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Expanded HAART Coverage is Associated with Decreased Population-level HIV-1-RNA and Annual New HIV Diagnoses in British Columbia, Canada

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Abstract

Background—Cohort studies and mathematical models have suggested that expanded coverage with highly active antiretroviral therapy (HAART) could decrease HIV transmission. This study focuses on the HIV epidemic, stratified by injection drug use, in the province of British Columbia, Canada, and seeks to estimate the association between plasma HIV-1-viral load, HAART coverage and number of new cases of HIV at the population-level.

Methods—HAART use, plasma HIV-1-viral level determinations, and rates of reportable sexually transmitted infections, including HIV, are all recorded in province-wide registries allowing for temporal comparisons of these parameters. Trends of new HIV positive tests and number of individuals on HAART were modeled using generalized additive models. Poisson log-linear regression models were used to estimate the association between the outcome new HIV

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positive tests (per 100 population) and the covariates viral load ($\log_{10}$ transformed), year, and number of individuals on HAART.

Conclusions—Our results demonstrate a strong association at the population-level between increasing levels of HAART coverage, decreased viral load and decreased new HIV diagnoses/year, against a background of increased HIV testing and increased rates of other STIs in the province. Our results support the proposed secondary benefit of HAART, used within current medical guidelines, on HIV transmission at a population level.

INTRODUCTION

Despite recent progress, neither a cure nor a preventive vaccine against Human Immunodeficiency Virus-Type 1 (HIV) infection is likely to become available in the near future. Several preventive strategies are effective, however, their effectiveness remains suboptimal for multiple reasons, including lack of support, logistic difficulties, poor implementation and underutilization.¹ As a result, the global impact of HIV/AIDS continues to grow. In 2008, an estimated 33.4 million people were living with HIV, with 2.0 million AIDS-related deaths.¹ Alarming, 2.7 million new HIV infections occurred in 2008. These developments have prompted the United Nations Joint Programme on HIV/AIDS (UNAIDS) to call for an urgent redoubling of the effort in the fight against HIV/AIDS.²

Remarkable advances have taken place since 1996 in HIV therapeutics, with the development and refinement of highly active antiretroviral therapy (HAART). HAART stops HIV replication on a sustained basis and, as a result, plasma HIV-1-RNA levels (henceforth viral load) typically become undetectable. This allows for immune reconstitution to take place, leading to long-term remission of the disease, and averting its otherwise fatal course.^{3–4} By 2006, at least 3 million years of life have been saved in the United States as a direct result of HAART.⁵ The life expectancy at age 20, among HIV-infected individuals on HAART in high income countries, was approximately two thirds of the life expectancy of the general population.⁶

More recently, there has been an increased interest in the possible secondary effect of HAART in reducing HIV transmission.^{7–13} In brief, it has long been understood that the higher the plasma HIV-1-RNA levels the higher the risk of HIV transmission in any given setting.^{14,15} It is also clear that in addition to decreasing plasma viral load to undetectable levels, HAART decreases viral load in other biological fluids, including semen and vaginal secretions.^{16,17} Although exceptions have been reported,^{18–21} from a public health perspective, the correlation between viral load and other bodily fluids is quite strong, particularly in the setting of long-term sustained effective HAART.²² Strong proof of principle regarding the impact of HAART on HIV transmission can be found in studies of vertical transmission, in resource-rich and resource-limited settings.²³

New evidence suggests that HAART can decrease HIV transmission in other settings. Reductions in rates of HIV transmission in excess of 90% were reported in several cohort studies of heterosexual HIV sero-discordant couples, when the index member of the couple was treated with HAART.^{24,25} Similarly, reduction in community viral load as a result of HAART was recently found to be a key determinant of decreasing HIV incidence within a cohort of injection drug users (IDUs) in Vancouver, Canada.²⁶ Finally, retrospective population-based observational studies have also documented this effect in Taiwan,²⁷ in the province of British Columbia (BC), Canada¹⁰ and in the city of San Francisco, USA.²⁸ However, results of mathematical models have varied dramatically in their estimation of the potential impact of increased HAART coverage on HIV transmission, predicting anywhere from elimination^{10,13} to potential worsening²⁹ of the HIV epidemic. We therefore conducted the present study to analyze, at the population-level, the potential association

between expansion of HAART coverage, viral load and new HIV diagnoses per year in a Canadian province with free access to HIV care. Sub-analyses stratified the population by IDU status.

METHODS

Data Sources

Two separate unlinked databases were used in this study. Data regarding provincial number of HIV tests performed and new HIV diagnoses in the province of British Columbia (BC), Canada, were obtained from the BC Centre for Disease Control (BCCDC).³⁰ The BCCDC is the single provincial agency that centralizes all HIV surveillance data for the province and has access to HIV testing data from the Provincial Public Health Reference Laboratory which conducts over 90% of HIV testing in BC. BC has had mandatory (nominal or non-nominal) HIV reporting legislation in place since 2003. The latter includes specifically determining whether a new HIV positive result results from a previously known HIV infected individual moving to BC, with a known prior HIV diagnosis. For individuals 18 months or older, BCCDC uses a screening test (ELISA) to detect HIV antibodies, with a confirmed HIV diagnosis based on a reactive Western Blot or Nucleic Acid Amplification Test.

All remaining data used in these analyses were extracted from the BC Centre for Excellence in HIV/AIDS (BC-CfE) population-based registries of all people on HAART or accessing viral load testing in the province. The BC-CfE is the single provincial agency responsible for providing centralized treatment free of charge to all HIV infected BC residents. The BC-CfE maintains a set of independently generated HIV/AIDS management guidelines, which have remained consistent with the International AIDS Society-USA (IAS-USA) Guidelines since 1996. In brief, the BC-CfE guidelines recommend that once an individual initiates treatment, viral load and CD4 testing be done at regular intervals (e.g. every 3 to 4 months), or after virologic rebound. Capture of baseline and on treatment viral load results by the BC-CfE is 100%, as all viral load determinations in BC are performed under the auspices of the BC-CfE by the virology laboratory at St Paul's Hospital, Providence Health Care. Table 1 shows the different HIV-1-RNA viral load assays used during the study period and their quantification range. For analytical purposes, we truncated the viral load data to the range <500 to >100,000 copies/mL. This range was selected because that these values were within the measurement range of all the assays used over the study period. Population or community level viral load was estimated using a conservative approach by recording the highest viral load for each individual in a given year. In order to accommodate irregular frequency of viral load measurements or missing values, the highest yearly value was carried forward until a new determination was available, or a patient was censored if the patient moved out of the province or died.

HIV, infectious syphilis, genital gonorrhea and genital chlamydia rates were estimated by dividing the yearly number of new diagnosed cases of each disease in BC by the yearly population in British Columbia, and then multiplied by 100,000. Population estimates for the years under observation were obtained from published reports from BC Stats, available at <http://www.bcstats.gov.bc.ca/data/pop/pop/popproj.asp>. The number of expected HIV diagnoses was calculated by applying the HIV case rate for the first year of the period under investigation (1996–2000, 2001–2003, and 2004–2009) to all subsequent years in that study period. A rate ratio was then calculated by dividing the number of observed cases over expected ones, with confidence intervals calculated using Byar's approximation methods.³¹

CD4 cell counts were measured by flow-cytometry (Beckman Coulter, Inc., Mississauga, Ontario, Canada). Baseline CD4 cell count obtained before the initiation of antiretroviral

treatment was obtained from the BC-CfE registry, which captures >80% of all CD4 tests done in the province. Antiretroviral therapy is free of charge through the BC-CfE, and physicians are requested to provide the patient's baseline information, including a pre-treatment CD4 cell count. HAART use data was obtained from the BC-CfE databases as the BC-CfE centrally distributes all antiretroviral drugs in BC.

Based on our previous work, which demonstrated that a reduction in community viral load as a result of HAART was a key statistically significant determinant of decreasing HIV incidence within a cohort of injection drug users (IDUs) in the Downtown Eastside of Vancouver,²⁶ these analyses were repeated after stratification by history of injection drug use. This relied primarily on self-reporting and case report forms completed by health care providers and public health nurses as collected by the BCCDC. Additionally, prior history of injection drug use data was enriched with linkages with all BC-CFE based cohort studies, including the Vancouver Injection Drug Users Study (VIDUS),²⁶ the At-Risk Youth Study (ARYS),³² the Scientific Evaluation of Supervised Injecting site (SEOSI)³³ and MAKa cohorts.³⁴

The BC-CfE has received ethical approval from the University of British Columbia Ethics Review Committee at its St. Paul's Hospital, Providence Health Care site (P05-123) to conduct the present study. The program also conforms to the province's Freedom of Information and Protection of Privacy Act.

Statistical Analysis

Trends of new HIV positive tests and number of individuals on HAART were modeled using generalized additive models. The motivation for using such models is the possibility of modelling the non-linear temporal effects without making strong assumptions about the parametric form of these trends. Poisson log-linear regression models were used to estimate the association between the outcome new HIV positive tests (per 100 population) and the covariates viral load ($\log_{10}$ transformed), year, and number of individuals on HAART. All models were used and implemented in R version 2.8.1, p-values are double sided and significance is at the 5% level. All p-values are for trend, unless otherwise specified.³⁵ In order to test the primary hypothesis of the study, we divided the follow up period into three discrete time periods based on HAART utilization data in BC, all of them consistent with contemporary treatment guidelines. The first period, from 1996 to 1999, relates to the initial roll out of HAART. The second period, from 2000 to 2003, relates to a steady state phase of HAART use. The third period, from 2004 to 2009, relates to the second HAART expansion.

Role of the Sponsors and Corresponding Author

The sponsors had no role in the design, data collection, data analysis, data interpretation, and writing or revisions of the report or manuscript. JSGM, as corresponding author, had full access to all data in the study and had final responsibility to submit for publication.

RESULTS

The number of individuals actively receiving HAART in BC increased from 837 to 5413 (+547%; $p = 0.002$) and the number of individuals newly testing positive for HIV per year declined from 702 to 338 cases from 1996 to 2009 (−52 %; $p = 0.001$). The overall correlation between the number of individuals actively receiving HAART and the number of individuals newly testing positive for HIV per year in BC from 1996 to 2009 was −0.89 ($p < 0.001$). As shown in Figure 1a, HAART usage and new HIV diagnoses per year showed three distinct phases during the study period. Between 1996 and 1999, we retrospectively observed a steep increase in the number of individuals on HAART (+258%; $p = 0.021$),

which reflects the initial roll out of HAART in the province, resulting from the 1996 IAS-USA guidelines. During this period, new HIV diagnoses per year decreased sharply (-40% ; $p=0.003$). Between 2000 and 2003, HAART use increased slightly ($+9\%$; $p<0.001$), due to the relative balance between treatment interruptions and HAART initiations (new and returning patients). During this period, new HIV diagnoses per year also remained relatively stable ($+5\%$; $p=0.954$). Between 2004 and 2009, we prospectively observed a second slower but steady increase in the number of individuals on HAART ($+51\%$; $p<0.001$), based on the emerging 2004 IAS-USA guidelines⁵⁶, which recommended against structured treatment interruptions. During this third period, new HIV diagnoses per year decreased substantially (-23% ; $p<0.001$). When the data were stratified by prior history of injection drug use, there was a $\sim 50\%$ decline in annual new diagnoses among individuals with prior history of injection drug use, from 159 cases in 1999 to 80 cases in 2009 ($p = 0.003$). In contrast, the number of new positive tests remained stable (p -value 0.6229) among individuals with no history of injection drug use.

Next, we estimated the number of new HIV diagnoses that would have been expected at steady state in each of the three periods under investigation (1996–2000, 2001–2003, and 2004–2009). We compared the actual number of new HIV diagnoses in a particular year to the number that would have been expected if the rate of new HIV diagnoses remained constant over the same period. For each period, the number of observed new HIV diagnoses was divided by expected new HIV diagnoses, to determine whether there was an increase or decrease in the number of new HIV diagnoses. As shown in Figure 1b, for 1996–2000, we determined that there were 30 % (Rate ratio [RR]: 0.70; 95% CI: 0.67 – 0.72) fewer new HIV diagnoses than expected. For 2001–2003, we showed that the number of observed and expected new HIV diagnoses were essentially the same – a decrease of 1.7% (RR: 0.98; 95% CI: 0.93 – 1.04). In the last period, 2004–2009, we observed a decline in new HIV diagnoses of 16.6% (RR: 0.83; 95% CI: 0.80 – 0.87).

Figure 2 shows yearly distribution of pre-HAART CD4 cell counts from 1996 until 2009, as a surrogate for the timing of HAART initiation. Substantial differences are apparent between the three study phases: pre-HAART CD4 cell counts were highest in 1996–99 (peak in 1997 – median 310 cells/mm³); lowest in 2000–03 (nadir in 2003 – median 150 cells/mm³); and steadily increasing in 2004–09 (peak in 2009 – median 270 cells/mm³). The trends in CD4 count at baseline (pre-HAART) were tested in each one of the study periods using Cochran-Armitage Trend Test for the proportion of CD4 $<200/\text{mm}^3$. We found that the baseline CD4 cell count decreased ($p = 0.024$) in the 1996 – 1999 period, and decreased again in the 2000 – 2003 period ($p < 0.001$), but it increased significantly ($p < 0.001$) in the 2004 – 2009 period.

To further explore the contribution of HIV viral load to the trends in the number of new HIV diagnoses in BC, we characterized the viral load per year in the province, stratified by prior history of injection drug use between 1996 and 2009. As shown in Table 2, the number of individuals with viral load < 500 c/mL, regardless of history of injection drug use, increased dramatically during the study period, starting from $<10\%$ in 1996 to over 50% in 2009 ($p < 0.001$). Additionally, between 2004 and 2009, the proportion of patients with no prior history of injection drug use with viral load below 500 and 50 copies/mL increased by 36% ($p<0.001$) and 42% ($p=0.001$), respectively. In contrast, the same proportion among patients with prior history of injection drug use increased by 82% ($p=0.001$) and 86% ($p=0.002$), respectively. Secondarily, from the Poisson regression modeling the association of new HIV positive tests, viral load, year and number of individuals on HAART, we estimated that for a 100 increase in the number of individuals on HAART, the estimated number of new HIV cases decreased by a factor of 0.97 (95% confidence interval 0.96–0.98), and per 1 log₁₀

decrease in viral load, the estimated number of new HIV cases decreased by a factor of 0.86 (95% confidence interval 0.75–0.98).

We considered whether the decreased number of new HIV diagnoses could result from decreased HIV testing during periods of increased HAART use, but found that the total number of HIV tests performed in the province had actually increased steadily over the study period. The average number of HIV tests performed was 137,585/year between 1996 and 1999 (or an average of 3.5% of the BC population), 139,464/year between 2000 and 2003 (or an average of 3.4% of the BC population) and 168,924/year between 2004 and 2008 (or an average of 4.0% of the BC population). Also of note, the rates of infectious syphilis, genital gonorrhea and genital chlamydia increased steadily during 1996–2008.³⁰ For infectious syphilis, the crude rate per 100,000 population increased from 0.5 in 1996 to 7.4 in 2008; for genital gonorrhea, the crude rate per 100,000 population increased from 12.6 in 1996 to 31.3 in 2008; and for genital chlamydia, the crude rate per 100,000 population increased from 106.2 in 1996 to 239.3 in 2008. The rate of hepatitis C decreased from 158.2 in 1996 to 87.0 in 2003 (–45% decrease; $p<0.001$) and to 55.8 per 100,000 population in 2008 (36% decrease from 2003; $p<0.001$).

DISCUSSION

Our results show a strong and statistically significant association between increased HAART coverage, decreased community viral load and decreased new HIV diagnoses per year at the population-level in a Canadian province. We had a unique opportunity to characterize the evolution of these parameters over fifteen years within a universal health care environment with centralized and free access to HAART. We did so as the pattern of use of HAART changed markedly based on contemporary therapeutic guidelines. Three distinct phases therefore were clearly apparent during the study, including two phases of steady HAART coverage expansion, separated by a period of stable HAART use between 2000 and 2003. Community viral load and annual new HIV diagnoses per year decreased substantially during both phases of HAART expansion. In contrast, community viral load and new HIV diagnoses per year remained stable while HAART use remained at a steady state between 2000 and 2003. As shown in figure 1b, we estimated that new HIV diagnoses declined by 30.3% in 1996–2000, remaining relatively stable in 2001–2003, with a decrease of 1.7%, declining again by 16.6% in 2004–2009. Of note, the rates of viral load suppression have increased steadily in BC since 1996, as recently reported.³⁶

Starting in the year 2000, we were able to stratify our data based on prior history of injection drug use. Based on these data, we found that the association between increased HAART coverage, decreased community viral load and decreased new HIV diagnoses per year was driven to a large extent by the subset of individuals with documented prior history of injection drug use, where new HIV diagnoses per year decreased by nearly 50% since 1999. Rates among individuals with a prior history of injection drug use decreased slowly between 2003 and 2007, falling precipitously in 2007–2008, in tandem with a decline in community viral load among individuals with a prior history of injection drug use. In contrast, rates among men who have sex with men increased post 2003 and remained relatively stable until 2008. In fact, our results show that the rate of undetectable plasma viral load increased by 42% among patients with no prior history of injection drug use in contrast to an 86% increase in this rate among patients with prior history of injection drug use. We attribute this to a specific outreach effort to facilitate access to HAART among medically eligible individuals with a prior history of injection drug abuse in the latter period.

The results of this study expand our previous observation in a small cohort of individuals with prior history of injection drug use, where the median community viral load was the

strongest driver of HIV sero-conversion.²⁶ These results are also consistent with those of Moupali Das-Douglas et al, who recently described an association between decreasing community plasma viral load and new HIV diagnoses over time in San Francisco.²⁸ Taken together these reports confirm that expanding HAART coverage within medical guidelines is associated with reductions in the population or community plasma viral load level. Reassuringly, this effect was also present among individuals with a prior history of injection drug abuse.³⁷ Further, the results of our multivariable Poisson log-linear regression model are consistent with the previously proposed secondary preventive benefit of HAART used within current therapeutic guidelines.

Our report is based on an ecological study, therefore our results cannot be taken as definitive proof of causality. However, it is noteworthy that the findings here described occurred against a background of increasing number of yearly HIV tests performed in the province, suggesting that case-finding efforts did not decline during the study period. Further, mandatory (nominal or non-nominal) reporting was implemented in the province starting in 2003, which resulted in better follow up and risk ascertainment. This would have allowed for better identification of HIV infected individuals migrating to the province and may have acted as a small liberal bias (for the entire cohort post 2003 this represented less than 2 per 1,000,000 population and overall HIV positive rates fell from 10 per 100,000 to 8 per 100,000 population). However, this is likely to be overcompensated by the conservative bias provided by the overall increase in the number of new cases identified by the new strategy. The latter would be consistent with findings from the US-CDC, which reported a 15% increase in HIV Diagnoses from 2004–2007 in 34 US States, partially attributable to enhanced testing efforts in these states.³⁸ Also of note, rates of STIs increased during the last 15 years of our study, which implies that our findings are not explained by decreasing sexual HIV risk behavior. Hepatitis C rates had an apparent decline during the study period, however, the timing of this decrease was clearly out of synchrony with the changes in new HIV diagnoses among IDUs. Furthermore, hepatitis C only became reportable in BC in 1993, and as a result, a large proportion of the cases newly identified in the ensuing years were prevalent rather than incident cases. Therefore the decline in yearly hepatitis C diagnoses from 1996 to 2003 in particular, likely represents a decline in the pool of prevalent cases identified rather than a steep decline in new cases among IDUs. This effect is less likely a contributor in latter years. Also of note, our results were internally reproducible, as we observed decreases in new HIV diagnoses per year during two distinct periods of HAART expansion separated by a stable period of HAART use. The latter characterized on a prospective basis¹⁰ and entirely consistent with the effect predicted by our mathematical models.^{39,40} Further, the associated declines in plasma viral load documented during the HAART expansion provide a plausible mechanistic pathway to explain this association. Finally, there is ample supportive evidence regarding the preventive effect of HAART on HIV transmission, derived from vertical transmission studies²³ and more recently cohort studies of sero-discordant couples,^{24,25} IDU cohorts²⁶ and population based studies.^{10,27,28} Thus, taken together the available evidence strongly suggest that community viral load is indeed a key driver of HIV new diagnoses that can be successfully modulated through the effective expansion of HAART coverage within medical guidelines.

In conclusion, our results demonstrate a strong association between levels of HAART coverage and decreased new HIV diagnoses despite increased HIV testing efforts. These results provide a strong rationale for the re-examination of the HIV prevention and treatment dichotomy, as it has been strongly advocated by the United Nations Joint Programme on HIV/AIDS (UNAIDS) as part of a comprehensive combination prevention strategy.⁴¹ Furthermore, our results should serve to re-energize the G8's Universal Access pledge as a means to curb the impact of AIDS and the growth of the HIV pandemic.

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Active on
HAART

837 1960 2597 2994 3079 3120 3211 3356 3585 3913 4255 4654 5123 5413

New HIV+
diagnoses
(All)

702 519 471 416 400 420 418 408 441 400 361 391 346 338

New HIV+
diagnoses
(ever IDU)

NA NA NA 159 152 149 168 149 156 137 128 128 65 80

HIV Tests
done in BC
(per 1000)

138 140 137 135 135 135 145 142 154 161 172 176 182 NA

Figure 1.

a. Number of active highly active antiretroviral therapy (HAART) participants in the British Columbia Centre for Excellence in HIV/AIDS and number of New HIV-positive diagnoses per year in British Columbia from 1996 to 2009. *p* refers to the *p*-value for trend obtained from the generalized additive model. IDU refers to those individuals who have ever injected illicit drugs.

b. Number of New HIV-positive diagnoses (blue = observed, red = expected) per year in British Columbia during the three phases of the study period, from 1996 to 2009. The *p*-values refer to the total observed number of HIV-positive diagnosis (blue square) compared to the total expected number of HIV-positive diagnosis (red square) at the end of each of the 3 time periods.

Figure 2. Distribution of annual pre-HAART CD4 cell count (cells/mm³) for all individuals initiating HAART in British Columbia from 1996 until 2009. Median yearly baseline CD4 cell counts are listed below the horizontal axis and illustrated (X) on the plot.

Table 1

HIV-1-RNA viral load assays from 1996 until 2009

Time Period	Assay Name	Range of Quantification (copies/mL)
June 1,1996	Roche HIV-1 monitor test ⇒ Microplate format	500–1,000,000
April 18,1997	Roche HIV-1 monitor test ⇒ Microplate format	400–750,000
October 27,1997	Roche HIV-1 monitor test version 1.5 ⇒ Included new primers to detect different HIV-1 subtypes	400–750,000
December 4,1998	Roche COBAS HIV-1 monitor test version 1.5 ⇒ First time using a automated amplification and detection, and the standard method was used for specimen preparation.	400–750,000
April 1,1999	Roche CO BAS HIV-1 Ampliprep Amplicor Monitor ultrasensitive assay version 1.5 ⇒ Automated amplification and detection and the ultrasensitivity method was used for specimen preparation	50–75,000
March 8,2000	Roche CO BAS HIV-1 Ampliprep Amplicor Monitor ultrasensitive assay version 1.5 ⇒ Automated amplification and detection and the ultrasensitivity method detection range changed over the years	50–100,000
February 1,2008 until present	Roche CO BAS HIV-1 Ampliprep Taqman assay ⇒ Method of automated amplification and detection changed	40–1,000,000

Table 2

Distribution of the highest HIV-1 RNA plasma level for all individuals in British Columbia who ever had a HIV-1 RNA levels in plasma test from 1996 until 2009.

Year of Follow-up	Individuals who have NEVER injected drugs				Individuals who have EVER injected drugs			
	Number of patients	Median HIV-1 RNA Plasma Level (Interquartile Range)	Percent of patients with <50 copies/mL	Percent of patients with <50 copies/mL	Number of patients	Median HIV-1 RNA Plasma Level (Interquartile Range)	Percent of patients with <50 copies/mL	Percent of patients with <50 copies/mL
1996	2093	35000 (6000 - > 100000)	8.5	NA	831	36000 (7600 - > 100000)	5.5	NA
1997	2848	18000 (2175 - 93000)	16.3	NA	1334	37000 (6100 - > 100000)	9.0	NA
1998	3324	8800 (<500 - 76000)	30.6	NA	1558	26000 (2100 - > 100000)	17.6	NA
1999	3740	6145 (<500 - 72000)	36.6	6.3	1707	20500 (805 - > 100000)	22.7	4.3
2000	4114	6270 (<500 - 76300)	38.2	25.8	1822	18650 (<500 - > 100000)	26.4	18.0
2001	4535	4260 (<500 - 69400)	41.3	29.2	1936	18450 (<500 - > 100000)	26.5	19.1
2002	4950	5545 (<500 - 88000)	42.2	30.9	2046	23550 (<500 - > 100000)	28.4	20.1
2003	5303	4820 (<500 - 76500)	42.8	32.4	2151	22200 (<500 - > 100000)	29.6	21.9
2004	5848	2355 (<500 - 59500)	45.5	35.5	2230	19100 (<500 - > 100000)	32.2	23.9
2005	6174	814 (<500 - 51000)	48.8	39.1	2297	13700 (<500 - 96400)	35.0	27.4
2006	6426	<500 (<500 - 41800)	51.8	42.7	2330	9015 (<500 - 89500)	38.7	30.5
2007	6745	<500 (<500 - 34500)	54.5	45.2	2335	5450 (<500 - 80900)	42.5	33.8
2008	7301	<500 (<500 - 25000)	58.1	45.0	2326	522.5 (<500 - 46500)	49.8	34.7
2009	8001	<500 (<500 - 16092)	62.0	50.5	2340	<500 (<500 - 20035)	58.6	44.4

$p < 0.001$, where p refers to the p -value for trend of median values for HIV-1 RNA levels in plasma obtained from the generalized additive model.