillips<sup>3</sup>  
on behalf of **The ERAS Study Group\****

*1. University of Liverpool, UK; 2. Busto Arsizio Hospital, Italy;  
3. University College London, UK*

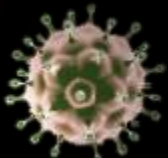
*\*Nicola Mackie; Jonathan Ainsworth; Anele Waters;  
Frank Post; Simon Edwards; Julie Fox*



# Does HIV continue to replicate during seemingly suppressive ART?

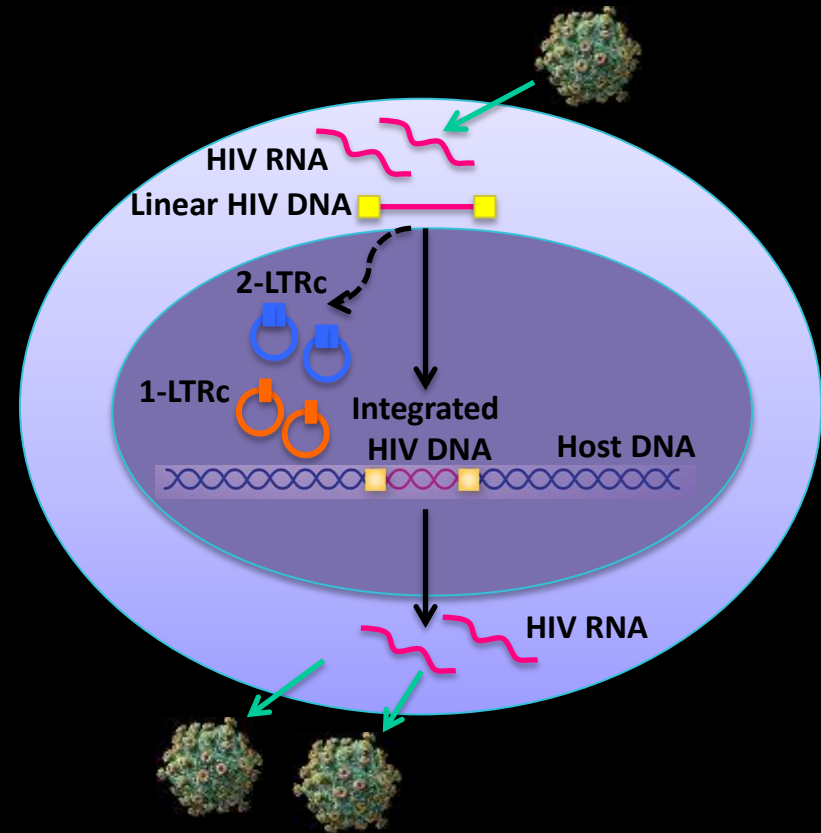
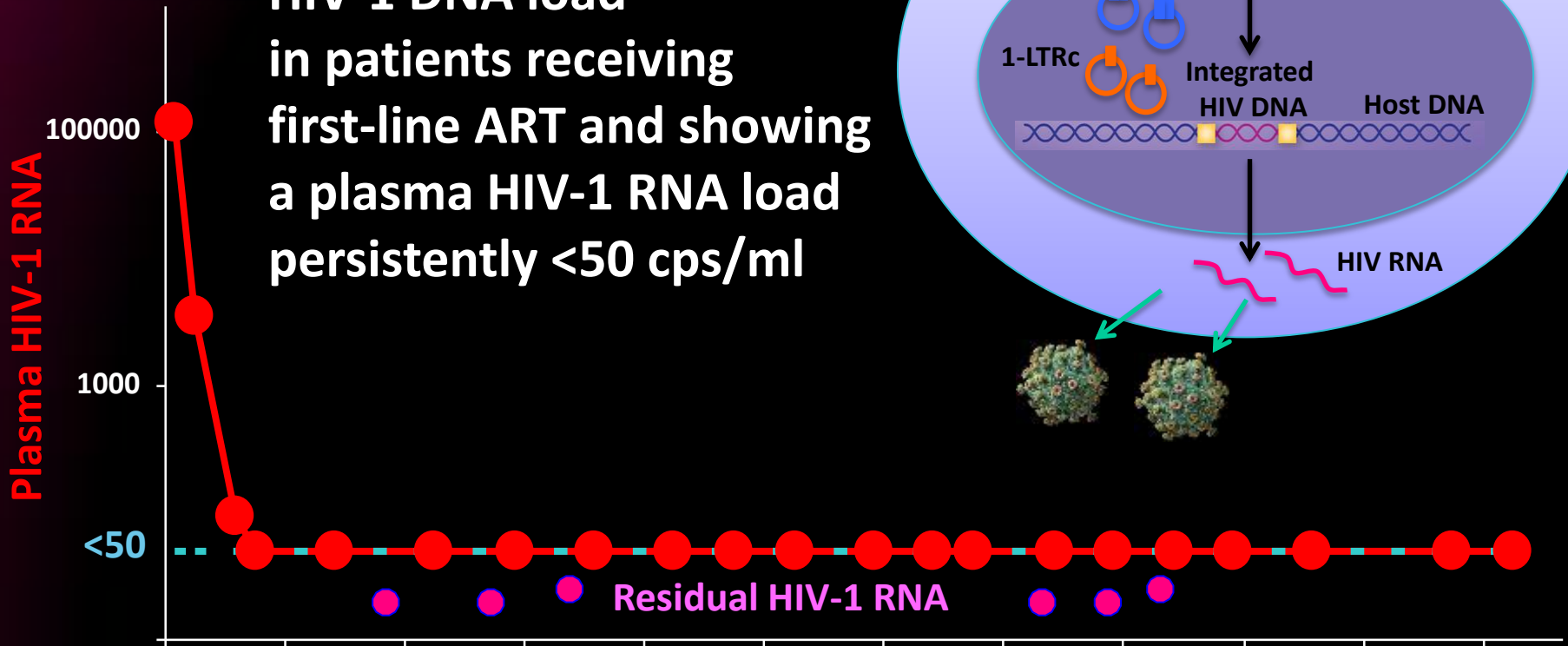
During long-term suppressive ART:

- ❖ Persistent detection of HIV-1 RNA in plasma
- ❖ Stable HIV-1 DNA load in CD4 T-cells
  - *However, heterogeneous study populations*
- ❖ The relationship between the two viral parameters and with other virus, host, and ART related factors remains unclear



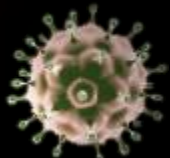
# Study aim

- ❖ To investigate residual plasma HIV-1 RNA detection and cellular HIV-1 DNA load in patients receiving first-line ART and showing a plasma HIV-1 RNA load persistently <50 cps/ml



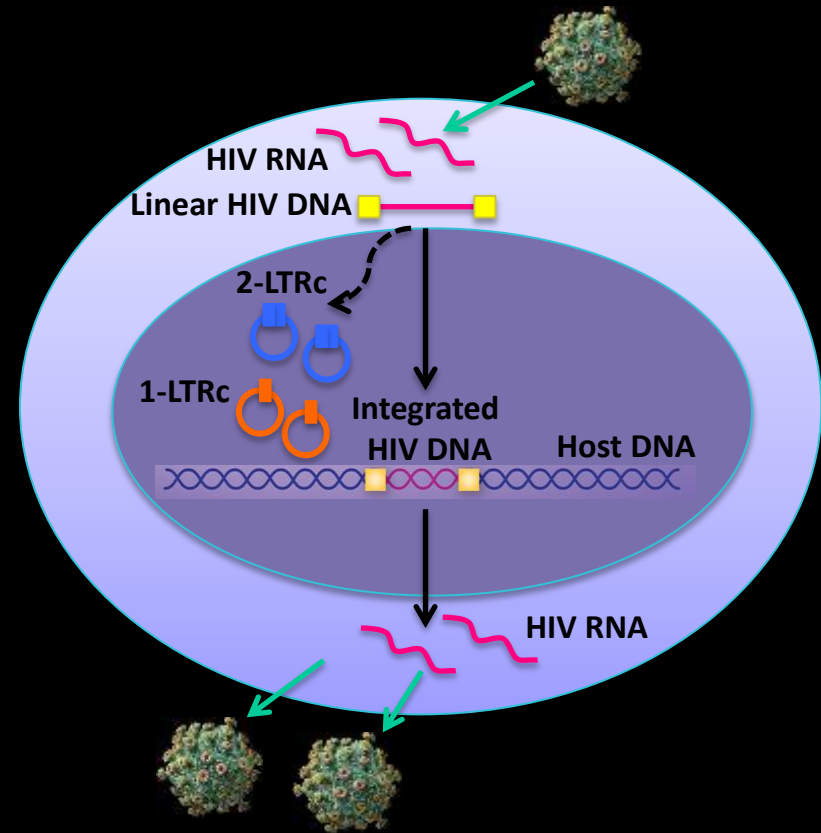
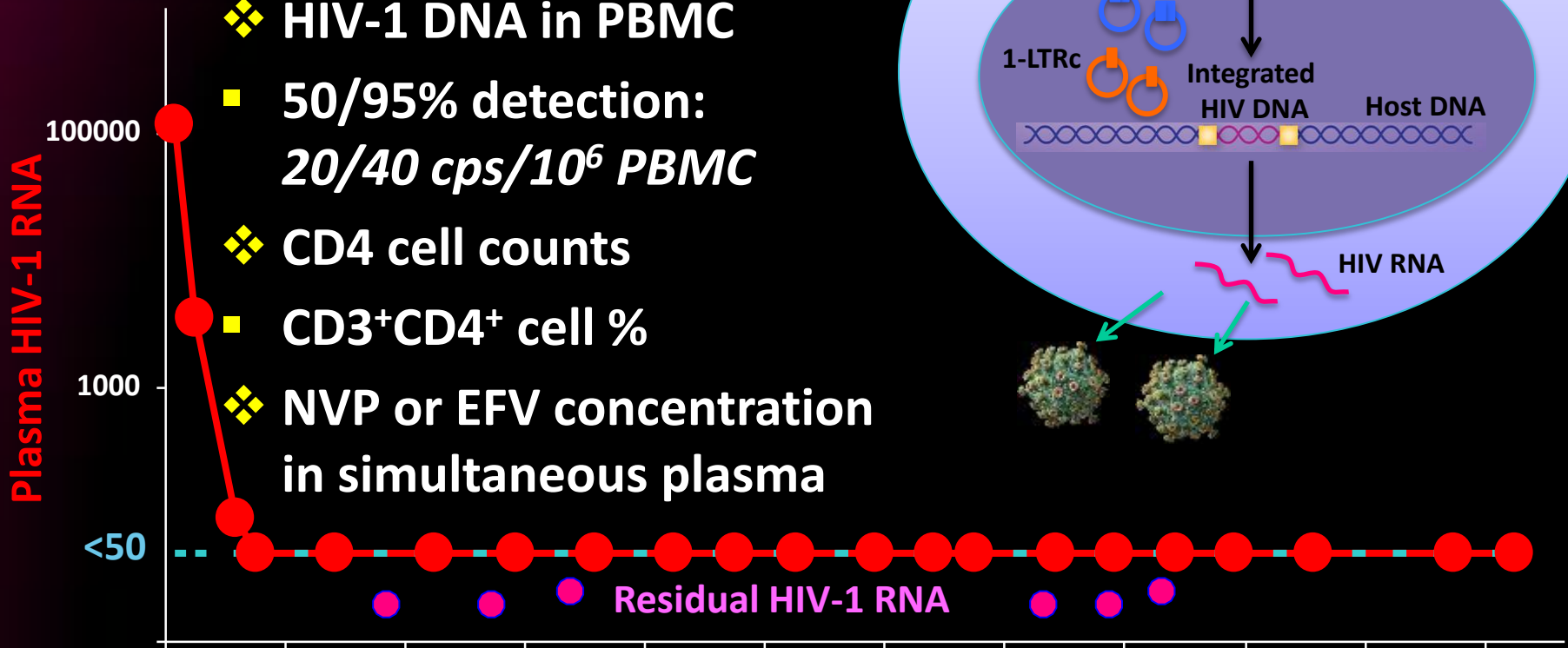
# Eligibility criteria

- ❖ First-line ART with either EFV or NVP + 2NRTIs
- ❖ No change of NNRTI allowed
- ❖ Change of NRTI allowed (e.g., for toxicity)
- ❖ VL <50 cps/ml within 6 months of starting ART
- ❖ All subsequent VL <50 cps/ml
  - *No blips, no treatment interruption*
- ❖ ≥2 VL measurements per year
- ❖ Patients recruited into 10 groups by duration of ART
  - *1 year to >10 years*



# Parameters measured

- ❖ HIV-1 RNA in plasma
  - 50/95% detection:  $1/3$  cps/ml
- ❖ HIV-1 DNA in PBMC
  - 50/95% detection:  $20/40$  cps/ $10^6$  PBMC
- ❖ CD4 cell counts
- CD3<sup>+</sup>CD4<sup>+</sup> cell %
- ❖ NVP or EFV concentration in simultaneous plasma



# Characteristics of the study population

	Years VL <50 cps/ml			Total (n=104)	P
	0-4 (n=31)	5-7 (n=33)	8-15 (n=40)		
Age, yrs*	44 (36, 49)	49 (39, 53)	49 (43, 55)	47 (40, 53)	0.055
Female n (%)	4 (12.9%)	6 (18.2%)	13 (32.5%)	23 (22.1%)	0.117
Risk group n (%)					0.409
MSM	20 (64.5%)	16 (48.5%)	17 (42.5%)	53 (51.0%)	
Hetero	11 (35.5%)	17 (51.5%)	21 (52.5%)	49 (47.1%)	
IDU	0	0	1 (2.5%)	1 (1.0%)	
Other/Unknown	0	0	1 (2.5%)	1 (1.0%)	
Ethnicity					0.789
White	20 (64.5%)	17 (51.5%)	22 (55.0%)	59 (56.7%)	
Black	10 (32.3%)	14 (42.4%)	17 (42.5%)	41 (39.4%)	
Asian	1 (3.2%)	2 (6.1%)	1 (2.5%)	4 (3.8%)	
Duration HIV diagnosis*	4 (3, 6)	7 (5, 8)	10 (8, 13)	8 (5, 10)	<0.001
Nadir CD4 cells*	286 (210, 370)	166 (123, 247)	144 (82, 215)	201 (110, 271)	0.082
Current CD4 cells*	558 (422, 646)	552 (464, 692)	629 (505, 813)	581 (473, 723)	<0.001
Pre-ART VL log <sub>10</sub> *	4.7 (4.0, 5.2)	4.9 (4.6, 5.2)	5.0 (4.7, 5.6)	4.9 (4.5, 5.4)	0.026

\*Median values (IQR)

# Treatment history

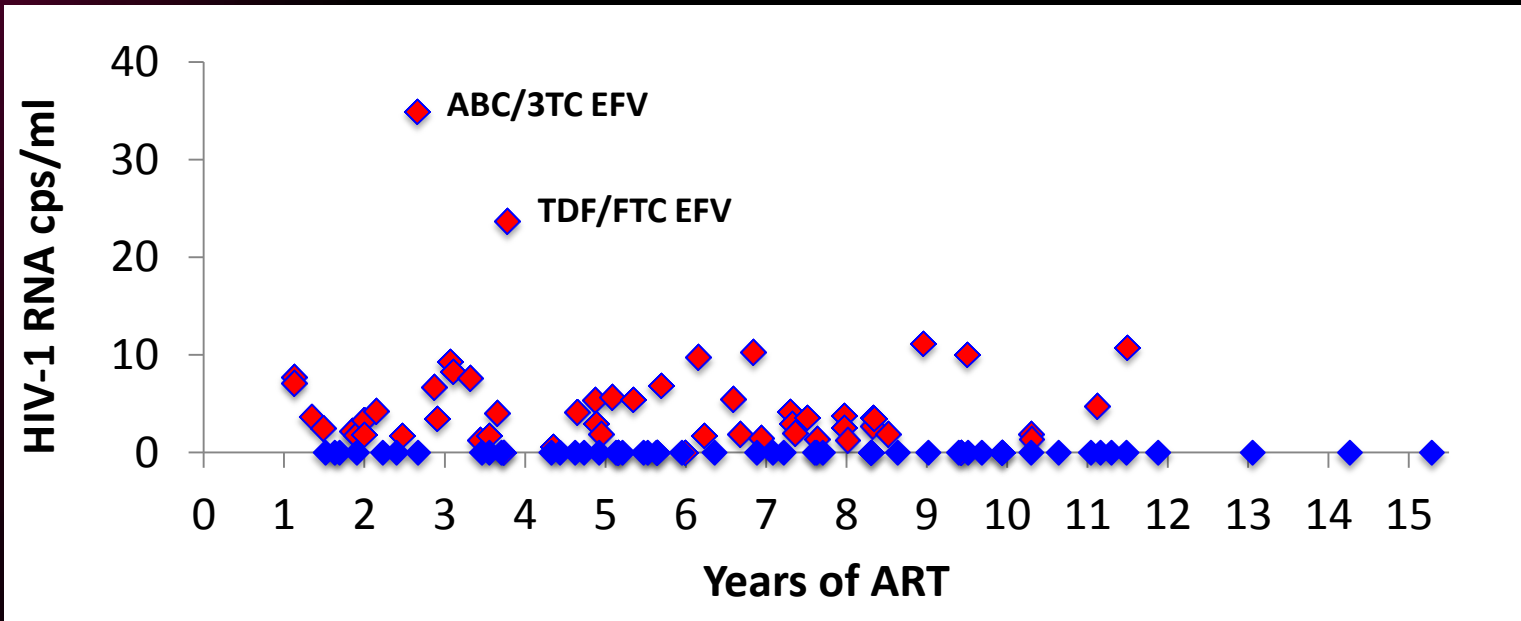
	Years VL <50 cps/ml			Total (n=104)	P
	0-4 (n=31)	5-7 (n=33)	8-15 (n=40)		
Year started ART*	2009 (08, 09)	2006 (05, 06)	2003 (01, 04)	2006 (03, 08)	<0.001
Started NVP n (%)	4 (12.9%)	2 (6.1%)	12 (30.0%)	18 (17.3%)	0.021
NRTI started n (%)					<0.001
ABC/3TC	3 (9.7%)	10 (30.3%)	1 (2.5%)	14 (13.5%)	
AZT/3TC	0 (0.0%)	3 (9.1%)	27 (67.5%)	30 (28.8%)	
TDF/FTC	28 (90.3%)	19 (57.6%)	2 (5.0%)	49 (47.1%)	
Other	0 (0.0%)	1 (3.0%)	10 (25.0%)	11 (10.6%)	
Changed NRTI n (%)	2 (6.5%)	10 (30.3%)	36 (90.0%)	48 (46.2%)	<0.001
EFV level ng/ml*	1513 (708, 2141)	1687 (870, 2238)	1531 (849, 2523)	1531 (843, 2238)	0.657
NVP level ng/ml*	4545 (2522, 6278)	5547 (2343, 8752)	6037 (3571, 7603)	5762 (3074, 7423)	0.523

\*Median values (IQR)



# HIV-1 RNA detection

❖ Plasma HIV-1 RNA detected in 52/104 (50%) patients



HIV-1 RNA cps/ml	Years VL <50 cps/ml			Total (n=104)	<i>P</i>
	0-4 (n=31)	5-7 (n=33)	8-15 (n=40)		
Median (range)	3 (1, 35)	3 (1, 10)	3 (1, 11)	3 (1, 35)	0.451
Mean log <sub>10</sub> (SD)	0.6 (0.3)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.451

## Linear Regression Analysis: HIV-1 RNA change per 10 yrs

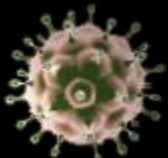
Change in HIV-1 RNA log <sub>10</sub> cps/ml		
	Mean (95% CI)	<i>p</i>
Unadjusted	-0.19 (-0.38, -0.01)	0.044
Adjusted <sup>1</sup>	-0.28 (-0.65, 0.09)	0.132

### *Adjustment:*

<sup>1</sup>age, gender, ethnicity, risk group, duration of HIV diagnosis, nadir CD4, pre-ART VL, NRTIs started, NNRTI used (EFV vs. NVP)

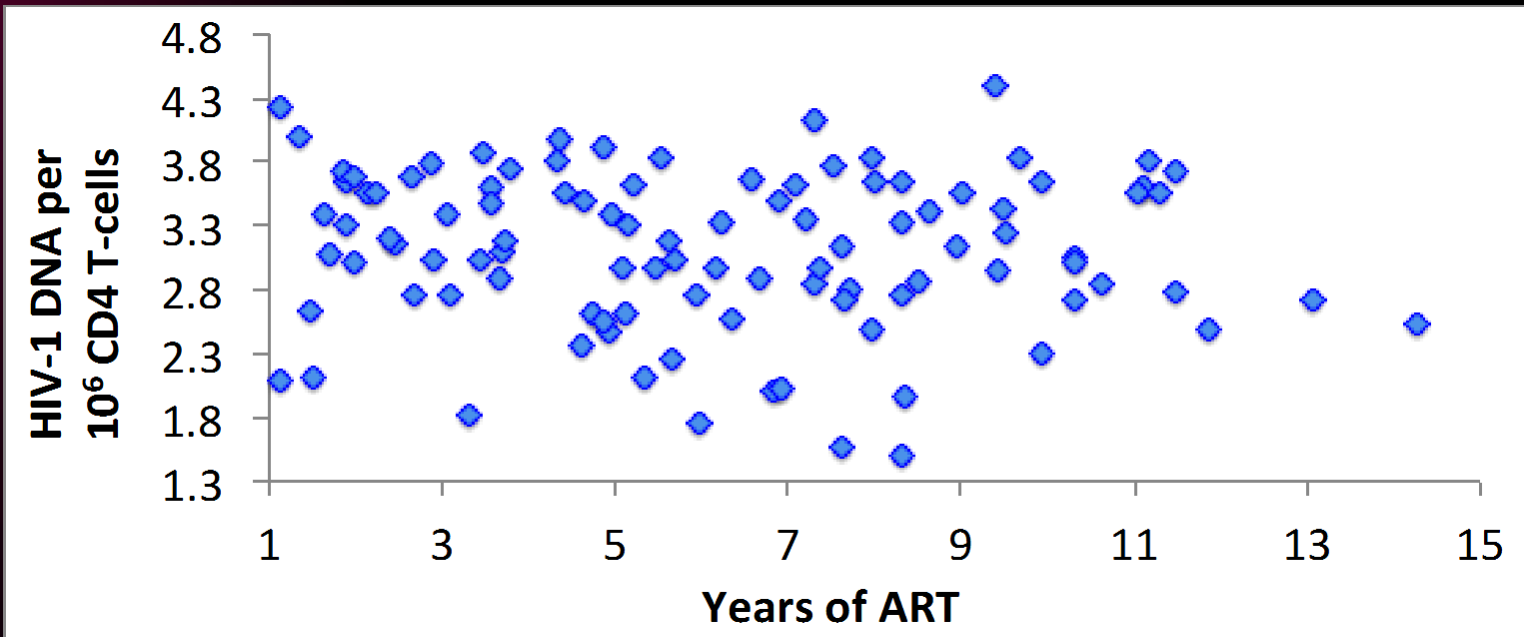
## Multivariate Analysis: Factors associated with mean HIV-1 RNA

- ❖ No association with age, gender, ethnicity, risk group, duration of HIV diagnosis, nadir & current CD4, pre-ART VL, NRTI started, change in NRTI, NNRTI used (EFV vs. NVP), EFV or NVP concentration, HIV-1 DNA load



# HIV-1 DNA detection

❖ HIV-1 DNA detected in 102/104 (98%) patients



HIV-1 DNA log <sub>10</sub> cps/10 <sup>6</sup> CD4 T- cells	Years VL <50 cps/ml			Total (n=104)	<i>P</i>
	0-4 (n=31)	5-7 (n=33)	8-15 (n=40)		
Median (range)	3.3 (2.1, 4.2)	3.0 (1.7, 4.1)	3.1 (1.5, 4.4)	3.2 (1.5, 4.4)	0.451
Mean (SD)	3.2 (0.5)	3.1 (0.6)	3.1 (0.6)	3.1 (0.6)	0.401

## Linear Regression Analysis: HIV-1 DNA change per 10 yrs

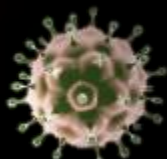
Change in HIV-1 DNA log <sub>10</sub> cps/10 <sup>6</sup> CD4 T-cells		
	Mean (95% CI)	<i>p</i>
Unadjusted	-0.10 (-0.47, 0.27)	0.600
Adjusted <sup>1</sup>	-0.65 (-1.27, -0.02)	0.043

### *Adjustment:*

<sup>1</sup>age, gender, ethnicity, risk group, duration of HIV diagnosis, nadir CD4, pre-ART VL, NRTIs started, NNRTI used (EFV vs. NVP)

## Multivariate Analysis: Factors associated with mean HIV-1 DNA

- ❖ pre-ART VL +0.32  
(0.17, 0.47; <0.001) per log higher
- ❖ NRTI change Yes vs. No +0.42  
(0.07, 0.76; p=0.019)
- ❖ Black vs. White +0.49  
(0.18, 0.80; p=0.002)
- ❖ No association with age, gender, risk group, duration of HIV diagnosis, nadir & current CD4, NRTI started, NNRTI used (EFV vs. NVP), EFV or NVP concentration, HIV-1 RNA level



## Linear Regression Analysis: HIV-1 RNA change per 10 yrs

Change in HIV-1 RNA log <sub>10</sub> cps/ml		
	Mean (95% CI)	<i>p</i>
Unadjusted	-0.19 (-0.38, -0.01)	0.044
Adjusted <sup>1</sup>	-0.28 (-0.65, 0.09)	0.132
Adjusted <sup>2</sup>	-0.14 (-0.39, 0.12)	0.284
Adjusted <sup>3</sup>	-0.25 (-0.64, 0.14)	0.204

### Adjustment:

<sup>1</sup>age, gender, ethnicity, risk group, duration of HIV diagnosis, nadir CD4, pre-ART VL, NRTIs started, NNRTI used (EFV vs. NVP)

<sup>2</sup>change in NRTI, EFV or NVP concentration, HIV-1 DNA level

<sup>3</sup>Factors listed in 1-2

## Linear Regression Analysis: HIV-1 DNA change per 10 yrs

Change in HIV-1 DNA log <sub>10</sub> cps/10 <sup>6</sup> CD4 T-cells		
	Mean (95% CI)	<i>p</i>
Unadjusted	-0.10 (-0.47, 0.27)	0.600
Adjusted <sup>1</sup>	-0.65 (-1.27, -0.02)	0.043
Adjusted <sup>2</sup>	-0.43 (-0.93, 0.06)	0.086
Adjusted <sup>3</sup>	-0.67 (-1.28, -0.05)	0.034

### Adjustment:

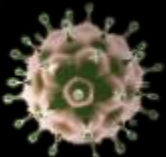
<sup>1</sup>age, gender, ethnicity, risk group, duration of HIV diagnosis, nadir CD4, pre-ART VL, NRTIs started, NNRTI used (EFV vs. NVP)

<sup>2</sup>change in NRTI, EFV or NVP concentration, HIV-1 RNA level

<sup>3</sup>Factors listed in 1-2

# Conclusions

- ❖ During long-term, seemingly suppressive ART, HIV-1 RNA remains detectable in plasma at levels below 10 copies/ml
- ❖ In this highly stably treated population, HIV-1 DNA load declined by  $0.7 \log_{10}$  copies/ $10^6$  CD4 T-cells over 10 years
  - *Inter-person variability, longitudinal data required to identify determinants*
  - *Contribution of defective HIV genomes to be clarified*
  - *Correlation with T-cell activation and inflammation parameters ongoing*
- ❖ The influence of black ethnicity on HIV-1 DNA load warrants further studies

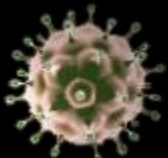


# Acknowledgements

- Nicola Mackie, Imperial College Healthcare NHS Trust
- Jonathan Ainsworth & Anele Waters, N. Middlesex Hospital
- Frank Post, King's College Hospital - KCL
- Simon Edwards, Central & Northwest London Community NHS Foundation Trust
- Julie Fox, St Thomas' Hospital - KCL



*Thank you*





---

British HIV Association  
**BHIVA**

---



**19th Annual Conference of the  
British HIV Association (BHIVA)**

**16–19 April 2013**

Manchester Central Convention Complex