Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherlands

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Background

A rising trend in plasma HIV-1 RNA concentration at set-point over calendar time might implicate an increase in the efficiency with which HIV-1 is transmitted. Contrasting results on the trend over time have been reported.

Objective

To determine whether the level of plasma HIV-1 RNA concentration and CD4 cell count measured 9-27 months after estimated HIV-1 seroconversion has changed between 1984 and 2007.

Methods

Patients

- Patients with recent HIV-1 infection (last negative and first positive test <1 year apart) and ⩾1 plasma HIV-1 RNA concentration available 9-27 months after seroconversion without having received antiretroviral therapy were selected from the ATHENA observational cohort.
- Analyses were repeated in MSM from W-Europe/N-America with a proven or likely subtype B infection to obtain results in a homogenous population.

Outcome:

HIV-1 RNA concentration and CD4 cell count at viral set-point. Defined as:

1. The earliest HIV-1 RNA and CD4 cell count measurement 9-27 months after seroconversion and without having received ART.
2. CD4 cell count and HIV-1 RNA concentration at 12, 18 and 24 months after seroconversion.
3. As a sensitivity analysis the earliest HIV-1 RNA and CD4 cell count measurement after seroconversion (without having received ART) was also analysed.

Statistical analyses

- Linear regression models with a normal error distribution were used.
- HIV-1 RNA concentration below the lower detection limit and above the upper detection limit were interval and right censored, respectively.
- CD4 cell counts were cube root transformed, HIV-1 RNA concentration $\log_{10}$ transformed
- Estimated calendar year of seroconversion was modeled using categories: 1984-1995, 1996-2002 and 2003-2007 and continuously using restricted cubic splines. Potential confounders were: gender, region of origin, age at seroconversion, HIV-1 subtype, transmission of resistant virus, interval between measurement and seroconversion, transmission risk group, HCV/HBV co-infection, sensitivity and technique of the quantitative HIV-1 RNA assay used.

Results

Estimated seroconversion between	1984-1995 N (%)	1996-2002 N (%)	2003-2007 N (%)
Total	163	232	511
MSM from W-Europe/N-America with proven/likely subtype B infection	114 (71)	143 (61)	355 (66)
Male gender	144 (88)	206 (89)	480 (94)
Transmission risk group			
MSM	119 (73)	162 (70)	410 (80)
Hetero	3 (2)	629 (21)	54 (11)
IDU	22 (13)	2 (3)	2 (0)
Subtype			
B	59 (36)	76 (33)	273 (53)
non-B	1 (1)	8 (3)	32 (7)
unknown	103 (63)	148 (64)	206 (40)
Amplification technique			
NASBA	163 (100)	53 (23)	44 (9)
RT-PCR		99 (42)	266 (41)
bDNA		66 (28)	175 (34)
Sensitivity of the assay			
1000 or 400 copies/ml	163 (100)	104 (23)	42 (8)
≤50 copies/ml		114 (42)	443 (87)
Region of origin			
W-Europe/N-America	134 (82)	188 (81)	420 (82)
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
Age (yrs)	34.4 (28-40)	33.8 (30-40)	36.4 (30-43)
Months between seroconversion and HIV-1 RNA measurement	11.6 (10-11)	10.9 (10-13)	10.9 (10-12)

Table 1. Baseline characteristics of 906 patients with recent HIV-1 infection and a plasma HIV RNA concentration 9-27 after seroconversion and before antiretroviral therapy started. CD4 cell counts were available for 811 (90%) patients.

HIV-1 RNA concentration

- Mean HIV-1 RNA concentration at set-point was 0.32 $\log_{10}$ copies/ml (95% CI 0.12-0.51; p=0.002) lower in women compared to men, 0.40 (0.14-0.67; p=0.003) $\log_{10}$ copies/ml lower in patients with non-B subtype infection compared to B subtype and 0.16 $\log_{10}$ copies/ml (0.00-0.32; p=0.04) higher in patients from W-Europe/N-America compared to elsewhere.
- HIV-1 RNA concentration at viral set-point and at 12, 18 and 24 months after seroconversion was significantly higher between 2003-2007 compared to 1984-1995 and 1996-2002 (Figure 1).
- Results were robust for type and sensitivity of assay and co-infection with HCV or HBV.
- Mean HIV-1 RNA concentration at viral set-point in 1985 was 4.46 $\log_{10}$ copies/ml (95% CI 4.27-4.65), was at its lowest value 4.21 $\log_{10}$ copies/ml (4.09-4.33) in 1995 and subsequently increased to 4.88 $\log_{10}$ copies/ml (4.76-5.01) in 2007 (Figure 1a).
- In a sensitivity analysis, including 751 patients with a maximum seroconversion interval of 6 months, the mean of the first HIV-1 RNA concentration taken after seroconversion was 0.48 $\log_{10}$ copies/ml (95% CI 0.26-0.71; p<0.0001) lower for seroconverters before 1996 and 0.17 (0.00-0.35; p=0.05) lower between 1996-2002 compared to 2003-2007.

CD4 cell count

- Mean CD4 cell count at viral set-point in patients from W-Europe/N-America with seroconversion between 2003-2007 was 507 cells/mm^3 (95% CI 485-530) compared to 466 cells/mm^3 (425-509, difference p=0.07) for elsewhere. No other confounders were found.
- Mean CD4 cell count at viral set-point was significantly lower in more recent calendar years and declined between 1984-2007 with 0.025 cube root cells/mm^3/year (95% CI 0.013, 0.039; p=0.0001); a decline of approximately 5 CD4 cells/mm^3/year (Figure2).

Conclusion

The HIV-1 RNA plasma concentration at viral set-point has increased over the last decade of the HIV epidemic in the Netherlands. This is accompanied by a decreasing CD4 cell count over the period 1984-2007 and may have implications for both the course of the HIV infection and the epidemic.

Figure 1. HIV-1 RNA concentration at viral set-point in **MSM from W-Europe/N-America with proven/likely subtype B infection**: a) first HIV-1 RNA 9-27 months after serocon-version (n=612), b) at 12 (n=552), c) 18 (n=370), d) at 24 months (n=315).

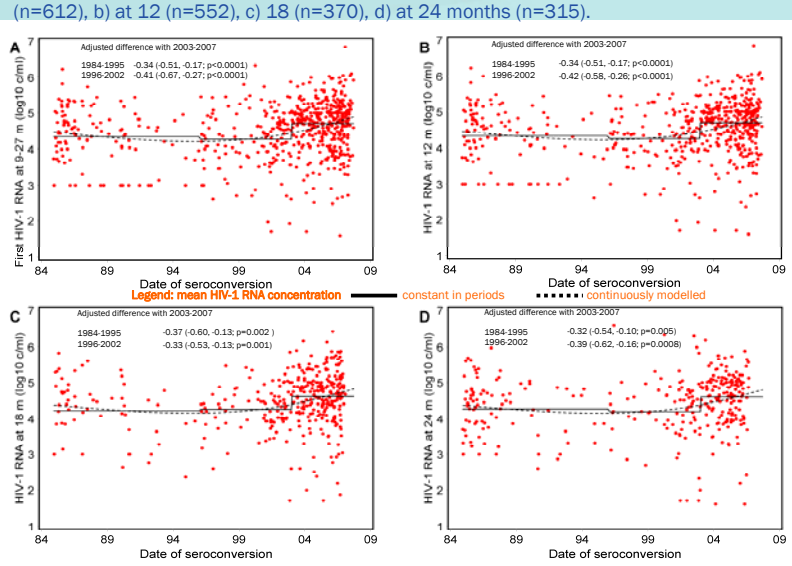

Figure 2. CD4 cell count at viral set-point in **MSM patients from W-Europe/N-America with proven/likely subtype B infection**: a) first CD4 cell count between 9-27 months after seroconversion, b) at 12 , c) at 18 and d) at 24 months.