

# Time with CD4 cell count above 500 cells/mm<sup>3</sup> allows HIV-infected men, but not women, to reach similar mortality rates to those of the general population: a seven-year analysis

Charlotte Lewden<sup>1,2</sup> on behalf of the Mortality Working Group of COHERE

<sup>1</sup>Inserm, U897, Bordeaux, France; <sup>2</sup>Univ. Bordeaux 2, ISPED, France

## ABSTRACT

Background. Successful combination Antiretroviral Therapy (cART) may be associated with a life expectancy of HIV-infected patients approaching that of the uninfected population. We compared age- and gender-specific death rates in HIV-infected adults after initiation of cART according to current CD4 cell count and time spent with CD4 ≥500 cells/mm<sup>3</sup>, with those of the general population.

Methods. HIV-infected adults (≥18 years) starting cART from naïve from 1998 onwards, enrolled in COHERE, a collaboration of 25 European observational cohorts and followed ≥1 day were eligible. Standardized mortality ratios (SMR) were estimated with reference to age- and gender-specific mortality rates in country-specific general populations using the Human Mortality Database or WHO data. Time of follow-up was categorised into 4 CD4 strata (<200; 200-349; 350-499 and ≥500 cells/mm<sup>3</sup>) using the lowest observed measurement within each year of follow-up. Missing data for CD4 were imputed using simple imputation including last observation carried forward since this method was robust through several sensitivity analyses.

Results. Among 80,642 adults, (70% men, median (IQR) age at cART initiation 37 years (31-43); 42% heterosexual, 33% sex between men and 16% injecting drug use), baseline median (IQR) CD4 cell count was 225 (107-357) cells/mm<sup>3</sup>, 3,813 (men: 2,979, women: 834) deaths occurred and median (IQR) duration of follow-up 3.5 years (1.5-6.1) years, i.e. 315,340 person-years. For current CD4 <200, 200-349, 350-499 and ≥500 cells/mm<sup>3</sup>, SMRs (95%CI) were 13.0 (12.5-13.5), 3.0 (2.8-3.2), 1.8 (1.7-2.0), 1.5 (1.4-1.7), respectively. Death rates among men with CD4 ≥500 cells/mm<sup>3</sup> reached those of the general population after at least 3 years spent above that threshold: SMR (95%CI) were 1.4 (1.2-1.6) after 1 year, 1.0 (0.8-1.3) after 3 years and 1.1 (0.8-1.7) over 5 years. Death rates among women with CD4 ≥500 cells/mm<sup>3</sup> remained higher than those of the general population even after 5 years spent above this threshold: 1.9 (1.3-2.6) after 1 year, 1.7 (0.9-2.9) after 3 years, 2.4 (1.0-5.0) after 5 years.

Conclusion. Whilst HIV-infected men who were successfully treated reached similar mortality rates to those in the general male population after 3 years, this was not the case among women. Though our results might be partly explained by other differences between HIV-infected and uninfected populations, they point to the importance of treatment adherence and early initiation of treatment.

## BACKGROUND

- In the combination antiretroviral therapy (cART) period, all-cause mortality rates among treated HIV-infected persons remain higher than those in the general population.

- The excess mortality risk may vary according to gender, age, IDU/hepatitis C status, time since HIV seroconversion and/or time since initiation of cART.

- Both the mortality rate and the excess mortality risk tend to be lower in those with higher CD4 counts.

- A previous study observed that mortality rates among individuals with CD4 counts ≥500/mm<sup>3</sup> after several years of cART were similar to those of the general population.

- We hypothesised that individuals on cART who attain high CD4 counts for longer periods of time may have similar mortality rates to those of the general population.

## OBJECTIVE

We wished to identify the optimal conditions for HIV-infected adults to attain similar mortality rates to those in the general population. Thus, we compared age- and gender-specific death rates in HIV-infected adults after initiation of cART with those of the general population according to:

- current CD4 cell count, and
- time spent with CD4 ≥500 cells/mm<sup>3</sup>.

## METHODS

### POPULATION

- Cohort participating in the COHERE Collaboration, a collaboration of 25 European observational cohorts of HIV-infected individuals after initiation of cART

- Age ≥ 18 years

- First cART ≥ 1998

- CD4 measurement within 6 months before cART

- ≥ 1 day of follow-up

### STATISTICAL ANALYSIS

- Death rates: calculated per 100 person-years (100PY)

- Standardized mortality ratios (SMR):

\* calculated as:

# observed deaths / # expected deaths

where # expected deaths was obtained by applying country-, age-, gender- and calendar year- specific mortality rates to the HIV-infected population.

\* computed by Poisson regression modeling

\* mortality rates obtained from:

Human Mortality Database

<www.mortality.org> (by 1 yr),

WHO data (if missing in HMD)

<www.who.int/whosis> (by 5 yrs)

\* estimated in the whole study population and according to:

- gender,
- age (18-39; 40-59; ≥ 60 years),
- mode of infection (intravenous drug users (IDU) / others),
- current CD4 (<200; 200-349; 350-499; ≥500/mm<sup>3</sup>, categorised using lowest measurement reported at each year of age)
- time spent with CD4 ≥500/mm<sup>3</sup> (>1; >2; >3; >4; >5 consecutive years).

- Missing CD4 values were imputed using a last observation carried forward approach; this method was found to be robust in sensitivity analyses.

### Mortality working group of COHERE

Charlotte Lewden (project lead), Vincent Bouteloup (statistician), Antonella d'Arminio Monforte, Alexandra Calmy, Antonella Castagna, Geneviève Chêne, François Dabis, Stéphane De Wit, Matthias Egger, Jade Ghosn, Virginia Isern, Ole Kirk, Catherine Lepout, Murielle Mary-Krause, Amanda Mocroft, Cristina Mussini, Niels Obel, Santiago Perez-Cachafeiro, Santiago Perez Hoyos, François Raffi, Annalisa Ridolfo, Caroline Sabin, Ard van Sighem, Paz Sobrino, Schlomo Staszewski, Christoph Stephan, Ramón Teira, Carlo Torti, Giota Touloumi, Jan Christian Wasnuth.

## RESULTS

- Among 95,421 of the COHERE database, 80,642 were eligible.

Eligible and non eligible individuals did not differ according to: gender, age, presumed mode of infection, clinical stage, year of cART initiation, death rate.

- European countries of follow-up of eligible individuals (n patients):

Belarus (78), Belgium (1136), Bulgaria (37), Croatia (39), Czech Republic (61), Denmark (1918), Estonia (58), Finland (30), France (32371), Germany (1991), Greece (429), Hungary (71), Ireland (19), Italy (9645), Latvia (56), Lithuania (42), Luxembourg (44), Netherlands (6696), Norway (140), Poland (419), Portugal (85), Romania (82), Russia (146), Serbia&Montenegro (42), Slovakia (35), Spain (10710), Sweden (54), Switzerland (3516), Ukraine (45), United Kingdom (10645).

**Table 1:** Characteristics of patients at initiation of ART and duration of follow-up

	Overall N=80,642	Men N=56,417	Women N=24,225
Women (%)	30	-	-
Age, median, IQR (years)	37 (31-43)	38 (33-45)	34 (29-40)
Mode of HIV transmission (%)			
drug injection	16	17	12
homo-bisexual	33	48	-
heterosexual	42	27	79
CD4 cell count, median, IQR(/mm <sup>3</sup> )	225 (107-355)	220 (98-349)	239 (128-377)
Year of starting cART (%)			
1998-1999	28	29	25
2000-2002	32	32	33
2003-2004	21	20	23
2005-2008	19	19	19
Median duration of follow-up, IQR (years)	3.5 (1.5-6.1)	3.6 (1.6-6.2)	3.4 (1.5-5.9)

**Table 2:** Death rates and SMRs according to gender and current CD4 count

	N	Person-years (PY)	Deaths (n)	Rate (/100 PY)	(95% CI)	SMR	(95% CI)
Overall	80,642	315,340	3,813	1.2	[ 1.2- 1.3]	4.4	[ 4.3- 4.6]
CD4 <200/mm <sup>3</sup>	36,158	61,826	2,394	3.9	[ 3.7- 4.0]	13.0	[ 12.5- 13.5]
CD4 200 to 349/mm <sup>3</sup>	49,945	83,616	699	0.8	[ 0.8- 0.9]	3.0	[ 2.8- 3.2]
CD4 350 to 499/mm <sup>3</sup>	44,030	74,157	367	0.5	[ 0.5- 0.6]	1.8	[ 1.7- 2.0]
CD4 ≥ 500/mm <sup>3</sup>	35,316	91,891	353	0.4	[ 0.4- 0.4]	1.5	[ 1.4- 1.7]
Men	56,417	223,333	2,979	1.3	[ 1.3- 1.4]	4.0	[ 3.8- 4.1]
CD4 <200/mm <sup>3</sup>	25,812	44,691	1,873	4.2	[ 4.0- 4.4]	11.5	[ 11.0- 12.1]
CD4 200 to 349/mm <sup>3</sup>	34,654	58,167	528	0.9	[ 0.8- 1.0]	2.6	[ 2.4- 2.8]
CD4 350 to 499/mm <sup>3</sup>	30,541	51,957	288	0.6	[ 0.5- 0.6]	1.7	[ 1.5- 1.9]
CD4 ≥ 500/mm <sup>3</sup>	24,479	65,697	290	0.4	[ 0.4- 0.5]	1.4	[ 1.3- 1.6]
Women	24,225	92,007	834	0.9	[ 0.9- 1.0]	7.8	[ 7.3- 8.4]
CD4 <200/mm <sup>3</sup>	10,346	17,135	521	3.0	[ 2.8- 3.3]	23.7	[ 21.8- 25.9]
CD4 200 to 349/mm <sup>3</sup>	15,291	25,450	171	0.7	[ 0.6- 0.8]	5.6	[ 4.8- 6.5]
CD4 350 to 499/mm <sup>3</sup>	13,489	22,201	79	0.4	[ 0.3- 0.4]	3.2	[ 2.6- 4.0]
CD4 ≥ 500/mm <sup>3</sup>	10,837	26,194	63	0.2	[ 0.2- 0.3]	2.2	[ 1.7- 2.9]

CI: confidence interval

## ACKNOWLEDGEMENTS: COHERE GROUP

### Steering committee:

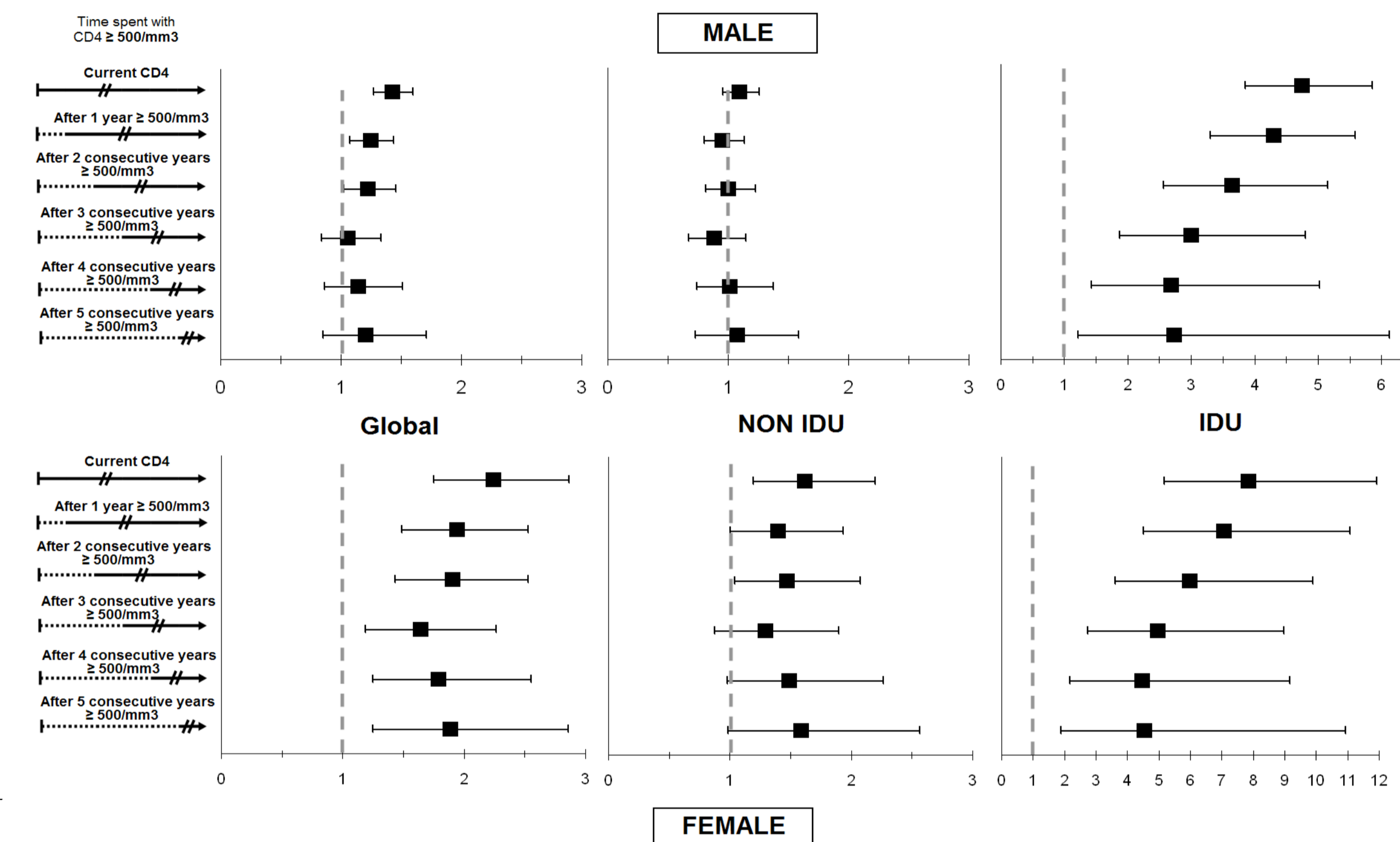
•Executive committee: Ian Weller (Chair, University College London), Dominique Costagliola (Vice-chair, FHDH), Bruno Ledergerber (Vice-chair, SHCS), Jens Lundgren (until July 2009, Head, Copenhagen Regional Co-ordinating Center), Geneviève Chêne (Head, Bordeaux Regional Co-ordinating Centre).

• Contributing cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Lepout (ANRS CO8 COPILOTE), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Kholoud Porter (CASCADE), Maria Dorrucci (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Julia Del Amo (Co-RIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Dolores Carnicer (NENEXP), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Pier-Angelo Tovo (ITLR), Maurizio de Martino (ITLR), Bernd Salzberger (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (McCHIV), Patrick Francioli (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH).

•European AIDS Treatment Group: Nikos Dedes.

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**Figure 1:** SMRs according to gender and time spent with CD4 cell count ≥ 500/mm<sup>3</sup> in individuals with CD4 ≥ 500/mm<sup>3</sup>



## DISCUSSION and CONCLUSION

- As expected, mortality rates dropped, and were closer to those of the general population, as the current CD4 cell count increased, reaching 0.4 per 100 person-years in those with a CD4 count ≥ 500/mm<sup>3</sup>.

- Despite comparable death rates between men and women, SMRs were higher in women in all CD4 strata. This might be related to unmeasured confounding (e.g. that due to socio-economic status).

- Mortality rates among HIV-infected men with a CD4 cell count ≥ 500/mm<sup>3</sup> reached similar levels to those of the general male population after 3 years in this CD4 strata: SMR:1.1 [95%CI: 0.8- 1.3].

- However, mortality rates among HIV-infected women with a CD4 cell count ≥ 500/mm<sup>3</sup> did not reach similar levels to those of the general female population, even after several years with a high CD4 cell count.

- IDUs had higher mortality rates than those in the general population, even after several years with a high CD4 cell count.

- Though our results might be partly explained by other differences between HIV-infected and uninfected populations, they point to the importance of maintaining high CD4 cell counts as well as long term treatment adherence.