The Clinical Impact of Viral Load Copy Years in Antiretroviral-Naïve HIV Seroconverters

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INTRODUCTION

- Ongoing viral replication may contribute to immune activation which may have deleterious effects additional to CD4 loss before antiretroviral therapy (ART) is started
- A measure of the cumulative exposure to HIV replication (viral load copy years, VCY) may therefore add important prognostic information in chronic HIV infection

METHODS

Data

- CASCADE - cohort collaboration of HIV-1 seroconverters

Inclusion criteria

- ART-naïve patients >15 years
- seroconversion (SC) dates after 1997
- viral load and CD4 measured within 4-12 months following SC

Patient follow-up

- began 4 months after SC
- censored at earliest of
  - ART start
  - CD4 <200 cells/µl
  - no VL and CD4 measurements for >12 months
  - 6 years after SC

Viral load (VL) variables

- current VL: last VL measurement carried forward in time
- Viral load copy years (VCY): time updated area under the VL curve (trapezoid rule)
- average VL: VCY divided by (time since SC)

→ **VCY = average VL * (time since SC)**
interaction between average VL and time since SC

Model

- Poisson model with outcome clinical AIDS or death,
- Each patient month between start and censoring is an observation

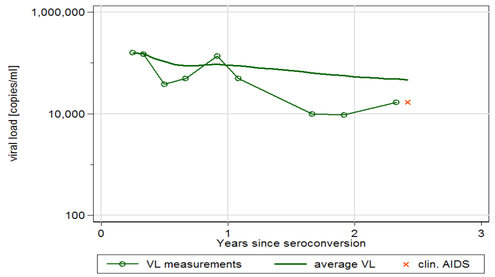
RESULTS

Characteristics of patients

- A total of 9,461 HIV seroconverters could be included
- Based on 15,553 person years of follow-up the overall incidence rate of clinical AIDS/death was 10.4/1000 person years

	without AIDS/death	with AIDS/death	p-value
Number of patients	9,300	161	
Age at SC, median (IQR)	33 (27 - 40)	36 (29 – 44)	< 0.001
Male sex, %	86.2	86.3	0.95
Transmission risk MSM, %	71.9	68.3	0.32
Transmission risk IDU, %	4.5	5.6	0.50

Example patient with current and average VL



Rate of clinical AIDS / death

- Based on 16111 person years of follow-up the overall incidence rate of clinical AIDS/death was 10.4/1000 person years

Time updated CD4 category	Person-years	Failures	Rate	95% CI
200 – 350 cells/µl	2070	42	0.020	(0.015, 0.028)
350 – 500 cells/µl	4827	61	0.013	(0.010, 0.016)
500 – 1000 cells/µl	7924	55	0.007	(0.005, 0.009)
> 1000 cells/µl	732	3	0.004	(0.001, 0.013)
Time updated average VL				
< 20.000 copies/ml	6861	29	0.004	(0.003, 0.006)
20.000 – 100.000 copies/ml	6193	67	0.011	(0.009, 0.014)
> 100.000 copies/ml	2500	65	0.026	(0.020, 0.033)

Poisson model of predictors for outcome clinical AIDS / death

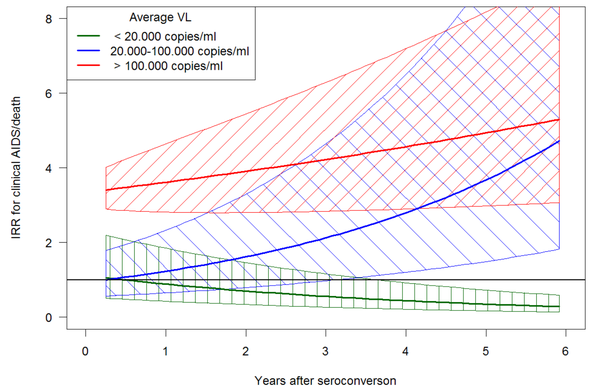
Alternative model – multivariable analysis
(Log likelihood = -1241.7)

	IRR	95% CI	p-value
Age at SC (per year)	1.03	(1.02, 1.05)	<0.001
Female **sex** (vs. male sex)	1.19	(0.67, 2.09)	0.72
Transmission risk **MSM** (vs. other)	0.83	(0.53, 1.28)	0.40
Transmission risk **IDU** (vs. other)	1.45	(0.70, 2.97)	0.31
CD4 category			
200 – 350 cells/µl	1.98	(1.31, 3.00)	0.001
350 – 500 cells/µl	1.51	(1.05, 2.19)	0.028
500 – 1000 cells/µl (Ref.)	1.00		
> 1000 cells/µl	0.71	(0.22, 2.27)	0.56
current VL category			
< 20.000 copies/ml	0.68	(0.43, 1.07)	0.097
20.000 – 100.000 copies/ml	1.00		
> 100.000 copies/ml	1.51	(1.02, 2.22)	0.037
VCY category			
< 20.000 copy years/ml	0.91	(0.54, 1.51)	0.71
20.000 – 100.000 copy years/ml	1.00		
> 100.000 copy years/ml	2.05	(1.39, 3.04)	<0.001
Baseline Rate	0.0005	(0.0003, 0.0009)	<0.001

Final model - Multivariable analysis
(Log likelihood = -1234.9)

	IRR	95% CI	p-value
Age at SC (per year)	1.03	(1.02, 1.05)	<0.001
Female **sex** (vs. male sex)	1.18	(0.67, 2.07)	0.57
Transmission risk **MSM** (vs. other)	0.80	(0.52, 1.25)	0.33
Transmission risk **IDU** (vs. other)	1.39	(0.68, 2.86)	0.37
CD4 category			
200 – 350 cells/µl	2.09	(1.39, 3.15)	<0.001
350 – 500 cells/µl	1.53	(1.06, 2.22)	0.022
500 – 1000 cells/µl (Ref.)	1.00		
> 1000 cells/µl	0.71	(0.22, 2.27)	0.56
average VL category			
< 20.000 copies/ml	1.05	(0.50, 2.20)	0.89
20.000 – 100.000 copies/ml	1.00		
> 100.000 copies/ml	3.41	(1.91, 6.06)	<0.001
VCY = average VL * (time since SC)			
< 20.000 copy years/ml	0.79	(0.58, 1.09)	0.15
20.000 – 100.000 copy years/ml	1.32	(1.12, 1.55)	0.001
> 100.000 copy years/ml	1.08	(0.87, 1.35)	0.49
Baseline Rate	IR 0.0004	(0.0002, 0.0008)	<0.001

Impact of average VL on rate of clinical AIDS/death changing with time after SC



CONCLUSION

- Higher average VL is associated with a higher risk of clinical AIDS/death.
- Accumulation of intermediate VL levels over time leads to higher risks comparable to those associated with high average VL.
- Choice on when to start ART may also be influenced by the duration and extent of previous HIV replication.

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Bucher, Martin Rickenbach, Patrick Francioli); Ukraine Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); United Kingdom Health Protection Agency (Gary Murphy), Royal Free haemophilia cohort (Caroline Sabin), UK Register of HIV Seroconverters (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker), University College London (Deenan Pillay). African cohorts: Genital Shedding Study (US: Charles Morrison; Family Health International, Robert Salata, Case Western Reserve University, Uganda: Roy Mugerwa, Makerere University, Zimbabwe: Tsungai Chipato, University of Zimbabwe); International AIDS Vaccine Initiative (IAVI) Early Infections Cohort (Kenya, Rwanda, South Africa, Uganda, Zambia: Pauli N. Amornkul, IAVI, USA; Jill Gilmour, IAVI, UK; Anatoli Kamali, Uganda Virus Research Institute/Medical Research Council Uganda; Etienne Karita, Projet San Francisco, Rwanda). 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