The clinical interpretation of viral blips in HIV patients receiving antiviral treatment: are we ready to infer poor adherence?

Supplemental Digital Content 1

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A. Flowchart of the mathematical model

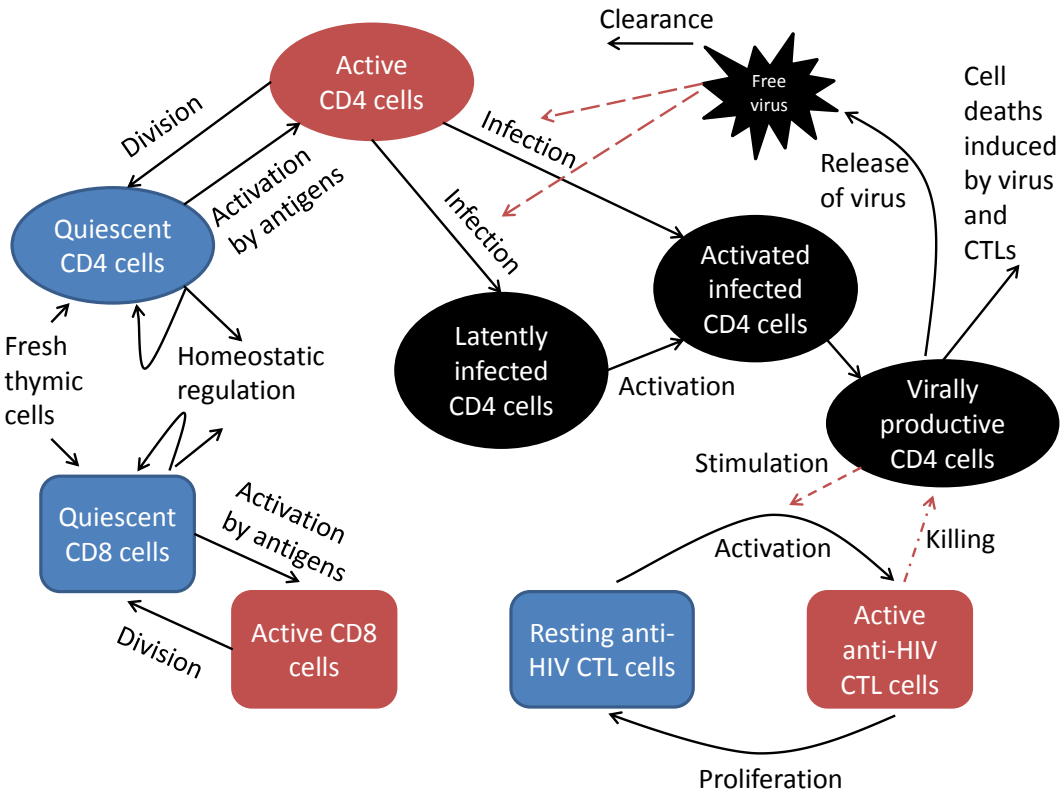


Figure S1 Flowchart representing the mathematical model used in this paper. Adapted from [1].

B. Drug adherence pattern

Simple drug adherence. Before the 'more realistic' drug adherence pattern as described in the main text was used in our study, a simple drug adherence pattern was used. This was represented by fixing the dose interval at 12 hours and then using the result of a binomial trial with a given probability to determine if the dose is taken. The setting of the probability allows the expected proportion of doses taken to be set. Ten simulations were performed to represent each pattern of adherence. This was used to investigate 'white coat compliance' and weekend 'drug holidays' as presented in this Supplementary Digital Content, Section G.

C. Pharmacokinetics

To incorporate the saturation effect of drug plasma concentration in relation to their antiviral actions, one feature was added to our original model [1]. The plasma concentrations of reverse transcriptase inhibitor(s) (RTI) and protease inhibitor(s) (PI) (denoted in square brackets as [RTI] and [PI]) are now converted into their effectiveness against the virus, according to the following equations:

$drug_{RTI}$ = [RTI]/([RTI]+1) and $drug_{PI}$ = [PI]/([PI]+1).

For illustrative purposes only, the half-life for RTI and PI used in the model were chosen to be 0.75 day and 0.16667 day respectively. The former is the half-life of Abacavir (18 hours) and the latter is that of Ritonavir (4 hours). The prescribed dose interval for both Abacavir and Ritonavir is 12 hours, which is also the prescribed dose interval in this modelling study [2]. Even if different values were chosen, our major conclusion would not be affected, as our results in this paper are primarily qualitative.

D. Sampling frame

For the <1-week sampling frame (definition set 1A), the viral load outputs (that were outputted every 100 flexible time steps, corresponding to every three to seven days) were plotted in Microsoft® Office Excel 2003 (Microsoft Corporation©) and the number of events of transient viraemia (or viral blips, defined below), was counted by eye. For the monthly and quarterly

sampling frames (definition sets 2A and 2B), a separate common separated values (CSV) file with monthly viral load measurement was outputted for each set of simulations. Viral blips were counted from month 97 onwards. The quarterly measurements were counted from the same set of monthly measurements, from month 97 onwards (month 97, 100…).

If we count the number of blips observed in the <1 week, monthly and quarterly sampling frames over the same period of time, the numbers and therefore incidence of viral blips are different. A less frequent sampling frame, like the quarterly sampling frame might miss some blips (data not shown). However, the *proportion* of observations that are blips are similar in both monthly and quarterly sampling frames. In our monthly and quarterly scenarios, we make eight and 24 observations in two years under cART. By measuring the proportion of observations classified as 'blips', the bias introduced by the choice of sampling frame can be removed (Figure S2).

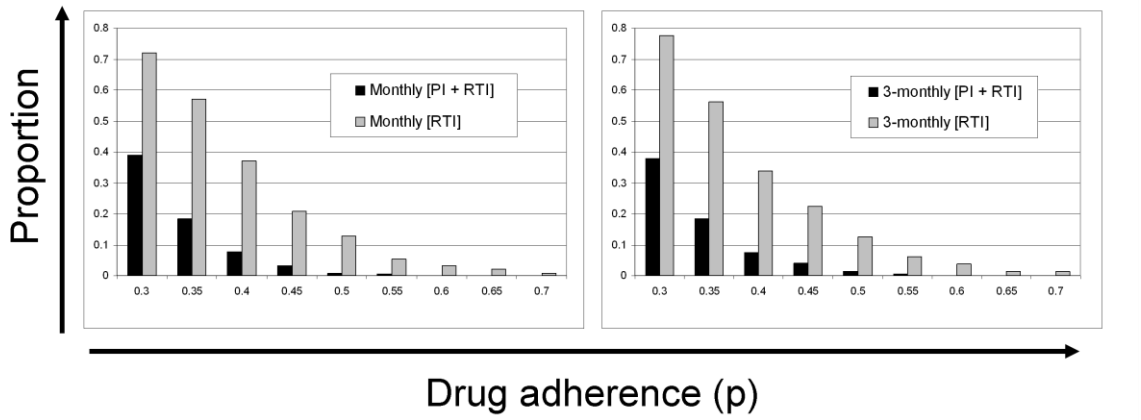


Figure S2 **Comparison of proportion of observations that are ≥ 50 copies/ml between the presence and absence of protease inhibitor (PI) in a more realistic drug adherence pattern.** Proportion of observations that were ≥ 50 copies/ml as observed under monthly (left) and quarterly (right) sampling frames over a period of 2 years under anti-retroviral therapy. Reverse transcriptase inhibitor (RTI)-only: 10 simulations per drug adherence level; PI+RTI: 100 simulations per drug adherence level.

E. Viral blip definition

Further to our description in the main text, in Figure 1, if the viral load samples were first taken three months after the onset of treatment, there would be fewer measurements that are classified as 'first' here. Figure 1 shows that a fraction of the 'blips' that were identified under definition set 2A (sampled every three months) were the first post-treatment viral load measurement that was still ≥50 copies/ml, of which many are followed by viral suppression. They were more likely an indication of viral load yet to be fully suppressed with therapy than an independent blip after successful suppression; and they would be excluded as 'blips' in the majority of studies in the literature. Figure 1 also shows that some 'blips' identified using definition set 2A were the last measurements before the end of the observation period and we are therefore unable to determine whether they would be followed by viral suppression (and hence 'blips') instead of continual rebound ('failure'). These further illustrate how a change in definition could affect our viral blip counts.

Using the RTI-only scenario as an example, if we adopt definition set 2B for viral blips and treatment failure (Figure S3), there were more 'blips' observed (Figure S3a) and more patients (8 out of 10) experienced 'blips' (Figure S4a), when $p = 0.4$. There were more events of treatment 'failure' as drug adherence is lower (Figure S3b) with the vast majority of patients with $p \leq 0.35$ experiencing failure (Figure S4b). At a lower adherence, more patients experienced slower viral decline (more 'first' measurements being ≥ 50 copies/ml; Figure S3c) and more patients experienced 'last' measurements being ≥ 50 copies/ml (Figure S3d).

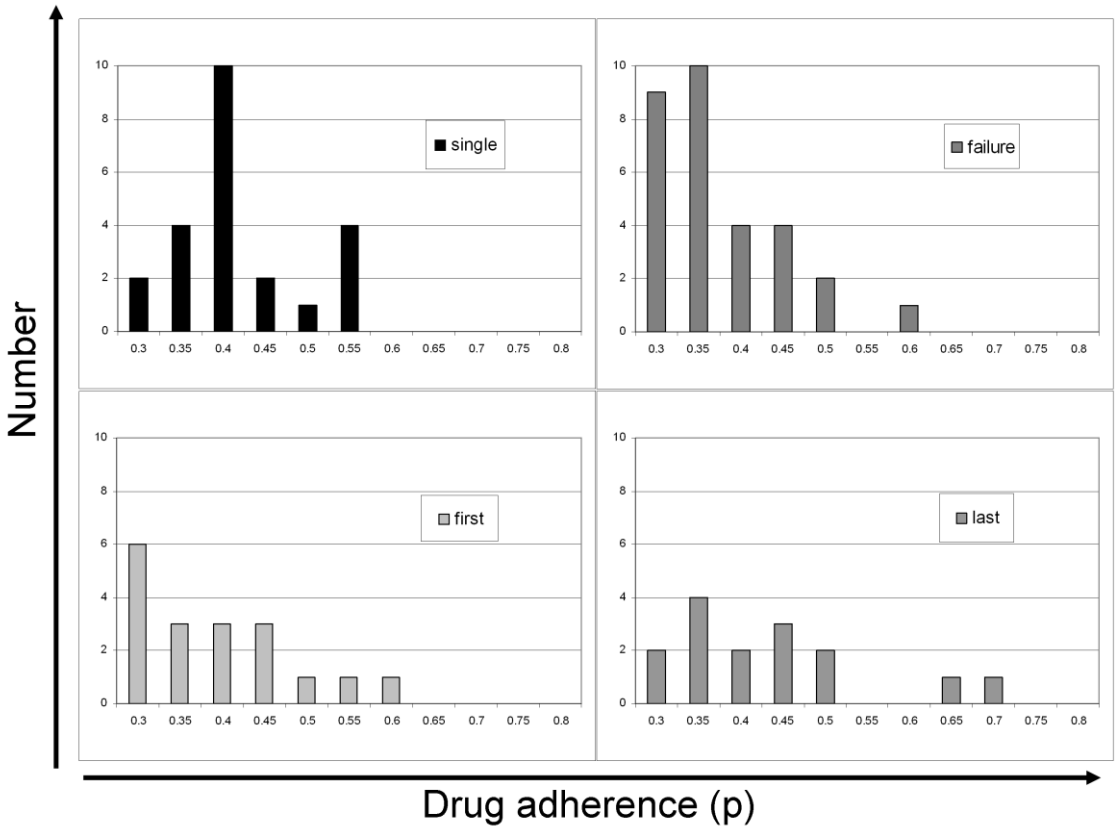
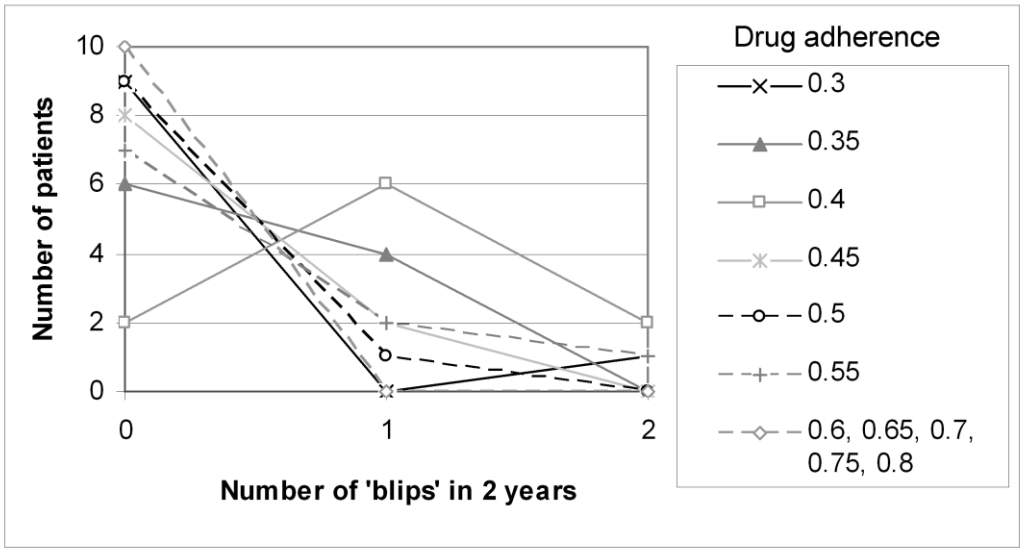


Figure S3 **Number of events as observed in a 3-monthly sampling frame of a more realistic drug adherence pattern.** Data were over a period of 2 years under anti-retroviral therapy of 10 simulations per scenario. For demonstrative purposes, only reverse transcriptase inhibitors were applied in this set of simulations. (a) Top left corner: 'single' refers to a single ≥50 copies/ml measurement both preceded and followed immediately by a <50 copies/ml measurement (Definition set 2B) (b) Top right corner: 'failure' refers events of 'treatment failure' defined as a period of consecutive measurements that are ≥50 copies/ml (Definition set 2B). One 'failure' event can be of 2 to 8 measurements here. (c) Bottom left corner: 'first' refers to the first post-treatment viral load measurement being ≥50 copies/ml regardless of whether it is followed immediately by a <50 copies/ml measurement. (d) Bottom right corner: 'last' refers to the last measurement being ≥50 copies/ml with a preceding <50 copies/ml measurement (therefore not 'single' nor 'failure').



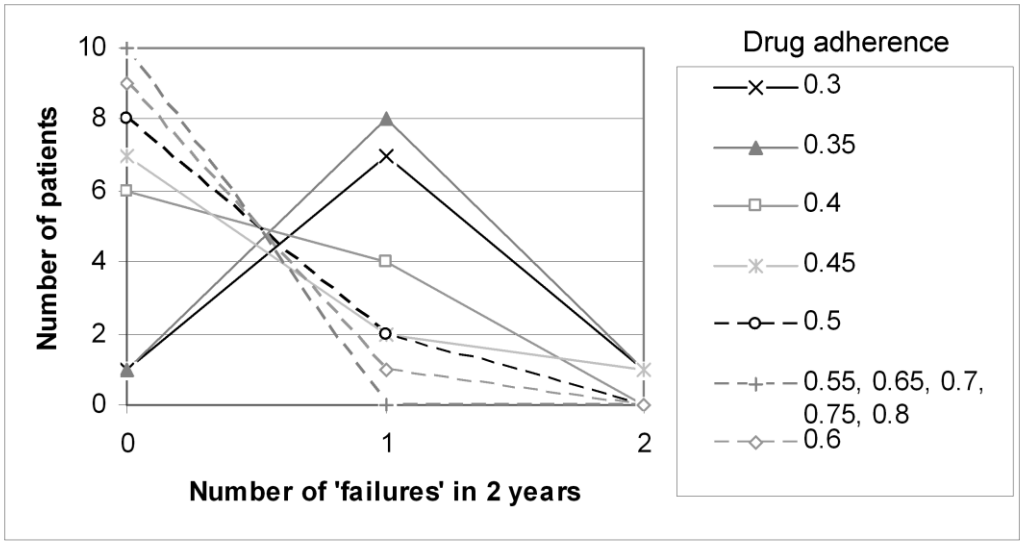


Figure S4 **Number of patients with (a) 'blips' (upper figure) and (b) 'failures' (lower figure), of a given number in years, out of 10 patients as observed in a quarterly sampling frame at each drug adherence level.** More realistic sampling frame was used; only reverse transcriptase inhibitors were taken; no protease inhibitors. This is to simplify the scenario in order to illustrate the point. Blips and failures were defined here according to Definition set 2B.

F. Cumulative viral load

Given that the time under treatment is the same for all simulations (two years), by calculating the area under the viral load curve, i.e. cumulative viral load (days * copies/ml), from the commencement of cART until the end of simulations, one can compare across drug adherence level the amount of virus present in two years under treatment and, therefore, the impact of the treatment. The cumulative viral load was calculated from outputs every 100 steps which represents between 2 and 7 days where the area under the curve was calculated using the trapezium rule. Figure S5 shows that in the presence of RTI only, for $p \geq 55$, the time-viral load is around 200,000 days*copies/ml for two years, and the exact time for dose-taking matters little in the impact of the treatment. For $35 \leq p \leq 50$, it is clear that variation in dose-taking time affects treatment efficacy, with the difference at $p = 45$ the greatest (11 times higher than strict timing). When $p = 30$, as drug adherence is low, the timing of dose taking makes little impact on the overall outcome.

Our mathematical model also allows us to calculate and compare the amount of virus produced in two years under treatment for different drug adherence levels and patterns. It is clear from Figure S5 that to achieve a reasonable viral suppression, a minimum drug adherence of 0.55 is required. It is also interesting to observe that variation in dose-taking time around the prescribed timing is important insofar as a relatively low range of drug adherence (0.35 – 0.5) is concerned. A higher drug adherence renders the effect of taking drugs a couple of hours earlier or later negligible. As it is known that the higher the amount of virus produced, the higher is the possibility of the emergence of drug resistance, mathematical modelling allows us to examine the impact of drug adherence levels and patterns and identify a particular adherence threshold below which the emergence of drug resistance is likely.

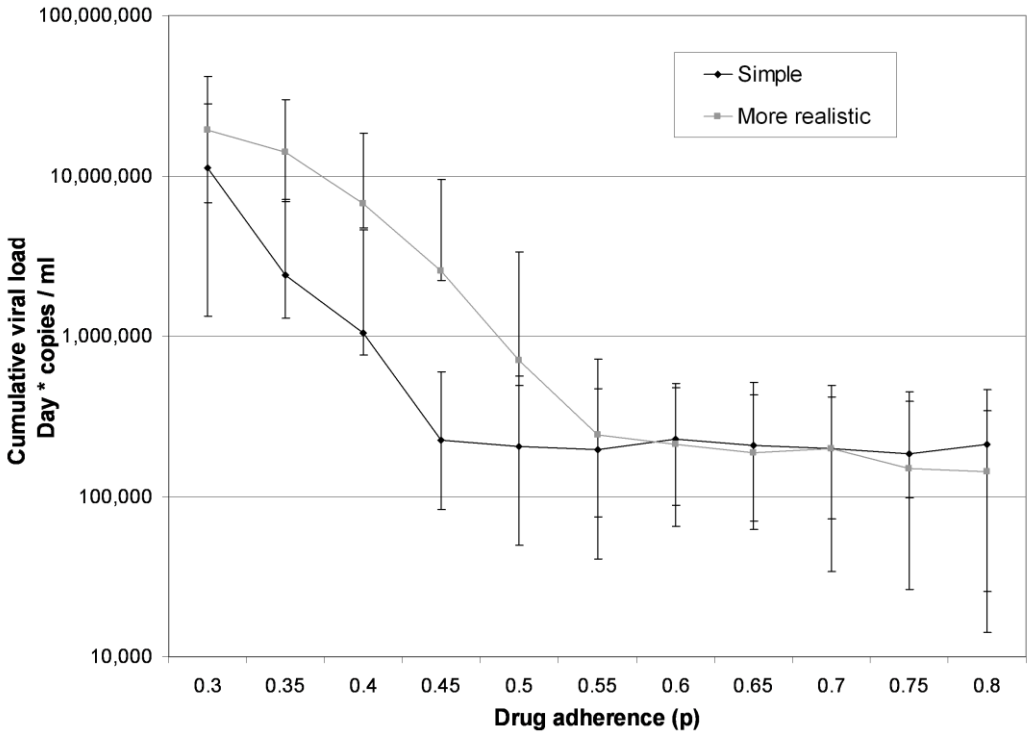


Figure S5 **Cumulative viral load (area under the viral load curve) since commencement of HAART for each drug adherence level (RTI only).** Ten simulations per drug adherence level. The data shown are the cumulative areas under the curve from the last measurement before commencement of antiretroviral therapy (RTI-only) (day 2920) in the <1 week sampling frame to the end of simulations (day 3650). Simple (black line): Simple drug adherence pattern with time of dose taking fixed; More realistic (grey line): More realistic drug adherence pattern with exact time of dose taking drawn from a normal distribution with a mean (prescribed time) and a standard deviation (2.5 hours). Median (Diamond for simple; Square for more realistic), and 25^{th} and 75^{th} percentile (lower and upper error bars) for 10 simulations. Note the log-scale for time-viral load (y-axis).

G. 'White coat compliance' and weekend 'drug holiday'

a. Methods and Results

We first used the simple adherence pattern with fixed dose-taking time to simulate random dose-missing, 'white coat compliance' and 'drug holiday' every weekend. We hypothesized that patients might tend to achieve a high drug adherence a few days before they visit their doctors: so-called 'white coat compliance' previously reported in the literature [3, 4]. To test whether such behaviour could mask poor adherence during clinic visits, we assumed that, no matter what the baseline drug adherence, patients' adherence will increase to 0.9 (i.e. 90% chance of taking a prescribed dose) three days before their three-monthly clinic visits and fall back to the baseline drug adherence after clinic visits. There was no significant difference in the results observed (Figure S6). We then tested the possibility that some patients regularly missed their doses every weekend. We tested the range of missing doses between 1 day (2 consecutive doses) to 3.5 days (7 consecutive doses). It is observed that missing more than 4 consecutive doses every week ($p <$ 71%) will lead to a significant increase in the number of periods of transient viraemia (Figure S6). As shown in Figure S7, regular cumulative failure of adherence is more harmful than random failure of adherence. If doses are missed on a regular basis with multiple missed doses (e.g. every weekend), a much higher drug adherence is required to prevent transient viraemia.

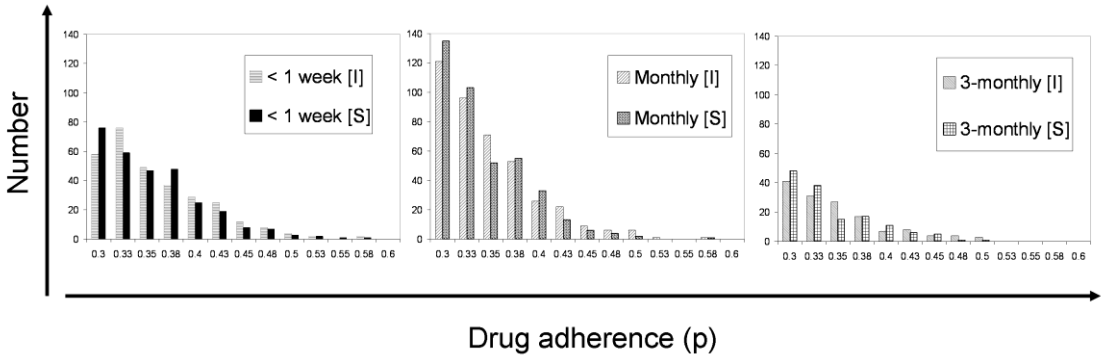


Figure S6 **Comparison between results of increased drug adherence three days before clinic visit [I] and that without [S].** Results shown are total number of period of transient viraemia (blips) as observed under different sampling frequencies over a period of 2 years under anti-retroviral therapy of ten simulations per scenario (y-axis) with respect to different drug adherence level (p). Only reverse transcriptase inhibitors were taken. There was no variation in the exact time of taking a dose.

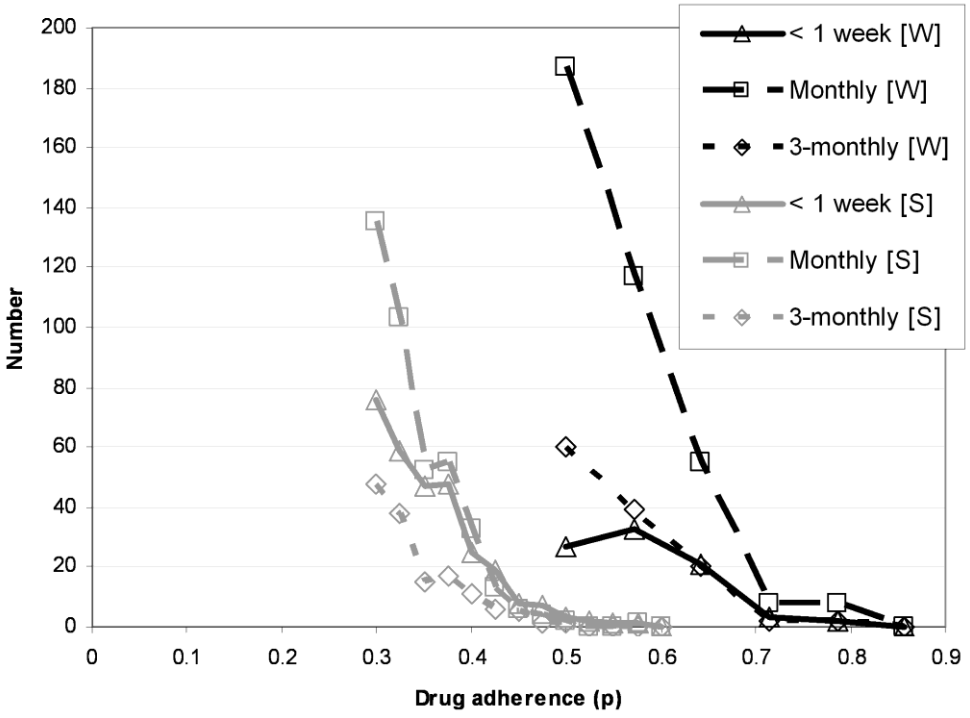


Figure S7 **Patient missing doses every weekend [W] compared with random missing doses [S].** The latter are the same results [S] as shown in Figure 1. Results shown are total number of period of transient viraemia (blips) as observed under different sampling frames (<1 week, monthly, 3-monthly) over a period of 2 years under anti-retroviral therapy of ten simulations per scenario (y-axis) with respect to different drug adherence level (p). Only reverse transcriptase inhibitors were taken. There was no variation in the exact time of taking a dose.

In real life, timing of dose taking is seldom exact and it varies across time and between patients. By comparing the results of the simple drug adherence pattern and that of a more realistic pattern, it was found that more blips were observed if the timing of every dose is not fixed exactly, but varied around the designated time (data not shown). This result indicated that in addition to the proportion of doses taken (*p*), the standard deviation of the random dose-timing error is also important (cf. [5]). Therefore, for further analysis, we focused on the data set of this more realistic adherence pattern. Furthermore, the difference in number of blips observed across different sampling frames is clear in both adherence patterns.

b. Discussion

'White coat compliance' has been observed in a clinical trial using electronic pill bottle caps (MEMS®; Medication Event Monitoring System) [4]. In that study, this behaviour – defined as perfect drug intake one to three days before pharmacokinetic sampling but ≤ 95% otherwise – was found among 66% of subjects. However, one should note that 'white coat compliance' only happened among 31% of visits in Podsadecki et al.'s study. In our study, increased adherence to cART (90%) just three days before the 3-monthly clinic visit and sampling was found to have little impact upon the number of blips observed and therefore cannot mask the underlying poor drug adherence. A possibility was that 90% adherence was not high enough for that purpose. One should be reminded that 'white coat compliance' is not observed in every population [6].

Next, we found that consecutive dose-missing incurs far more damage than random dose-missing, given the same overall adherence level (proportion of doses taken). This phenomenon has previously been observed in a cohort of HIV patients, in whom among those who achieved poorer compliance in the weekends than on weekdays, a higher proportion of patients with global cognitive impairment or specific impairment in the attention domain of the brain was found [7]. This highlights the need to understand whether and how the life-styles of patients affect their drug adherence pattern during weekends or other holidays in order to provide adequate counselling and care to minimise the possibility of missing consecutive doses.

H. Model validation

a. Sensitivity analysis

A summary of the number of simulations across the range of percentages of observations ≥ 50 copies / ml, as presented in Figures 2 and 3, can be found in Table A2. The confidence with which we can translate the proportion of measurements where there are blips into level of adherence for a given set of parameters is dependent upon the number of simulated patients with a given number of blips. However, to generate the results, we specify the adherence level. Therefore, this number of simulated patients can vary in each category of frequency of blips as specified in Table A2.

Average infection rate of an activated CD4 T cell per virion (β). In this paper, we assume β = 754 as in [8]. However, in our paper, β = 754 produces too low a CD4 count by 1- years of HIV infection. If we decrease β, we shall have better CD4 estimation (~200 by 10 years of infection). Also, a smaller β will lead to few blips. Therefore, for a given number of viral blips observed, one has achieved a worse adherence level than is predicted in this model. We performed a sensitivity analysis by varying β. It was found that by decreasing β by 10-fold (from 754 to 75.4), CD4 cell count at month 120 (the last monthly sample) doubles or triples, in the presence or absence of HAART respectively (Figure S8). If β was increased by 10-fold (from 754 to 7540), CD4 cell count would decrease by two- or three-fold if drug adherence is 0.5 or 0.25 respectively, but it would stay roughly the same if drug adherence is 0 or 0.75.

The variation in viral load at month 120 with respect to β was great (Figure S9). The major variation was found with drug adherence 0.25 and 0.5. If β was reduced by 10-fold, even a drug adherence as low as 0.25 can achieve viral suppression. If β was increased by 10-fold, a drug adherence was unable to control viral replication. Therefore, the success or failure of the range of drug adherence levels tested in this study to suppress viral replication is highly contingent to the choice of β, which is chosen to be 754, following a previously established model [8] on which our model is based.

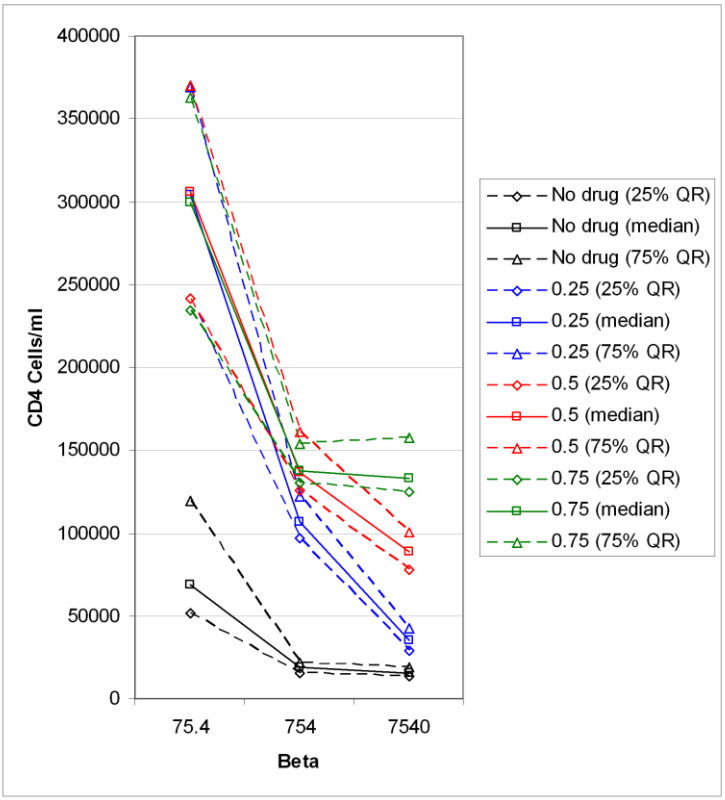


Figure S8 **Variation of *β* on CD4 T cell count at month 120.** Drug adherence levels: (black) 0, (blue) 0.25, (red) 0.5 and (green) 0.75; (broken line with diamond): 25% quartile range (QR), (line with square) median and (broken line with triangle): 75% QR.

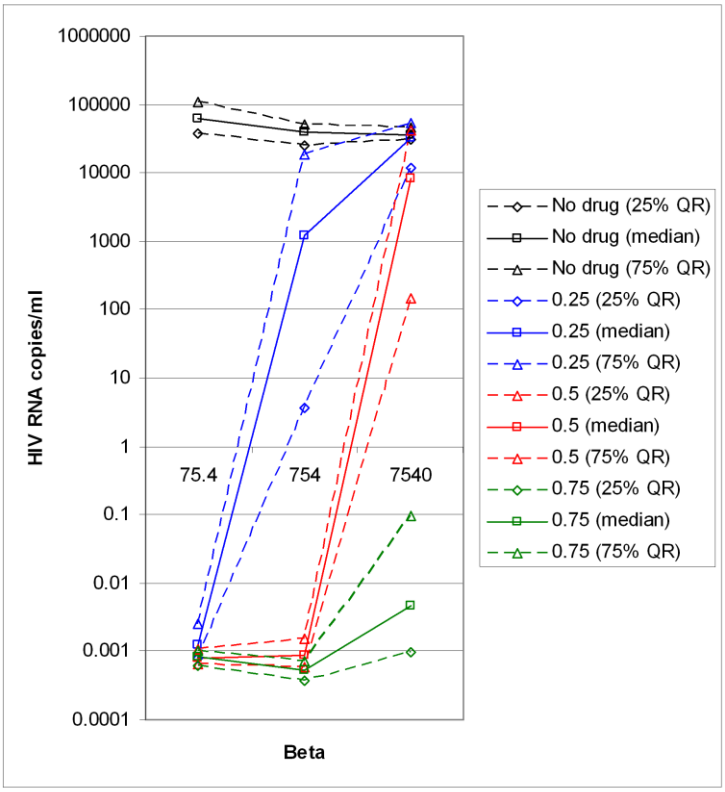


Figure S9 **Variation of *β* on viral load at month 120.** Drug adherence levels: (black) 0, (blue) 0.25, (red) 0.5 and (green) 0.75; (broken line with diamond): 25% quartile range (QR), (line with square) median and (broken line with triangle): 75% QR.

Other parameters. Sensitivity analysis for the other parameters (Table A3 and Figures S10 and S11) found that the parameters that influence the CD4 cell activation process are the most influential; these are: average rate of T cells activation per antigenic exposure (a_0), relative T cell pool size below which T cell activation fails due to exhaustion of repertoire (x_S), average probability of an activated T cell successfully dividing in an individual free of HIV (p_A), average clearance rate in antigenic exposure model (ϑ), and average exposure rate in antigenic exposure model (τ). It is important to point out that the choice of values used in the sensitivity analysis is judged according to biological plausibility and therefore the percentage change is not uniformed across the parameters (see Table A3). Figures S10 and S11 show the change in proportion of the CD4 cell count and viral load at month 120 if a particular parameter is changed (to an extent stated in Table A3). More detailed sensitivity analysis results are tabulated in Table A4 (Median CD4 counts) and Table A5 (Median viral load). Apart from the 'no treatment' scenario presented in Figures S10 and S11, sensitivity analysis of scenarios of drug adherence at 25%, 50% and 75% were also performed. It is worthy to note that for median viral load, the scenario of drug adherence level of 25% saw the greatest variation across parameters (Table A4).

Initial value for antigenic stimulation (k_4 and k_8). We also performed a sensitivity analysis on the initial value for antigenic stimulation. The initial value of k_4 and k_8 were set to 5 in all previous simulations. We changed this value to 1, 3, 7, or 9. We found that these changes made no difference to the outcomes, both in terms of CD4 cell count or viral load, measured in month 120 (the last monthly measurement) (data not shown).

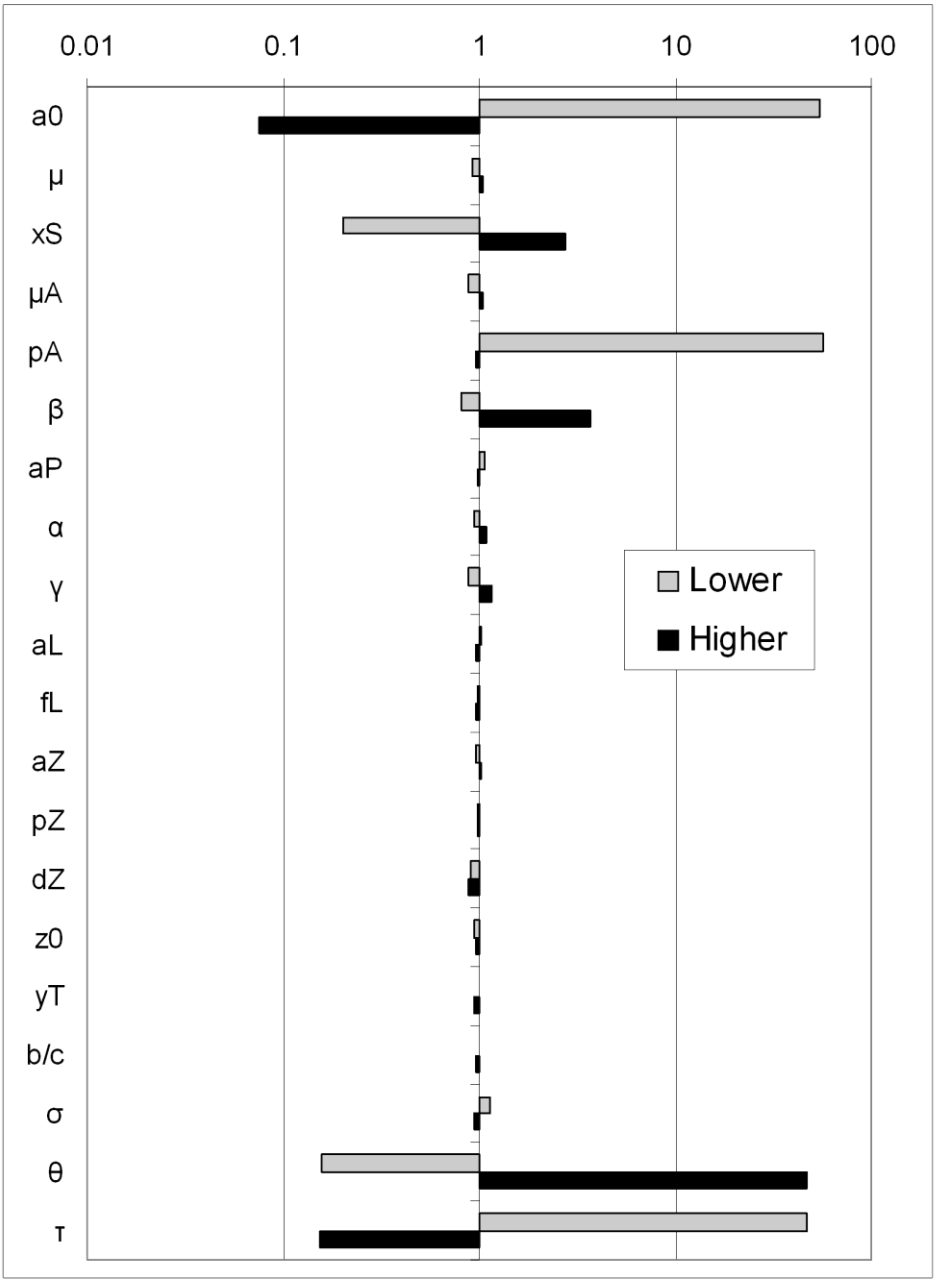


Figure S10 **Variation of initial value of parameters on CD4 cell count in month 120.** Note the x-axis is on log-scale, indicates how many times the parameters vary.

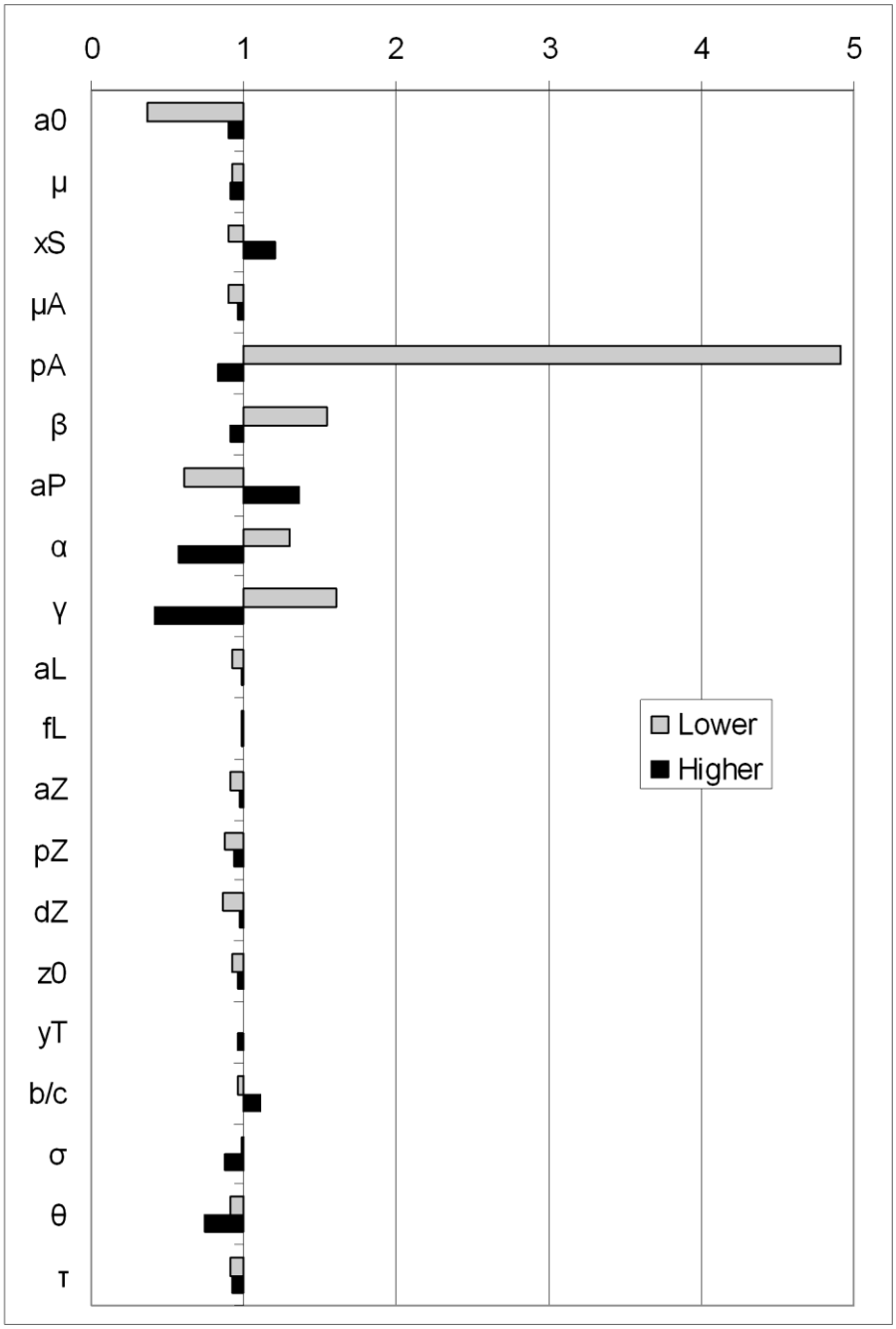


Figure S11 **Variation of initial value of parameters on viral load in month 120.** The x-axis indicates how many times the parameters vary.

b. Comparison with ATHENA cohort of the Netherlands

In the main text, we suggest that the ATHENA cohort data [9] corresponds to a drug adherence level around 40%. We then further analysed the data for a more detailed comparison. Figure S12 shows that the great majority of measurements ≥50 copies/ml, were >1000 copies/ml. If we consider the proportion of single blips (defined according to Definition set 2B) among those measurements that were 50-1000 copies/ml (Figure S13), we found that it gradually increase from zero at drug adherence between 0 and 0.1, to over 0.7 at drug adherence of 0.5. This is due to the decreasing number of measurements that are >50 copies/ml and therefore decreasing number of measurements that are 'consecutive'. When p>0.6, all measurements were <50 copies/ml.

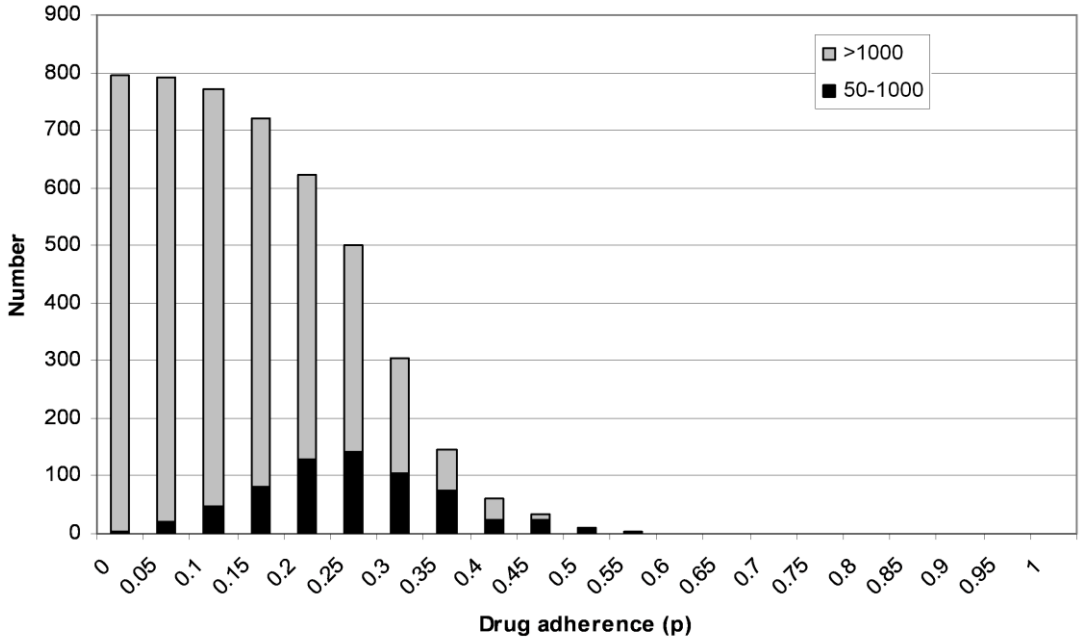


Figure S12 **Number of viral load measurements that were (black) 50-1000 copies/ml and (grey) >1000 copies/ml, out of 100 patients as observed in two years in a quarterly sampling frame at each drug adherence level.** This is a re-analysis of data of Figure 1.

In van Sighem's studies [9], with a total follow-up of 11,187 person-years after viral suppression of a study population of 4447 patients, there were 36,940 viral load measurements made, of which

2216 were between 50 and 1000 copies/ml. There were 1711 episodes of low-level viraemia (50-1000 copies/ml), of which 81.8% consisted of only one measurement (i.e. 'Single blip' according to Definition set 2B). Therefore, 63% of measurements between 50 and 1000 copies/ml were 'single blips'. This falls between the range of drug adherence 0.45 and 0.55 in Figure S13. This is not too far away from our 'prediction' of drug adherence 40%. However, given the absence of drug adherence data in the ATHENA cohort, we are unable to test our model predictions against empirical data. Readers are reminded that this model only incorporated non-compliance in cART and not other possible factors of viral blips in it; the occurrence of drug resistant strains is not modelled either.

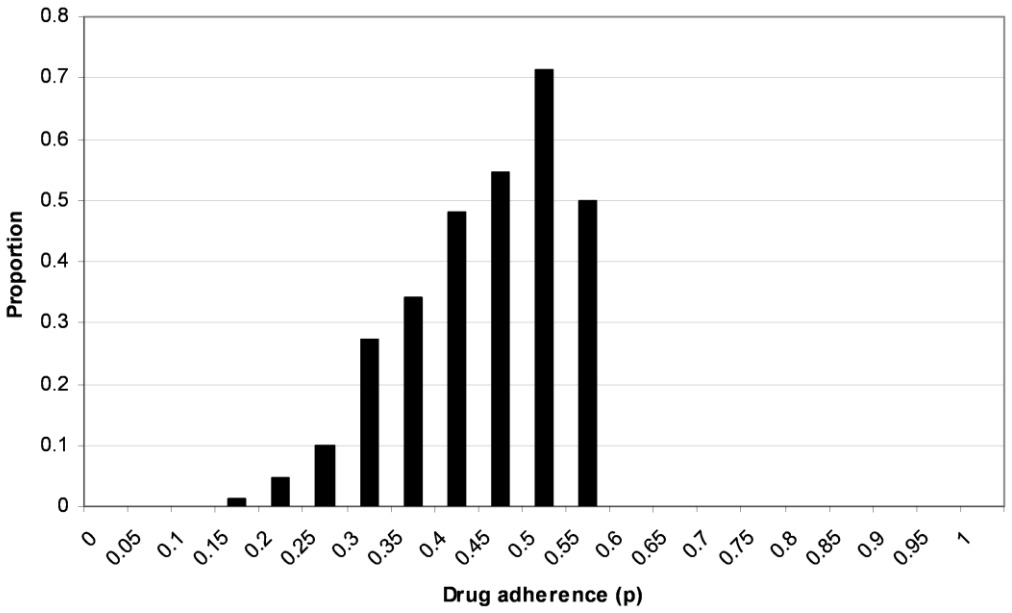


Figure S13 **Proportion of single blips among measurements that were 50-1000 copies/ml at each drug adherence level, out of 100 patients as observed in two years in a quarterly sampling frame at each drug adherence level.** This was a re-analysis of data of Figure 1. Single blips were defined here according to Definition set 2B and therefore exclude those measurements classified as 'first', 'last' and 'consecutive' (cf. Figure 1 legend). As the number of measurements that were 50-1000 copies/ml varies across drug adherence levels (cf. Figure S10), the denominator for each drug adherence is different. The reason for low proportion at the low end of the drug adherence spectrum is that most measurements were >1000 copies/ml, and the reason for zero proportion at p≥0.65 is the absence of measurements that were ≥50 copies/ml.

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Table A1 **Summary of studies on viral blips: study type, sample size, prevalence, incidence and follow-up period**

Study	*Study type*	*Sample size*	*Prevalence of blips, n (%)*	*Incidence of blips (blips/100 person-years)*	*Follow-up period, median*
Cohen Stuart et al[10]	case series	15	n/a	n/a	27 months after 'relapse'
Easterbrook et al[11]	retrospective cohort	765	122 (16%) of all patients initiating HAART; 27% of patients who initially attained an undetectable VL	-	27.9 (IQR 22.6-31.3) months for sustained undetectable VL group and 29.5 (IQR 25.2-32.5) months for intermittent viraemia group (P=0.003) from PI/NNRTI initiation
Garcia-Gasco et al[12]	retrospective cohort	2720	458 (17%) developed blips	-	8 years
Greub et al[13]	retrospective cohort	2055	704 'blips' = 490; 'bumps' = 155. *Also 71 of 176 patients who experienced rebound to >500 copies/ml return to ≤ 50 copies/ml.	37.4; see [14, 15]	17.7 months, after first VL measurement
Havlir et al[16]	retrospective study in a clinical trial	241	40% (20% if ≥200 copies/ml)	-	84 weeks; and 46 weeks after first intermittent viraemia episode
Macias et al[17]	retrospective cohort	330	37 (11%)	-	120 (range 36-156) weeks after the blip
Martinez et al[18]	retrospective cohort	43	8 (19%)	-	18 (range 6-24) months
Masquelier et al[19]	prospective cohort	219	20 (9%)	-	2 years
Miller et al[20]	case-control	128	32 (25%); of which only 28 had complete drug adherence data and were used in the analysis	-	12 weeks
Mira et al[21]	retrospective case-control in a prospective cohort	same cohort as in [17]	same cases as in [17]	-	120 (range 36-156) weeks after the blip
Moore et al[22]	retrospective cohort	553	192 (35%) experienced at least one measurement of >50 copies/ml; of 154 who had had a single measurement of >50 copies/ml and had not altered their therapy, 54% returned to <50 copies/ml, while 46% was >50 copies/ml.	-	56 (range 4 – 174) weeks
Nettles et al[23]	prospective cohort	10	9 (90%)	-	99.4 days (range, 12 weeks – 127 days)
Podsadecki et al[3]	retrospective studies of 2 clinical trials	223	60 (27%)	-	96 weeks
Raboud et al[24]	retrospective study of 3 clinical trials	358; 165 achieved undetectable VL in the first place	85 of 165 experienced VL rebound, of which 35 became undetectable again in the next measurement.	-	52 weeks
Sklar et al[14]	retrospective cohort	448	122 (27.2%)	22.5	485 days (69 weeks)
Stosor et al[25]	retrospective study in a prospective cohort	56	n/a	n/a	n/a
Sungkanuparph et al[15]	retrospective cohort	244 (NNRTI group); 136 (PI group)	53 (21.7%) of NNRTI group; 34 (25.0%) of PI group	19.4 (overall); 19.2 (NNRTI group); 19.7 (PI group)	NNRTI group: 24.0 (IQR 15.0-42.3); PI group: 23.0 (IQR 16.4-33.7)
van Sighem et al[9]	retrospective study in a prospective cohort	4447	1281 (28.8%)	-	total 11187 person-years after success

IQR, interquartile range; LLOQ, lower limit of quantification; n/a, not applicable; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

Table A2 **Number of simulations per data point in Figures 2 and 3.**

Percentage of observations ≥ 50 copies/ml	Monthly sampling frame θ = 754	3-monthly sampling frame		
		θ = 754	θ = 75.4	θ = 7540
0.0	1156	1245	1639	614
4.2	85	-	-	-
8.3	52	-	-	-
12.5	32	105	93	79
16.7	28	-	-	-
20.8	28	-	-	-
25.0	18	69	44	70
29.2	17	-	-	-
33.3	26	-	-	-
37.5	16	63	47	61
41.7	17	-	-	-
45.8	16	-	-	-
50.0	26	47	40	78
54.2	17	-	-	-
58.3	21	-	-	-
62.5	17	56	33	91
66.7	18	-	-	-
70.8	20	-	-	-
75.0	26	76	39	113
79.2	24	-	-	-
83.3	32	-	-	-
87.5	43	109	49	198
91.7	48	-	-	-
95.8	82	-	-	-
100.0	235	330	116	796
Total	2100	2100	2100	2100

Table A3 **Sensitivity analysis as shown in percentage change in CD4 count and viral load.**
Results showing high sensitivity are shown in bold.

Para-meters	Description	Model values	Sensitivity analysis values	%	value (25% quartile range, 75% quartile range) as a percentage of the median of the control values CD4 count	 Viral load
Median CD4 count when all parameters follow the model values					**18703 (15258, 21615) cells /ml i.e. 100% (82%, 116%)**	**39955 (25600, 51260) RNA copies / ml i.e. 100% (64%, 128%)**
a_0	average rate of T cells activation per antigenic exposure	10^{-4}	10^{-3}	1000%	**7.6% (5.9%, 10.3%)**	90% (81%, 99%)
			10^{-5}	10%	**5420% (5394%, 5440%)**	36% (21%, 51%)
μ	daily rate of non-antigen-driven homeostatic T cell division	0.01	0.1	1000%	105% (83%, 135%)	91% (70%, 96%)
			0.001	10%	91% (78%, 107%)	92% (70%, 117%)
x_S	relative T cell pool size below which T cell activation fails due to exhaustion of repertoire	0.05	0.1	2000%	273% (232%, 338%)	121% (85%, 166%)
			0.01	20%	20% (15%, 27%)	89% (69%, 105%)
μ_A	activated T cell division rate	1	2	200%	105% (89%, 130%)	96% (64%, 116%)
			0.5	50%	88% (74%, 108%)	90% (71%, 120%)
p_A	average probability of an activated T cell successfully dividing in an individual free of HIV	0.55	0.8	145%	95% (80%, 114%)	83% (65%, 120%)
			0.3	55%	**5700% (4600%, 6300%)**	**492% (380%, 623%)**
β	average infection rate of an activated CD4 T cell per virion	754	7540	1000%	81% (70%, 103%)	91% (76%, 116%)
			75.4	10%	367% (276%, 639%)	155% (93%, 266%)
a_P	activated infected cells become virally productive	1	2	200%	97% (81%, 114%)	61% (45%, 76%)
			0.5	50%	107% (87%, 127%)	137% (103%, 170%)
α	death rate of infected cells in the absence of CTL	1	2	200%	108% (85%, 130%)	57% (41%, 85%)
			0.5	50%	93% (83%, 110%)	130% (95%, 157%)
γ	death rate of productively infected cell in the absence of CTL	1	2	200%	115% (96%, 137%)	42% (30%, 58%)
			0.5	50%	89% (75%, 106%)	160% (123%, 201%)
a_L	rate of reactivation of latent infected cells	0.01	0.1	1000%	95% (80%, 116%)	98% (64%, 118%)
			0.001	10%	103% (80%, 123%)	92% (76%, 118%)
f_L	proportion of successful infections that result in latency	10^{-5}	10^{-4}	1000%	96% (78%, 120%)	98% (67%, 123%)
			10^{-6}	10%	98% (79%, 120%)	98% (70%, 135%)
a_Z	rate of CTL activation per productive infected cells	1.3334 * 10^{-8}	1.3334 * 10^{-7}	1000%	102% (82%, 127%)	97% (70%, 141%)
			1.3334 * 10^{-9}	10%	96% (81%, 116%)	91% (66%, 115%)
p_Z	maximum proliferation of anti-HIV CTLs	1	2	200%	97% (78%, 116%)	93% (66%, 130%)
			0.5	50%	97% (81%, 120%)	88% (61%, 120%)
d_Z	death rate of resting CTLs	0.01	0.1	1000%	88% (76%, 109%)	97% (68%, 119%)
			0.001	10%	91% (78%, 114%)	86% (64%, 117%)
z_0	pre-infection frequency of anti-HIV CTL	10^{-6}	10^{-5}	1000%	97% (81%, 117%)	96% (69%, 115%)
			10^{-7}	10%	94% (80%, 114%)	93% (71%, 122%)
y_T	threshold value of infected cells for the logistic proliferative response of CTL to HIV	$10^{-3.5}$	$10^{-2.5}$	1000%	93% (76%, 120%)	97% (71%, 115%)
			$10^{-4.5}$	10%	100% (82%, 123%)	100% (76%, 124%)
b/c	ratio of viral production rate in productively infected cells and viral clearance rate	292	320	110%	96% (80%, 112%)	110% (77%, 138%)
			265	91%	99% (84%, 123%)	96% (70%, 123%)
σ	maximum rate of CTL killing of HIV-infected cells	10^4	10^5	1000%	93% (78%, 114%)	98% (68%, 117%)
			10^3	10%	113% (93%, 144%)	87% (63%, 112%)
ϑ	average clearance rate in antigenic exposure model	0.02	0.1	500%	**4740% (4691%, 4779%)**	74% (0.53%, 116%)
			0.004	20%	16% (13%, 18%)	91% (88%, 95%)
τ	average exposure rate in antigenic exposure model	0.1	0.5	500%	15% (14%, 17%)	92% (84%, 97%)
			0.02	20%	**4679% (4580%, 4782%)**	91% (0.001%, 184%)

Table A4 **Sensitivity analysis: Median CD4 count, cells/ml (25% quartile range, 75% quartile range)**

Para-meters	Model values	Sensitivity analysis values	Drug adherence level 0	25	50	75
Median CD4 count when all parameters follow the model values			**18703 (15258, 21615)**	**106997 (97158, 122090)**	**136756 (125839, 161024)**	**137191 (130036, 153958)**
a0	10^{-4}	10^{-3}	1413 (1100, 1929)	8467 (5826, 11026)	44251 (30896, 61885)	259658 (237603, 283764)
		10^{-5}	1013685 (1008845, 1017383)	1030615 (1028000, 1033548)	1032080 (1028035, 1034328)	1029795 (1026168, 1032540)
μ	0.01	0.1	19655 (15592, 25304)	115224 (103440, 139156)	158915 (136509, 202931)	169376 (142667, 206376)
		0.001	17101 (14532, 19960)	98577 (89541, 107839)	132253 (126510, 137304)	132010 (128028, 136197)
x_S	0.05	0.1	51110 (43430, 63212)	190404 (160685, 218123)	235268 (202646, 260325)	234857 (204164, 276865)
		0.01	3758 (2806, 5092)	51327 (40809, 61732)	123759 (120461, 128979)	126531 (121875, 129978)
μ_A	1	2	19565 (16688, 24314)	135649 (126589, 157653)	156895 (137620, 200627)	157180 (138225, 196441)
		0.5	16487 (14026, 20184)	68572 (61278, 86361)	134751 (124399, 145588)	136677 (127758, 160428)
p_A	0.55	0.8	17811 (15000, 21228)	171939 (161951, 181071)	244592 (223292, 269430)	248187 (225855, 268270)
		0.3	1057205 (869558, 1176423)	1153110 (992652, 1280358)	1192935 (1070220, 1303458)	1124030 (983299, 1268383)
β	754	7540	15227 (13169, 19273)	35585 (28901, 42557)	88468 (77793, 100014)	132643 (125318, 157081)
		75.4	68723 (51559, 119576)	303740 (241606, 369617)	305744 (241698, 370289)	299637 (234531, 362950)
a_P	1	2	18165 (15066, 21231)	88719 (77987, 98812)	140420 (129640, 170258)	141108 (128015, 163165)
		0.5	20092 (16219, 23795)	123438 (113477, 155353)	144688 (131951, 166697)	143640 (132701, 175140)
α	1	2	20142 (15977, 24343)	118882 (108588, 137257)	145605 (131869, 165763)	142526 (130635, 161702)
		0.5	17456 (15576, 20502)	91230 (82113, 103125)	144129 (131051, 168710)	142127 (128873, 163439)
γ	1	2	21552 (17880, 25619)	130519 (121960, 154873)	147126 (132570, 178437)	155015 (138481, 197348)
		0.5	16592 (14053, 19802)	70425 (63504, 78036)	136896 (128284, 161899)	136325 (126887, 168519)
a_L	0.01	0.1	17835 (14935, 21674)	109833 (99850, 124044)	142108 (130183, 157085)	141550 (127438, 161631)
		0.001	19294 (14986, 22936)	104800 (95398, 118893)	135619 (125655, 161781)	139945 (130695, 160775)
f_L	10^{-5}	10^{-4}	18050 (14539, 22487)	105198 (94763, 125825)	132694 (125957, 158032)	137810 (127035, 155214)
		10^{-6}	18366 (14721, 22506)	109454 (98958, 122563)	136404 (128207, 161448)	136991 (128727, 156409)
a_Z	$1.3334 * 10^{-8}$	$1.3334 * 10^{-7}$	19114 (15254, 23659)	110127 (96231, 125810)	138347 (127471, 159118)	139516 (129261, 162679)
		$1.3334 * 10^{-9}$	18018 (15163, 21245)	106879 (94159, 123938)	136601 (125684, 156466)	137848 (129091, 162043)
p_Z	1	2	18227 (14515, 21749)	106475 (96113, 122830)	139197 (126036, 162546)	141047 (131141, 166993)
		0.5	18176 (15215, 22378)	109248 (97486, 120734)	139341 (126922, 154445)	137986 (128733, 160472)
d_Z	0.01	0.1	16366 (14131, 20296)	108196 (98226, 120333)	137561 (126390, 160892)	136839 (128097, 157445)
		0.001	16942 (14618, 21259)	109271 (97136, 122993)	135598 (127035, 154792)	135152 (128467, 165605)
z_0	10^{-6}	10^{-5}	18062 (15070, 21918)	107625 (98043, 122688)	137144 (129129, 162756)	138457 (128116, 157607)
		10^{-7}	17508 (15053, 21279)	106745 (98147, 119922)	137568 (128434, 157221)	135181 (129315, 160000)
y_T	$10^{-3.5}$	$10^{-2.5}$	17470 (14229, 22592)	106435 (96021, 120308)	136627 (128839, 159683)	138277 (130193, 160393)
		$10^{-4.5}$	18684 (15251, 23027)	108515 (96639, 125398)	136713 (125892, 165772)	138076 (129727, 159095)
b/c	292	320	17923 (14967, 20961)	100082 (86047, 110666)	149557 (130903, 179513)	144962 (129431, 167986)
		265	18529 (15749, 23041)	109511 (99087, 129619)	140302 (128599, 163717)	136375 (129372, 153524)
σ	10^4	10^5	17408 (14511, 21317)	104463 (93268, 123848)	137290 (125621, 162959)	139882 (129107, 162876)
		10^3	21179 (17361, 26959)	105279 (94710, 118075)	140855 (130162, 168184)	142608 (129582, 160778)
θ	0.02	0.1	886503 (877391, 893867)	926640 (918938, 933852)	930140 (922006, 937308)	928672 (922752, 935127)
		0.004	2954 (2518, 3346)	16100 (13637, 20147)	129824 (110656, 146138)	187828 (176779, 199356)
τ	0.1	0.5	2868 (3225, 2633)	16791 (14362, 18981)	128216 (112898, 140085)	191411 (185553, 196577)
		0.02	875012 (856537, 894443)	920447 (904828, 934519)	921428 (906080, 936615)	921480 (902296, 936628)

Table A5 **Sensitivity analysis: Median viral load, copies/ml (25% quartile range, 75% quartile range)**

Para-meters	Model values	Sensitivity analysis values	Drug adherence level 0	25	50	75
Median viral load when all parameters follow the model values			**39955 (25600, 51260)**	**1203 (3.72, 18401)**	**0.00086 (0.000583, 0.001519)**	**0.000517 (0.000381, 0.000732)**
a_0	10^{-4}	10^{-3}	35928 (32490, 39561)	19320 (4055, 80015)	1578 (16, 45368)	0.033492 (0.001806, 1.145378)
		10^{-5}	14359 (8254, 20487)	0.000195 (0.000136, 0.001041)	0.00012 ($9.45 \cdot 10^{-5}$, 0.000157)	0.000126 ($9.61 \cdot 10^{-5}$, 0.000141)
μ	0.01	0.1	36397 (27821, 49444)	1289 (36, 27314)	0.001169 (0.000697, 0.002221)	0.00076 (0.000517, 0.000972)
		0.001	36700 (27908, 46705)	547 (24, 15680)	0.000393 (0.000307, 0.000975)	0.000287 (0.000249, 0.000325)
x_S	0.05	0.1	48328 (33829, 66425)	4762 (100, 34716)	0.000662 (0.000394, 0.006212)	0.000294 (0.000273, 0.000342)
		0.01	35754 (27694, 41947)	654 (1.528353, 14265)	0.001038 (0.000804, 0.001701)	0.00077 (0.000665, 0.00095)
μ_A	1	2	38522 (25428, 46384)	1.841985 (0.103289, 543)	0.000778 (0.000521, 0.001087)	0.000612 (0.000431, 0.000892)
		0.5	36085 (28530, 47996)	14332 (658, 65817)	0.007454 (0.001323, 0.060693)	0.000584 (0.000386, 0.000882)
p_A	0.55	0.8	33155 (25918, 47945)	1953 (29, 43886)	0.000445 (0.000317, 0.001471)	0.000298 (0.000254, 0.000332)
		0.3	196516 (151234, 248753)	24017 (1014, 101113)	0.003936 (0.002045, 0.019956)	0.001506 (0.001158, 0.001812)
β	754	7540	36240 (30182, 46281)	31974 (11722, 54580)	8248 (145, 41529)	0.004565 (0.000953, 0.097449)
		75.4	61882 (37140, 106457)	0.001231 (0.000806, 0.002533)	0.000779 (0.000632, 0.001052)	0.000832 (0.00062, 0.00103)
a_P	1	2	54589 (41314, 67808)	13878 (608, 52942)	0.003143 (0.000885, 0.026458)	0.000738 (0.000519, 0.000938)
		0.5	24394 (17951, 30598)	87 (0.425039, 3170)	0.000455 (0.000316, 0.000664)	0.000346 (0.000264, 0.000476)
α	1	2	22767 (16334, 33939)	21 (0.378833, 3861)	0.000453 (0.000311, 0.000746)	0.000358 (0.000262, 0.000443)
		0.5	51926 (37919, 62681)	6951 (242, 37219)	0.001938 (0.000915, 0.004371)	0.000737 (0.000513. 0.001096)
γ	1	2	16606 (12014, 23364)	0.553038 (0.055311, 71)	0.000324 (0.00218, 0.000467)	0.000277 (0.000213, 0.00037)
		0.5	63980 (80462, 49390)	45245 (10116, 95824)	0.015835 (0.002381, 0.3453)	0.001137 (0.000838, 0.001646)
a_L	0.01	0.1	39307 (25376, 47306)	306 (2.016655, 16769)	$3.14 \cdot 10^{-32}$ ($1.56 \cdot 10^{-32}$, $1.15 \cdot 10^{-31}$)	$1.43 \cdot 10^{-32}$ ($9.79 \cdot 10^{-33}$, $2.05 \cdot 10^{-32}$)
		0.001	36765 (30454, 47260)	1796 (36, 18561)	0.829539 (0.708741, 1.20517)	0.675614 (0.617063, 0.721061)
f_L	10^{-5}	10^{-4}	39234 (27050, 48967)	2312 (139, 27718)	0.009085 (0.005168, 0.021507)	0.004043 (0.005249, 0.007191)
		10^{-6}	39351 (28032, 53850)	961 (9.828723, 26663)	$7.61 \cdot 10^{-5}$ ($5.55 \cdot 10^{-5}$, 0.000232)	$5.19 \cdot 10^{-5}$ ($3.83 \cdot 10^{-5}$, $6.91 \cdot 10^{-5}$)
a_Z	$1.3334 * 10^{-8}$	$1.3334 * 10^{-7}$	38691 (27800, 56411)	4468 (32, 20874)	0.000764 (0.000575, 0.001548)	0.000486 (0.000399, 0.000735)
		$1.3334 * 10^{-9}$	36500 (26472, 45845)	1715 (4.798633, 21639)	0.000786 (0.000534, 0.00133)	0.000477 (0.000388, 0.000711)
p_Z	1	2	37292 (26342, 51875)	2407 (10, 12690)	0.000872 (0.000598, 0.001594)	0.000504 (0.000385, 0.000684)
		0.5	35140 (24508, 48027)	600 (12, 13214)	0.000923 (0.000603, 0.002205)	0.000518 (0.000379, 0.000687)
d_Z	0.01	0.1	38822 (27214, 47661)	1639 (17, 25114)	0.000952 (0.000627, 0.001738)	0.000523 (0.000373, 0.000741)
		0.001	34302 (25725, 46878)	1890 (18, 18254)	0.000861 (0.000575, 0.001719)	0.000488 (0.000351, 0.000728)
z_0	10^{-6}	10^{-5}	38258 (27724, 45990)	844 (12, 11024)	0.000784 (0.000553, 0.001707)	0.000508 (0.000365, 0.000736)
		10^{-7}	36966 (28401, 48694)	384 (2.752213, 11178)	0.000872 (0.000589, 0.001716)	0.000482 (0.000375, 0.000685)
γ_T	$10^{-3.5}$	$10^{-2.5}$	38607 (28522, 46022)	3061 (45, 25136)	0.000934 (0.000571, 0.00167)	0.000491 (0.000381, 0.000722)
		$10^{-4.5}$	39884 (30232, 49405)	1522 (18, 24154)	0.000917 (0.000611, 0.002424)	0.00053 (0.000389, 0.000739)
b/c	292	320	44027 (30585, 55135)	1801 (39, 22217)	0.001037 (0.00674, 0.002868)	0.000584 (0.000457, 0.000823)
		265	38391 (28058, 49028)	5509 (9226, 0.000417)	0.000672 (0.000417, 0.001727)	0.000435 (0.000335, 0.000574)
σ	10^4	10^5	34819 (25371, 44865)	974 (6.11591, 31190)	0.000848 (0.000602, 0.001567)	0.000575 (0.000385, 0.000799)
		10^3	39314 (27000, 46739)	1506 (19, 23039)	0.000856 (0.000518, 0.002065)	0.000523 (0.000414, 0.00071)
θ	0.02	0.1	29632 (211, 46299)	0.024014 (0.002408, 0.178227)	0.000229 (0.000187, 0.000302)	0.000234 (0.000193, 0.000303)
		0.004	36462 (35084, 37892)	17337 (3849, 70019)	722 (15, 38070)	0.000398 (0.000311, 0.000803)
τ	0.1	0.5	36746 (33693, 38606)	16739 (2384, 71770)	2863 (19, 42919)	0.000363 (0.000314, 0.000597)
		0.02	36368 (0.481267, 77376)	0.028471 (0.005236, 0.556132)	0.000258 (0.000145, 0.000428)	0.000265 (0.000143, 0.000355)