Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study

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Summary

Background **Results of cohort studies and mathematical models have suggested that increased coverage with highly active antiretroviral therapy (HAART) could reduce HIV transmission. We aimed to estimate the association between plasma HIV-1 viral load, HAART coverage, and number of new cases of HIV in the population of a Canadian province.**

Methods **We undertook a population-based study of HAART coverage and HIV transmission in British Columbia, Canada. Data for number of HIV tests done and new HIV diagnoses were obtained from the British Columbia Centre for Disease Control. Data for viral load, CD4 cell count, and HAART use were extracted from the British Columbia Centre for Excellence in HIV/AIDS population-based registries. We modelled trends of new HIV-positive tests and number of individuals on HAART using generalised additive models. Poisson log-linear regression models were used to estimate the association between new HIV diagnoses and viral load, year, and number of individuals on HAART.**

Findings **Between 1996 and 2009, the number of individuals actively receiving HAART increased from 837 to 5413 (547% increase; p=0·002), and the number of new HIV diagnoses fell from 702 to 338 per year (52% decrease; p=0·001). The overall correlation between number of individuals on HAART and number of individuals newly testing positive for HIV per year was –0·89 (p<0·0001). For every 100 additional individuals on HAART, the number of new HIV cases decreased by a factor of 0·97 (95% CI 0·96–0·98), and per 1 $\log_{10}$ decrease in viral load, the number of new HIV cases decreased by a factor of 0·86 (0·75–0·98).**

Interpretation **We have shown a strong population-level association between increasing HAART coverage, decreased viral load, and decreased number of new HIV diagnoses per year. Our results support the proposed secondary benefit of HAART used within existing medical guidelines to reduce HIV transmission.**

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Introduction

Despite recent progress, neither a cure nor a preventive vaccine against HIV-1 infection is likely to become available in the near future. Several preventive strategies have not been wholly effective for several reasons, including insufficient support, logistical difficulties, poor implementation, and underuse.[1] As a result, the global effect of HIV/AIDS continues to grow. In 2008, an estimated 33·4 million people were living with HIV, there were 2·0 million AIDS-related deaths,[1] and an alarming 2·7 million new HIV infections occurred. These developments have prompted the UN Joint Programme on HIV/AIDS to call for an urgent redoubling of efforts in the fight against HIV/AIDS.[2]

HIV treatment has advanced remarkably since 1996, 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 concentrations (henceforth viral load) typically become undetectable. This change allows for immune reconstitution to take place, leading to long-term disease remission and aversion of the otherwise fatal course.[3,4] By 2006, at least 3 million years of life had been saved in the USA as a direct result of HAART within a decade.[5] In high-income countries, life expectancy of HIV-positive individuals aged 20 years who were taking HAART was roughly two-thirds of that of the general population.[6]

Interest has increased in the possible secondary effect of HAART—reduction of HIV transmission.[7–13] The association between high plasma HIV-1 RNA concentration and high risk of HIV transmission has long been understood.[14,15] 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 association between viral load and other bodily fluids is quite strong, especially in the setting of long-term, sustained, and effective HAART.[22] Strong proof of principle regarding the effect of

HAART on HIV transmission has been shown in studies of vertical transmission in resource-rich and resource-poor settings.[23]

New evidence suggests that HAART can decrease HIV transmission in other settings. Reductions in rates of HIV transmission of more than 90% have been reported in several cohort studies of heterosexual HIV-serodiscordant couples in whom the index partner was treated with HAART.[24,25] Similarly, reduction in community viral load as a result of HAART was shown to be a key determinant of decreasing HIV incidence in a cohort of injecting drug users (IDUs) in Vancouver, Canada.[26] Investigators have also documented this effect in retrospective population-based observational studies in Taiwan,[27] the province of British Columbia, Canada,[10] and the city of San Francisco, USA.[28] However, the estimated effect of increased HAART coverage on HIV transmission varies greatly between mathematical models, with results ranging from elimination[10,13] to potential worsening[29] of the HIV epidemic. We therefore undertook this study with the aim of analysing at a 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.

Methods

Study design and participants

We used two separate unlinked databases in this population-based cohort study. Data for number of HIV tests done and new HIV diagnoses in the province of British Columbia, Canada, between 1996 and 2009, were obtained from the British Columbia Centre for Disease Control (BCCDC).[30] BCCDC is the single provincial agency that centralises all HIV surveillance data for the province and has access to HIV testing data from the provincial public health reference laboratory, which does more than 90% of all HIV testing in British Columbia. Mandatory (nominal or non-nominal) HIV reporting legislation has been in place in the province since 2003. This includes specific establishment of whether a new HIV positive result is from an individual previously known to be infected with HIV, but who has moved to the area from elsewhere. For individuals aged 18 months or older, BCCDC uses a screening test (ELISA) to detect HIV antibodies, with HIV diagnosis confirmed on the basis of a reactive western blot or nucleic acid amplification test.

Data for viral load, CD4 cell count, and HAART use were extracted from the British Columbia Centre for Excellence in HIV/AIDS (BCCFE) population-based registries, which include all people on HAART or accessing viral load testing in the province. BCCFE is the single provincial agency that centrally distributes all antiretroviral drugs in the province, providing treatment free of charge to all residents who are infected with HIV. BCCFE 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. BCCFE guidelines recommend that once an individual starts treatment, viral load and CD4 cell count be tested at regular intervals (eg, every 3–4 months) or after virological rebound. Capture of baseline and on-treatment data for viral load by BCCFE is 100%, because all viral load measurements in the province are done under the auspices of BCCFE by the virology laboratory at St Paul's Hospital (Providence Health Care, Vancouver, BC, Canada).

Procedures

Table 1 shows the different HIV-1 RNA viral load assays that were used during the study period and their quantification ranges. For analytical purposes, we truncated data for viral load to the range 500–100 000 copies per mL, because these values were within the measurement range of all assays used during the study. We estimated population-level or community-level viral load using a conservative approach by recording the highest viral load for every individual in a specific year. To accommodate irregular frequency of viral-load measurements or missing values, the highest yearly

	Assay	Range of quantification (copies per 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
Oct 27, 1997	Roche HIV-1 monitor test version 1.5; included new primers to detect different HIV-1 subtypes	400–750 000
Dec 4, 1998	Roche COBAS HIV-1 monitor test version 1.5; first time automated amplification and detection were used, and the standard method was used for specimen preparation	400–750 000
April 1, 1999	Roche COBAS HIV-1 Ampliprep Amplicor Monitor ultrasensitive assay version 1.5; automated amplification and detection and the ultrasensitivity method was used for specimen preparation	50–750 000
March 8, 2000	Roche COBAS HIV-1 Ampliprep Amplicor Monitor ultrasensitive assay version 1.5; automated amplification and detection and the ultrasensitivity method detection range changed with time	50–100 000
Feb 1, 2008 (until present)	Roche COBAS HIV-1 Ampliprep Taqman assay; method of automated amplification and detection changed	40–1 000 000

Table 1: **HIV-1 RNA viral load assays used in British Columbia, Canada, 1996–2009**

value was carried forward until a new measurement was available, and patients were censored if they moved out of the province or died.

We divided follow-up into three discrete time periods on the basis of data for HAART use in British Columbia, all of which were consistent with contemporary treatment guidelines. The first period, from 1996 to 1999, relates to the initial rollout of HAART. The second, from 2000 to 2003, relates to a steady-state phase of HAART use. The third, from 2004 to 2009, relates to the second HAART expansion. We estimated rates of HIV, infectious syphilis, genital gonorrhoea, and genital chlamydia by dividing the yearly number of new diagnosed cases of each disease in British Columbia by the yearly population of the province, and then multiplied by 100 000. Population estimates for the years studied were obtained from British Columbia Stats reports. We applied the HIV case rate for the first year of each study period to all subsequent years in that period to estimate the number of new HIV diagnoses that would have been expected had the case rate remained constant during each phase of the study. We then calculated rate ratios by dividing the number of reported cases by the expected number of cases, and calculated confidence intervals using Byar's approximation methods.[31]

CD4 cell counts were measured by flow cytometry (Beckman Coulter Inc, Mississauga, ON, Canada). Baseline CD4 cell counts measured before initiation of antiretroviral treatment were obtained from the BCCFE registry, which captures more than 80% of all tests of CD4 cell count done in the province. Physicians are requested to provide patients' baseline information before initiation of antiretroviral therapy, including a pretreatment CD4 cell count. We tested trends in baseline CD4 cell count in each of the study periods using the Cochran-Armitage trend test for the proportion of measurements lower than 200 cells per µL.

We have shown previously that reduction in community viral load as a result of HAART was a key determinant of decreasing HIV incidence in a cohort of IDUs in the downtown eastside of Vancouver.[26] Therefore, we repeated analyses in the present study after stratification by history of injecting drug use. Grouping of patients on the basis of injecting drug use relied mainly on self-reports and case-report forms completed by health-care providers and public health nurses, which were collected by the BCCDC. Additionally, data for history of injecting drug use were strengthened by linkages to all BCCFE-based cohort studies, including the Vancouver Injection Drug Users Study,[26] the At-Risk Youth Study,[32] the Scientific Evaluation of Supervised Injecting site,[33] and MAKA cohorts.[34]

The BCCFE received ethics approval from the University of British Columbia ethics review committee at the St Paul's Hospital, Providence Health Care site (P05-123) to undertake this study. The programme also conforms to the province's Freedom of Information and Protection of Privacy Act.

Statistical analysis

We modelled trends of new HIV positive tests and number of individuals on HAART using generalised additive models. Our motivation for using such models was the potential to model 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]

Role of the funding source

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

For **British Columbia Stats reports** see http://www.bcstats.gov.bc.ca/data/pop/pop/popproj.asp

Results

Between 1996 and 2009, the number of individuals actively receiving HAART in British Columbia increased from 837 to 5413 (547%; p=0·002), and the number new HIV diagnoses fell from 702 to 338 cases per year (–52%; p=0·001). The overall correlation between number of individuals on HAART and number of new HIV diagnoses per year was –0·89 (p<0·0001).

HAART usage and new yearly HIV diagnoses showed three distinct phases during the study (figure 1). Between 1996 and 1999, we retrospectively noted a steep increase in number of individuals on HAART (258%; p=0·021), during the initial rollout of HAART in the province as a result of 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<0·0001) because of the balance between treatment interruptions and HAART initiations (new and returning patients). During this period, new HIV diagnoses per year also remained fairly stable (5%; p=0·954). Between 2004 and 2009, we prospectively recorded a second slow but steady increase in the number of individuals on HAART (51%; p<0·0001), attributable to the emerging 2004 IAS-USA guidelines, which recommended against structured treatment interruptions. During this third period, new HIV diagnoses per year decreased substantially (–23%; p<0·0001). When data were stratified by history of injecting drug use, there was about a 50% reduction in new diagnoses per year in individuals with a history of injecting drug use, from 159 cases in 1999, to 80 cases in 2009 (p=0·003). By contrast, the number of new positive tests remained stable (p=0·6229) in individuals with no history of injecting drug use.

We compared the number of new HIV diagnoses that would have been expected if the rate of new diagnoses

Figure 1: **Number of active HAART participants and number of new HIV diagnoses per year in British Columbia, Canada, 1996–2009**
p values are for trend and were obtained from the generalised additive model. Injecting drug user (IDU) refers to individuals who have ever injected illicit drugs. HAART=highly active antiretroviral therapy. BC=British Columbia. NA=not available.

Figure 2: **Reported and expected number of new HIV diagnoses per year in British Columbia, Canada, during the three phases of the study, 1996–2009**
p values refer to the total reported number of HIV diagnoses compared with the total expected number of HIV diagnoses at the end of each study phase.

had remained constant in each of the three study phases with the number of diagnoses reported. For 1996–2000, we noted that there were 30% (rate ratio 0·70, 95% CI 0·67–0·72) fewer new HIV diagnoses than were expected (figure 2). For 2001–03, we showed that the number of reported and expected new HIV diagnoses were almost the same—a decrease of 2% (0·98, 0·93–1·04). In the last period, 2004–09, there was a 17% (0·83, 0·80–0·87) reduction in new HIV diagnoses compared with expected values.

Figure 3 shows yearly distribution of pre-HAART CD4 cell counts from 1996 to 2009, as a surrogate measure for 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 [IQR 170–460] cells per μL), lowest in 2000–03 (nadir in 2003, 150 [60–230] cells per μL), and steadily increased in 2004–09 (peak in 2009, 270 [150–363] cells per μL). Baseline CD4 cell count decreased in 1996–99 (p=0·024) and in 2000–03 (p<0·0008), but increased significantly (p<0·0001) in 2004–09.

To further explore the contribution of HIV viral load to trends in number of new HIV diagnoses, we characterised the viral load per year in the province, stratified by history of injecting drug use. As shown in table 2, the number of individuals with viral load lower than 500 copies per mL, irrespective of history of injecting drug use, increased

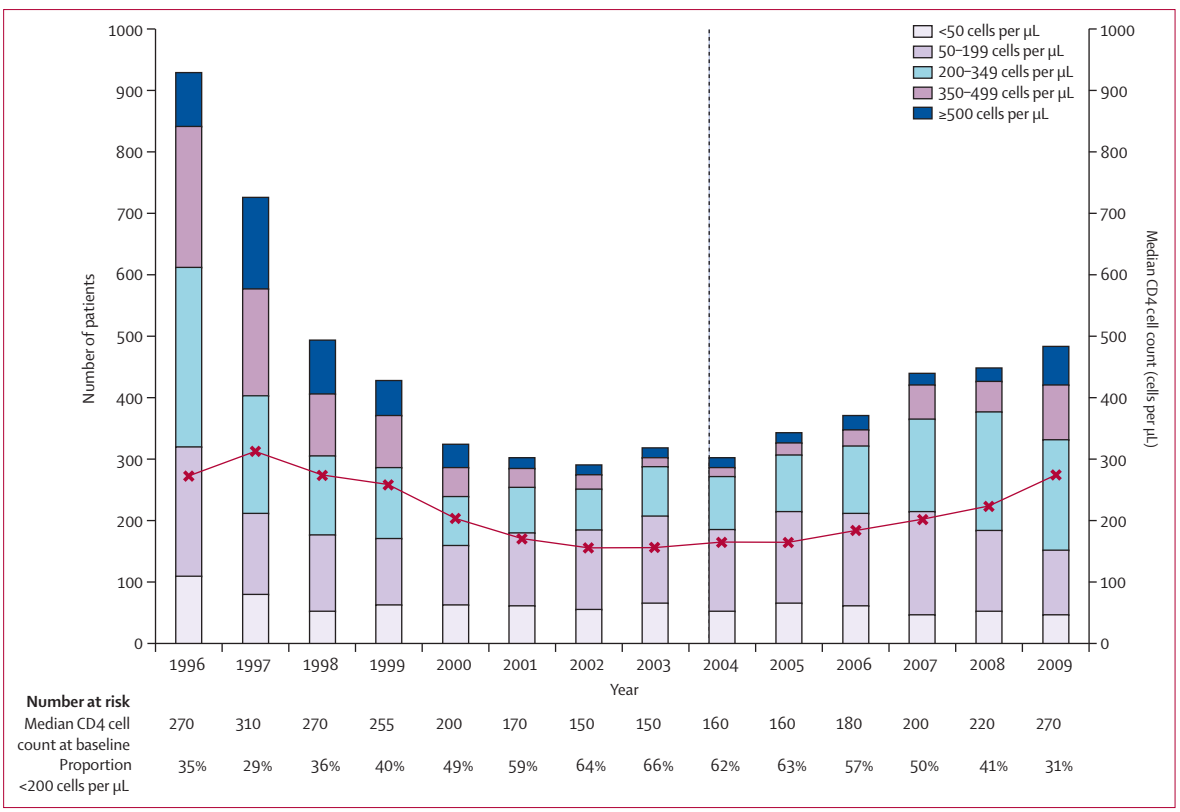

Figure 3: **Distribution of yearly pre-HAART CD4 cell counts for all individuals initiating HAART in British Columbia, Canada, 1996–2009**
HAART=highly active antiretroviral therapy.

strikingly during the study, rising from lower than 10% in 1996, to more than 50% in 2009 (p<0·0001). Additionally, between 2004 and 2009, the proportion of patients with no history of injecting drug use who had a viral load lower than 500 copies per mL increased by 36% (p<0·0002) and lower than 50 copies per mL by 42% (p=0·001). By contrast, the same proportions in patients with a history of injecting drug use increased by 82% (p=0·001) and 86% (p=0·002), respectively. Poisson regression modelling of the association between new HIV diagnoses, viral load, year, and number of individuals on HAART showed that for every 100 additional individuals on HAART, the estimated number of new HIV cases decreased by a factor of 0·97 (95% CI 0·96–0·98), and per 1 $\log_{10}$ decrease in viral load, the estimated number of new HIV cases decreased by a factor of 0·86 (0·75–0·98).

We considered whether the fall in new HIV diagnoses could have resulted from reduced HIV testing during periods of increased HAART use, but concluded that the total number of HIV tests done in the province had actually increased steadily during the study. The average number of HIV tests done was 137 585 per year between 1996 and 1999 (an average of 3·5% of the population), 139 464 per year between 2000 and 2003 (3·4%), and 168 924 per year between 2004 and 2008 (4·0%). Also of note, rates of infectious syphilis, genital gonorrhoea, and genital chlamydia increased steadily between 1996 and 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 gonorrhoea, 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 per 100 000 population in 1996, to 87·0 per 100 000 population in 2003 (45% decrease; p<0·0001), and to 55·8 per 100 000 population in 2008 (36% decrease from 2003; p<0·0001).

Discussion

Our results show a strong and significant association between increased HAART coverage, reduced community viral load, and decreased number of new HIV diagnoses per year in the population of a Canadian province. We had a unique opportunity to characterise the evolution of these variables during a 15-year period within a universal health-care environment with centralised and free access to HAART. During our study, the pattern of use of HAART changed strikingly on the basis of contemporary therapeutic guidelines. Three distinct phases were noted: two phases of steady expansion of HAART coverage, separated by a period of stable HAART use between 2000 and 2003. Community viral load and new HIV diagnoses

	Individuals who have never injected drugs				Individuals who have ever injected drugs			
	n	Median HIV-1 RNA plasma concentration (copies per mL; IQR)	Patients with <500 copies per mL (%)	Patients with <50 copies per mL (%)	n	Median HIV-1 RNA plasma concentration (IQR)	Patients with <500 copies per mL (%)	Patients with <50 copies per mL (%)
1996	2093	35 000 (6000 to >100 000)	178 (9%)	NA	831	36 000 (7600 to >100 000)	46 (6%)	NA
1997	2848	18 000 (2175 to 93 000)	464 (16%)	NA	1334	37 000 (6100 to >100 000)	120 (9%)	NA
1998	3324	8800 (<500 to 76 000)	1017 (31%)	NA	1558	26 000 (2100 to >100 000)	274 (18%)	NA
1999	3740	6145 (<500 to 72 000)	1368 (37%)	234 (6%)	1707	20 500 (805 to >100 000)	388 (23%)	73 (4%)
2000	4114	6270 (<500 to 76 300)	1572 (38%)	1060 (26%)	1822	18 650 (<500 to >100 000)	481 (26%)	328 (18%)
2001	4535	4260 (<500 to 69 400)	1874 (41%)	1324 (29%)	1936	18 450 (<500 to >100 000)	513 (27%)	370 (19%)
2002	4950	5545 (<500 to 88 000)	2091 (42%)	1529 (31%)	2046	23 550 (<500 to >100 000)	581 (28%)	412 (20%)
2003	5303	4820 (<500 to 76 500)	2270 (43%)	1718 (32%)	2151	22 200 (<500 to >100 000)	636 (30%)	471 (22%)
2004	5848	2355 (<500 to 59 500)	2663 (46%)	2075 (36%)	2230	19 100 (<500 to >100 000)	718 (32%)	533 (24%)
2005	6174	814 (<500 to 51 000)	3013 (49%)	2414 (39%)	2297	13 700 (<500 to 96 400)	803 (35%)	629 (27%)
2006	6426	<500 (<500 to 41 800)	3331 (52%)	2747 (43%)	2330	9015 (<500 to 89 500)	902 (39%)	710 (31%)
2007	6745	<500 (<500 to 34 500)	3675 (55%)	3049 (45%)	2335	5450 (<500 to 80 900)	993 (43%)	789 (34%)
2008	7301	<500 (<500 to 25 000)	4241 (58%)	3283 (45%)	2326	522·5 (<500 to 46 500)	1159 (50%)	807 (35%)
2009	8001	<500 (<500 to 16 092)	4960 (62%)	4040 (51%)	2340	<500 (<500 to 20 035)	1372 (59%)	1038 (44%)
p value			0·0002	0·001			0·001	0·002

Data are n, median (IQR), or n (%).

Table 2: **Distribution of the highest HIV-1 RNA plasma concentrations for all individuals in British Columbia, Canada who ever had an HIV-1 RNA level in a plasma test, 1996–2009**

per year decreased substantially during both phases of HAART expansion. By contrast, community viral load and new HIV diagnoses per year remained stable during the intervening steady period of HAART use. New HIV diagnoses fell by 30% in 1996–2000, remained fairly stable in 2001–03 (2% reduction), and decreased by 17% in 2004–09. Notably, rates of viral load suppression have increased steadily in British Columbia since 1996, as reported by Gill and colleagues.[36]

From 2000, we were able to stratify our data by history of injecting drug use. On the basis of these results, we showed 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 a documented history of injecting drug use, in whom new HIV diagnoses per year decreased by nearly 50% during the study. Rates of new HIV diagnoses decreased slowly in these individuals between 2003 and 2007, then fell precipitously in 2007–08, in tandem with a fall in their community viral load. By contrast, rates of new HIV diagnoses in men who have sex with men increased after 2003, and remained stable until 2008. The rate of undetectable plasma viral load increased by 42% in patients with no history of injecting drug use, compared with an 86% increase in patients with a history of injecting drug use. We attribute this finding to a specific outreach effort to facilitate access to HAART in medically eligible individuals with a history of injecting drug use during the final period of our study.

These results expand our previous findings in a small cohort of individuals with histories of injecting drug use, in whom median community viral load was the strongest driving force behind HIV seroconversion.[26] The results are also consistent with those of Das and colleagues,[28] who described an association between decreasing community plasma viral load and new HIV diagnoses in San Francisco. Taken together, the reports confirm that expansion of HAART coverage within medical guidelines is associated with reductions in population or community plasma viral load. Reassuringly, this effect was also present in individuals with a history of injecting drug use.[37] Furthermore, the results of our multivariable Poisson log-linear regression model are consistent with the previously proposed secondary preventive benefit of HAART used within existing therapeutic guidelines.

Since our report is based on an ecological study, our results cannot be taken as definitive proof of causality. Notably, however, our findings occurred against a background of an increasing number of HIV tests done each year in the province, suggesting that case-finding efforts did not decrease during the study. Furthermore, mandatory (nominal or non-nominal) reporting was implemented in the province in 2003, which improved follow-up and risk ascertainment. This change would have allowed for improved identification of individuals migrating to the province who were infected with HIV, and might have produced a small liberal bias (for the entire cohort after 2003 this subset represented fewer than two per 1000 000 population, and overall, HIV positive rates fell from ten per 100 000 to eight per 100 000 population). However, the liberal bias is likely to have been overcompensated for by a conservative bias resulting from the overall increase in number of new cases identified by the new strategy. A rise in cases associated with increased screening is consistent with

findings from the US Centers for Disease Control and Prevention, which showed a 15% increase in HIV diagnoses between 2004 and 2007 in 34 US states, partly attributable to enhanced testing efforts in these states.[38]

Rates of sexually transmitted infections increased during the last 15 years of our study, which implies that our findings cannot be accounted for by decreasing sexual HIV risk behaviour. Rates of hepatitis C decreased during the study, however, the timing of this decrease was clearly out of synchrony with the changes in new HIV diagnoses in IDUs. Furthermore, hepatitis C only became reportable in British Columbia 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 fall in yearly hepatitis C diagnoses, from 1996 to 2003 in particular, probably represents a reduction in the pool of prevalent cases identified rather than a steep decrease in new cases in IDUs. This effect is less likely to have been a contributor in later years of the study.

Notably, our results were internally reproducible, since we recorded decreases in new HIV diagnoses per year during two distinct periods of HAART expansion that were separated by a stable period of HAART use. The stable period was characterised on a prospective basis[10] and was entirely consistent with the effect predicted by our mathematical models.[39,40] Furthermore, the reductions in plasma viral load that were documented during HAART expansion provide a plausible mechanistic pathway to account for the association. Ample supportive evidence exists regarding the preventive effect of HAART on HIV transmission, derived from vertical transmission studies[23] and from cohort studies of serodiscordant couples,[24,25] IDU cohorts[26] and population-based studies.[10,27,28] Thus, taken together, the available evidence strongly suggests that community viral load is a key driving force of new HIV diagnoses and can be successfully modulated through effective expansion of HAART coverage within medical guidelines. Our results provide a strong rationale for re-examination of the HIV prevention and treatment dichotomy, as has been strongly advocated by the UN Joint Programme on HIV/AIDS as part of a comprehensive combination prevention strategy.[41] Furthermore, our results should serve to re-energise the G8's universal access pledge as a means to curb the effect of AIDS and the growth of the HIV pandemic.

Contributors

JSGM, VDL, RB, EW, TK, KS, PRH, and RSH contributed to conception and design of the study. Data collection and linkages were undertaken by VDL, RB, EW, TK, KS, PRH, RSH, PD, and PK. Data analysis was done by VDL and BY. JSGM, VDL, RB, BY, EW, TK, KS, PRH, RSH, PD, and PK interpreted the results. JSGM and VDL drafted the report. JSGM, VDL, RB, BY, EW, TK, KS, PRH, RSH, PD, and PK contributed to editing and review of the report. JSGM secured financial support.

Conflicts of interest

JSGM has received funding from Merck, Gilead and ViiV Healthcare to support research into Treatment as Prevention, consultancy fees from Merck, and speakers' fees from Clinical Care Options. PRH holds the GlaxoSmithKline/Canadian Institutes of Health Research Chair in Clinical Virology. RSH has received a research grant from Merck and a conference travel grant from GlaxoSmithKline. PRH has received honoraria from Viiv, Virco, Quest, and Merck, travel grants to attend conferences from Viiv and Quest, research grants from Abbott, Viiv, Pfizer, and Merck, and speakers' fees from Viiv. VDL, TK, EW, KS, RB, PD, PK, and BY declare that they have no conflicts of interest.

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References

1 Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. *Lancet* 2008; **372:** 845–59.
2 Sidibé M. Letter to Partners 2010. Geneva, Switzerland: Joint UN Programme on HIV/AIDS, 2010. http://data.unaids.org/pub/BaseDocument/2010/20100216_exd_lettertopartners_en.pdf (accessed April 5, 2010).
3 Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet* 1997; **349:** 1294.
4 The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006; **367:** 817–24.
5 Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis* 2006; **194:** 11–19.
6 The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372:** 293–99.
7 Blower S, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. *Science* 2000; **287:** 650–54.
8 Velasco-Hernandez JX, Gershengorn HB, Blower SM. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? *Lancet Infect Dis* 2002; **2:** 487–93.
9 Salomon JA, Hogan DR, Stover J, et al. Integrating HIV prevention and treatment: from slogans to impact. *PLoS Med* 2005; **2:** e16.
10 Montaner JSG, Hogg R, Wood E, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006; **368:** 531–36.
11 Wood E, Braitstein P, Montaner JSG, et al. Extent to which low-level use of antiretroviral treatment could curb the AIDS epidemic in sub-Saharan Africa. *Lancet* 2000; **355:** 2095–100.
12 Cohen MS, Gay C, Kashuba AD, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. *Ann Intern Med* 2007; **146:** 591–601.
13 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:** 48–57.
14 Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses* 2001; **10:** 901–10.
15 Quinn TC, Wawer MJ, Sewankambo N, et al, for the Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.

16 Vernazza PL, Gilliam BL, Flepp M, et al. Effect of antiviral treatment on the shedding of HIV-1 in semen. *AIDS* 1997; **11:** 1249–54.

17 Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. *AIDS* 2000; **14:** 415–21.

18 Lorello G, la Porte C, Pilon R, Zhang G, Karnauchow T, MacPherson P. Discordance in HIV-1 viral loads and antiretroviral drug concentrations comparing semen and blood plasma. *HIV Med* 2009; **10:** 548–54.

19 Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS* 2009; **23:** 2050–54.

20 Marcelin AG, Tubiana R, Lanbert-Niclot S, et al. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1RNA in blood plasma. *AIDS* 2008; **22:** 1677–79.

21 Neely MN, Benning L, Xu J, et al. Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007; **44:** 38–42.

22 Pietro Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. *Schweiz Arzteztg* 2008; **89:** 165–69.

23 De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000; **283:** 1175–82.

24 Attia S, Egger M, Müller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009; **23:** 1397–04.

25 Donnell D, Baeten JM, Kiarie J, et al, for the Partners in Prevention HSV/HIV Transmission Study Team. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375:** 2092–98.

26 Wood E, Kerr T, Marshall B, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009; **338:** b1649.

27 Fang C, Hsu H, Twu S, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. *J Infect Dis* 2004; **190:** 879–85.

28 Das M, Chu PL, Santos G-M, et al. Decreases in community viral load are accompanied by reductions in new HIV diagnoses in San Francisco. *PLoS One* 2010; 5: e11068.

29 Smith RJ, Okano JT, Kahn JS, Bodine EN, Blower S. Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco. *Science* 2010; **327:** 697–701.

30 BC Centre for Disease Control. 2008 Annual Summary of Reportable Diseases. http://www.bccdc.ca/util/about/annreport/default.htm (accessed May 25, 2010).

31 Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. The design and analysis of cohort studies. IARC Scientific Pub No 82. Lyon, France: International Agency for Research on Cancer, 1987.

32 Kerr T, Stoltz JA, Marshall BD, Lai C, Strathdee SA, Wood E. Childhood trauma and injection drug use among high-risk youth. *J Adolesc Health* 2009; **45:** 300–02.

33 Lloyd-Smith E, Wood E, Zhang R, Tyndall MW, Montaner JS, Kerr T. Determinants of cutaneous injection-related infection care at a supervised injecting facility. *Ann Epidemiol* 2009; **19:** 404–09.

34 Shannon K, Kerr T, Strathdee SA, Shoveller J, Montaner JS, Tyndall MW. Prevalence and structural correlates of gender based violence among a prospective cohort of female sex workers. *BMJ* 2009; **11:** b2939.

35 Wood SN. Generalized additive models: an introduction with R (texts in statistical science). New York, USA: Chapman & Hall/CRC, 2006.

36 Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clin Infect Dis* 2010; **50:** 98–105.

37 Volkow ND, Montaner J. Enhanced HIV testing, treatment, and support for HIV-infected substance users. *JAMA* 2010; **303:** 1423–24.

38 US Centers for Disease Control and Prevention. Questions and answers: the 15% increase in HIV diagnoses from 2004–2007 in 34 states and general surveillance report questions. http://www.cdc.gov/hiv/topics/surveillance/resources/qa/surv_rep.htm (accessed May 25, 2010).

39 Lima VD, Johnston K, Hogg RS, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. *J Infect Dis* 2008; **198:** 59–67.

40 Lima VD, Hogg RS, Montaner JS. Expanding HAART treatment to all currently eligible individuals under the 2008 IAS-USA guidelines in British Columbia, Canada. *PLOS One* 2010; **5:** e10991.

41 Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet* 2008; **372:** 669–84.