Development and Validation of Decision Rules to Guide Frequency of Monitoring CD4 Cell Count in HIV-1 Infection before Starting Antiretroviral Therapy

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Appendix S2: Evaluation of viral load monitoring

The use of viral load as a biomarker for HIV disease progression is less well defined than for CD4 cell count. It is not usually interpreted in terms of a decision threshold for starting antiretroviral therapy, and a fair number of patients show no detectable time trend over the whole asymptomatic phase of HIV-1 infection. We therefore limited our evaluation of viral load monitoring before treatment to general considerations based on our literature review, as a strategy based on specific rules was not thought necessary.

Literature review

For viral load progression, we were able to extract data from 6 studies [1,2,3,4,5,6] and one review [7] among 10 publications identified that described the natural evolution of CD4 counts in untreated HIV-1 infected patients (Table 1). This biomarker is highly variable, both between and within patients. The reproducibility of current assays is 0.1–0.2 $\log_{10}$ copies/mL (i.e. 25–60%) [8,9], while intra-individual variability, including biological fluctuation, is 0.26–0.31 $\log_{10}$ copies/mL [10,11,12,13]. Compared with CD4 count, viral load shows a less clear overall trend among HIV-infected individuals. Beyond the initial set point after the seroconversion peak, some authors have estimated average slopes not significantly different from zero [1,14], while others have reported a significant upward trend [2,15,16]. Viral load evolution is affected by gender [2,17,18,19], race [17], inflammatory state [20,21], and genetics [22], and correlates with the rate of fall in CD4 count and prognosis [16,23,41].

Viral load monitoring performances

A variogram after a single viral load measurement is shown in Figure 5, based on average parameters extracted from the literature. Both the mild degree of steepness expected in

the population and the importance of intra-patient variability show that early remeasurement has very little chance of capturing any significant trend beyond noise. Only after 5 years will the magnitude of the average increase equal the magnitude of intra-patient variability. This unfavourable signal/noise ratio and the absence of a clear threshold for therapeutic decision-making militate against regular viral load monitoring in patients who do not yet require antiretroviral therapy. A single measurement of viral load about 6 months after presumed seroconversion bears information about the activity of HIV infection and can influence the decision to initiate therapy in terms of CD4 threshold. Rechecking the value just before starting treatment remains important for future assessment of the virological response.

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Appendix S2: Table

Published estimates of viral load increase rate and variability in untreated HIV-infected individuals

Parameters derived from linear mixed effect model in the log scale. β: slope and σ_b: inter-individual slope variability in $\log_{10}$ copies/mL/year; α: intercept, σ_a: inter-individual intercept variability and σ_e: intra-individual variability in $\log_{10}$ copies/mL; ρ_{ab}: correlation between α and β; N: number of individuals, n: average number of samples par individual; average duration of observation in years.

Reference	**β**	**σ_b**	**α**	**σ_a**	**σ_e**	**ρ_{ab}**	**N·n**	**duration**
Boscardin 1998 [2]	0.15	--	4	0.6	0.5	--	141·6	1.3
Hubert 1999 [4]	0.03	0.14*	4	0.8	0.5	--	330·7	4.3
Sabin 2000 [5]	0.11	--	3.3	--	--	--	105·8	>10
Lyles 2000 [3]	0.03	--	4.5	0.5*	--	--	4	3
Touloumi 2004 [6]	0.1 °	0.13	3.3 to 4.4†	1	--	-0.14†	1864·5	4.3
Rodríguez 2006 [1]	0.06	0.08*	--	--	--	--	1289·8	3
Phillips 2007 [7]	0.11 to 0.21‡	0.3	4	0.5	--	--‡	(review)	
Average	**0.1**	**0.15**	**4**	**0.7**	**0.5**	**0**	(rounded value)	

Parameters derived from linear mixed effect model in the log scale. β: slope and σ_b: inter-individual slope variability in $\log_{10}$ copies/mL/year; α: intercept, σ_a: inter-individual intercept variability and σ_e: intra-individual variability in $\log_{10}$ copies/mL; ρ_{ab}: correlation between α and β; N: number of individuals, n: average number of samples par individual; average duration of observation in years.

* half interquartile range
° higher in case of symptoms on seronconversion (present: 0.15)
† intercept depending on subgroup (sex, age, intravenous drug use or haemophilia)
‡ slope depending on initial viral load (0.11 at $<10^3$, then 0.13, 0.14, 0.15, 0.17, 0.18 and 0.2 for every $10^{0.5}$ step up to 0.21 at $>10^6$/mL)

Appendix S2: Figure

Variogram for viral load monitoring

This variogram, based on the *Snap-shot rule* for an initial determination of a viral load of 1000 copies/mL (3 log units/mL), shows the highest load that a subsequent measurement can be expected to reach, with a probability of 5% (dashed line) or 10% (dotted line). The continuous line indicates the viral load trajectory predicted in an average patient, taking about 12 years to increase by 1 log unit. After 6.7 years one patient in 20, and after 9.2 years one patient in 10, can be expected to have a 2 log unit increase (i.e. to 100 000 copies/mL, arrows).