

Perspective

Treatment as Prevention: Toward an AIDS-Free Generation

In British Columbia, Canada, intensive efforts have been made to implement and maintain a treatment-as-prevention strategy among the HIV-infected population. Acceleration of antiretroviral therapy coverage has resulted in a substantial increase in the median CD4+ cell count at which treatment is initiated and a dramatic decline in community plasma HIV RNA levels. This has resulted in a reduction in diagnoses of new cases of HIV infection, including among injection drug users. Proportions of individuals with viral suppression have steadily increased and the expansion of antiretroviral therapy coverage has not been associated with increased levels of HIV resistance. Further, adoption of routine HIV testing in acute care settings has been very well accepted and has captured new cases at a rate of 5 per 1000 tests outside of high-risk populations, offering an additional strategy for identifying and linking at least some individuals with undiagnosed HIV infection to care. Deriving optimal individual and social health outcomes in HIV infection requires improvement in every element of the cascade of care. This article summarizes a presentation by Julio S. G. Montaner, MD, at the IAS–USA continuing education program held in San Francisco, California, in March 2013.

Keywords: HIV, AIDS, treatment, prevention, community viral load, routine HIV testing

In British Columbia, Canada, as in other relatively resource-rich locales, there was a dramatic decline in death rate from HIV disease and an increase in life expectancy following the advent, in 1996, of potent antiretroviral therapy. At the same time it was seen that whereas new cases of HIV infection decreased between 1996 and 1999, the rate of new cases of syphilis increased. It was thus hypothesized that effective antiretroviral therapy was producing a secondary benefit in terms of reducing HIV transmission.

This hypothesis, of a secondary preventive effect of antiretroviral therapy, was supported by the observation that the number of infants born with HIV infection in Canada decreased dramatically after 1996, in the absence of a decrease in the number of infants exposed to HIV-infected mothers, as a result of the introduction of effective antiretroviral therapy during pregnancy. During the

past 7 years, only 2 children in British Columbia have been born with HIV infection. In both cases, HIV infection in the mother was not identified prior to birth, because the mother was not engaged in health care.

In 2006, a case was made for expanding access to antiretroviral therapy in order to curb the growth of the HIV epidemic.¹ This was based on the premise that antiretroviral therapy stops HIV replication; as a result, viral load drops to undetectable levels in both plasma and sexual fluids, which

can result in long-term remission and, secondarily, lead to a sharp reduction in HIV transmission. Some residual replication can occur when viral load is reduced to undetectable levels, but it is unclear what impact this has on the preventive benefit of antiretroviral therapy.

Extensive efforts have been made in British Columbia to support a treatment-as-prevention strategy, including expanding and accelerating HIV testing and supporting and facilitating access to antiretroviral therapy, as a means to improve patient-centered outcomes (ie, prevention of morbidity and mortality) and societal outcomes (ie, prevention of HIV transmission).

Antiretroviral Therapy Outcomes Among Injection Drug Users in Vancouver, Canada

Reducing HIV transmission among injection drug users (IDUs) poses particular problems, largely because IDUs may frequently share needles (sometimes several times per day). As a result, there has been concern that IDUs may be exposed to some cell-associated HIV that may decrease the effectiveness of treatment as prevention.

The Downtown Eastside neighborhood of Vancouver—a highly marginalized district that is one of the poorest in Canada—is an area where injection

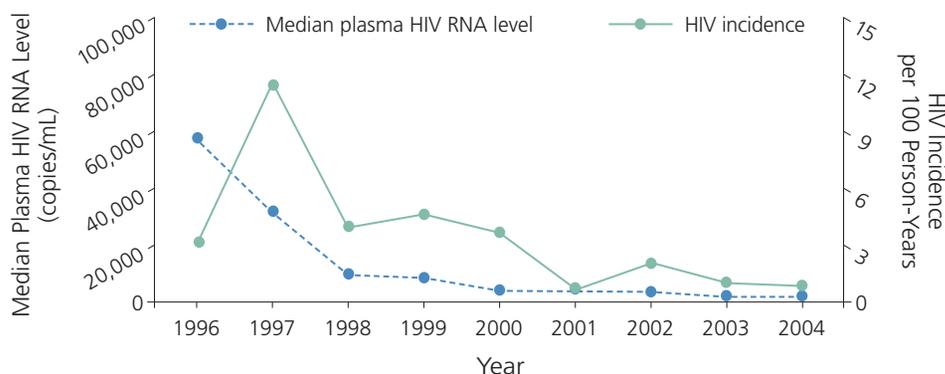


Figure 1. Longitudinal community plasma HIV RNA levels and incidence of HIV infection among a cohort of injection drug users in inner city Vancouver, Canada. Adapted from Wood et al.²

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drug use is heavily concentrated. As part of a prospective epidemiologic cohort study in this district, Dr Montaner and colleagues collected blood samples from residents for approximately a decade, allowing them to monitor plasma HIV RNA concentrations in the community as a sentinel exercise. After 1996, with the introduction of potent antiretroviral therapy, median plasma HIV RNA levels in the community were sharply reduced. As shown in Figure 1, this reduction was mirrored by a reduction in HIV incidence rate.²

Similar findings were observed in the ALIVE (AIDS Linked to the Intravenous Experience) cohort in Baltimore, Maryland. Starting in 1997, HIV incidence decreased by 74% for each log₁₀ copy/mL decline in community HIV RNA level. In a separate model, the data showed that within the IDU cohort, HIV incidence decreased by 5% for each 1% increase in antiretroviral therapy coverage.³

Underscoring these observations are the findings of the HPTN (HIV Prevention Trials Network) 052 study of HIV-serodiscordant couples. The study, conducted predominantly among heterosexual couples, showed that immediate (compared with delayed) antiretroviral therapy was associated with a 96.3% reduction in HIV transmission, irrespective of whether the index member of the couple was a man or a woman.⁴ The study also showed that immediate treatment was associated with an individual-level benefit in terms of reducing the incidence of a combined end point of morbidity and mortality, defined a priori, indicating that the strategy of immediate antiretroviral therapy is associated with a benefit to the individual as well as to the public.

The only event of HIV seroconversion observed in the immediate-treatment group was ultimately shown to have occurred around the time of treatment initiation. Such observations strongly suggest that in settings in which HIV-infected individuals have effective viral suppression, transmission risk can be virtually eliminated.

Increasing Antiretroviral Therapy Coverage in British Columbia

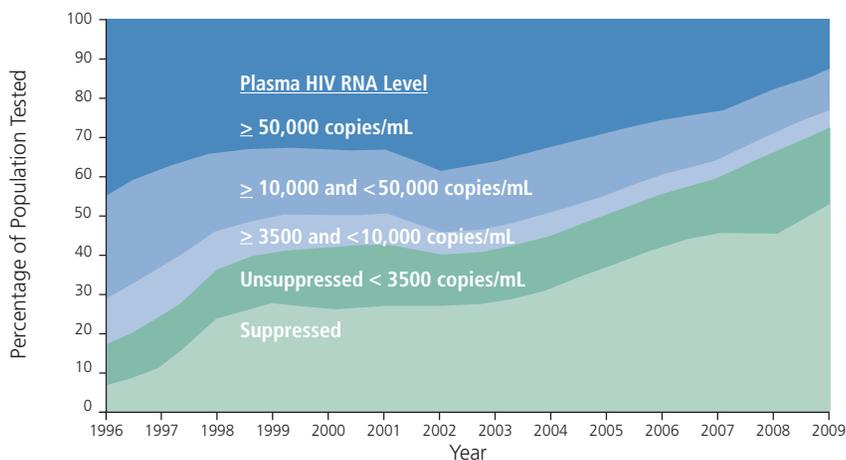
The expansion of antiretroviral therapy coverage in British Columbia has occurred in 3 phases within the context of evolving treatment guidelines. The first phase, between the summer of 1996 and the summer of 2000, was marked by a steep increase in participation in antiretroviral therapy following the introduction of triple-drug therapy. From the summer of 2000 through the end of 2003, there was little growth in the number of patients receiving antiretroviral therapy. Changes in treatment guidelines and the conviction that treatment was contributing to more than just improvement in individual health outcomes inspired a campaign to accelerate access to antiretroviral therapy, resulting in another steep increase in the number of patients receiving antiretroviral therapy beginning in 2004.

Since 2004, the median CD4+ cell count at the start of antiretroviral therapy in British Columbia has increased from below 200/μL to above 350/μL as of 2011 (the last year for which full data are available). The proportion of patients starting therapy at CD4+ cell counts less than 200/μL has steadily decreased over the last several years. This achievement has required persistent outreach efforts to diagnose

infected individuals and to engage and maintain them in care. The incidence of AIDS had been reduced by 80% since the pre-potent antiretroviral therapy era and further declined between 2004 and 2010. Finally, the frequency of all-cause mortality among HIV-infected persons, which had been reduced by more than 90% with the potent antiretroviral therapy era, also declined over the past several years during the campaign to accelerate access to antiretroviral therapy.

There has been concern in some quarters that expanding coverage of antiretroviral therapy may increasingly involve patients with additional comorbidities or social challenges and that this may result in decreased adherence rates and potentially lead to increased prevalence of resistance to antiretroviral drugs.^{5,6} This has not been seen in British Columbia, where the proportion of individuals with suppression of plasma HIV RNA level to below 50 copies/mL has been at 90% or higher since 2007. Levels of antiretroviral resistance, including single- and multi-drug resistance, have decreased with the increasing level of viral suppression in the community.

The overall improvement in community viral load as a result of the antiretroviral therapy expansion effort can be seen in Figure 2.⁷ This figure



Denominator	2882	3864	4227	4440	4627	4895	5090	5302	5569	5744	5877	6159	6334	6596
Actively on antiretroviral therapy	837	1960	2597	2994	3079	3120	3211	3356	3585	3913	4255	4654	5123	5413
No. of plasma HIV RNA tests	4896	10,803	12,930	14,117	15,888	17,673	19,663	21,259	22,677	23,110	23,815	24,897	26,009	26,818

Figure 2. Plasma HIV RNA levels over time of all HIV-infected individuals tested in British Columbia, Canada, irrespective of whether they ever received antiretroviral therapy. Adapted with permission from Nosyk et al.⁷

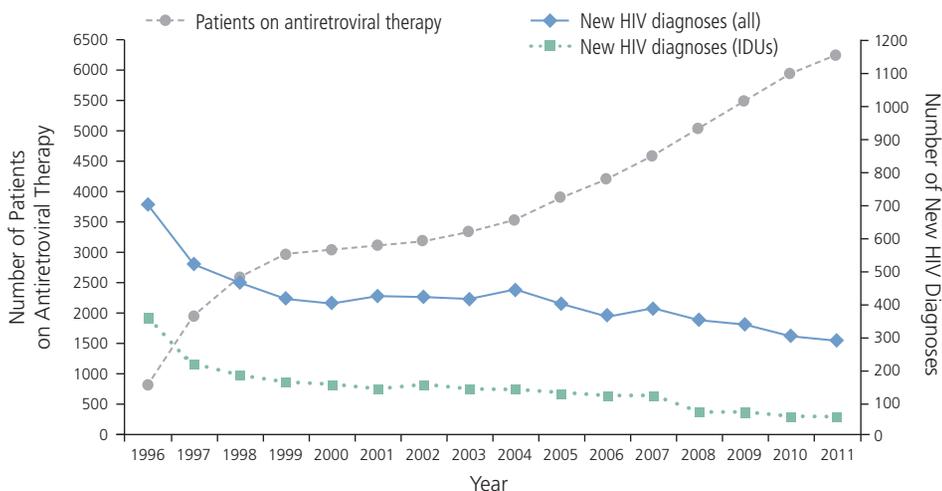


Figure 3. Changes in incidence of new diagnoses of HIV infection among injection drug users (IDUs) and in non-IDUs in British Columbia, Canada. Adapted from Montaner et al.⁸

shows the HIV RNA levels of individuals diagnosed with HIV infection in British Columbia, irrespective of whether they have ever been on antiretroviral therapy. The proportion of those with undetectable HIV RNA has increased over time, approaching 50% in 2009, along with the number of HIV-infected persons engaged in care and the number receiving antiretroviral therapy. In 2009, nearly 27,000 viral load measurements were performed on 6596 patients, 5413 of whom were on antiretroviral therapy. As shown in Figure 3, the improvement in community viral load has been accompanied by substantial reductions in new diagnoses of HIV infection among IDUs and non-IDUs.⁸ The number of diagnoses of HIV infection has continued to decline in recent years. There were 301 new cases in British Columbia in 2010, 289 new cases in 2011, and 248 new cases in 2012. This progress has been achieved at a time when rates of hepatitis C virus infection have remained stable and those for syphilis, gonorrhea, or chlamydial infections have increased in the province.

HIV Testing

Further reduction of HIV transmission requires, first and foremost, enhancement of HIV testing. It is estimated that 20% of HIV-infected individuals are unaware of their infection and that more than half of new infections are

attributable to this group. Numerous options are available for point-of-care testing, and there is no excuse for not implementing such strategies.

A program of routine testing in emergency departments or internal medicine wards was implemented in 3 hospitals in British Columbia with very distinct demographics. The program included only individuals with no prior HIV diagnoses and no known risk factors or indications for HIV testing. Preliminary results demonstrate that overall, there was 94% patient acceptance of the HIV screening test, with approximately 5 positive results per 1000 HIV screening tests found in this population that had no suspicion of HIV infection. The Centers for Disease Control and Prevention (CDC) has estimated that such screening is highly cost-effective in settings where rates are higher than 1 positive result per 1000 screening tests. Based on

these findings, British Columbia has implemented this strategy of screening in acute care settings province-wide and hopes to see a marked reduction in the proportion of HIV-infected individuals who remain undiagnosed and unconnected to care.

HIV Treatment

For the treatment-as-prevention strategy to work optimally, treatment must begin early. The IAS-USA was the first to support more liberal guidelines encouraging early treatment, including treatment for HIV-serodiscordant couples, which it encouraged ahead of the completion of the HPTN 052 study results.⁹ The recommendations of the US Department of Health and Human Services (DHHS) and, more recently, the World Health Organization (WHO) have moved in the same direction.^{10,11}

Cascade of HIV Care

Increased HIV testing and guidelines encouraging earlier access to antiretroviral therapy are not sufficient for a successful treatment-as-prevention strategy. It is also necessary to strengthen the cascade of care, from diagnosis,

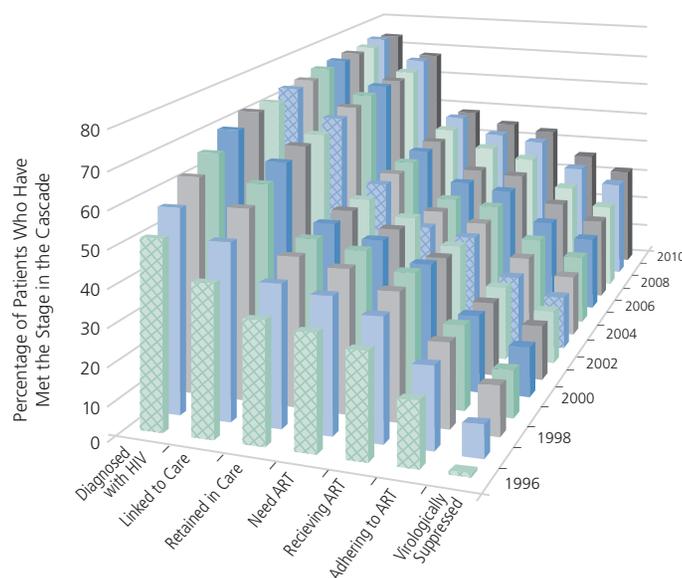


Figure 4. Changes over time in stages in the cascade of care in British Columbia, Canada: diagnosis of HIV infection, linkage to care, retention in care, and proportions of individuals needing and receiving antiretroviral therapy (ART), adhering to ART, and having sustained viral suppression on ART. Adapted with permission from Nosyk et al.^{7,13}

linkage, and retention through maximizing receipt of and adherence to antiretroviral therapy among patients eligible for treatment. Strengthening of the cascade of care requires the establishment and maintenance of supportive environments in which HIV-infected individuals can access treatment and achieve optimal health outcomes.

Gardner and colleagues recently estimated that of approximately 1.1 million HIV-infected individuals in the United States, 874,000 were diagnosed, 656,000 were linked to care, 437,000 were retained in care, 350,000 needed antiretroviral therapy, 262,000 were on antiretroviral therapy, and 210,000 were adherent to antiretroviral therapy and had undetectable viral loads (approximately 19% of the entire HIV-infected population).¹² The CDC recently revised the estimated proportion of HIV-infected individuals with undetectable viral load to 28%. Whether the proportion is 20% or 30%, it is still too low to achieve optimal population health outcomes. Changes in components of the cascade of care in British Columbia over time are shown in Figure 4.¹³ Current levels of viral suppression among all diagnosed and undiagnosed persons with HIV infection are estimated at approximately 40% to 50% depending on the definition of sustained viral suppression. Although the improvement in the cascade of care that has already been achieved is heartening, there is clearly more work to be done.

Programmatic Focus

A programmatic focus is needed to improve HIV care and optimize prevention. If HIV care is going to be made available throughout health care systems without a clear and aggressive focus, the effort will be diluted and the opportunity to achieve optimal prevention of HIV disease will be missed. The gains achieved in British Columbia thus far are the result of an intense programmatic focus. Of note, British Columbia remains the only province in Canada with truly free health care services, including no copayments or deductibles for HIV/AIDS-specific services (ie,

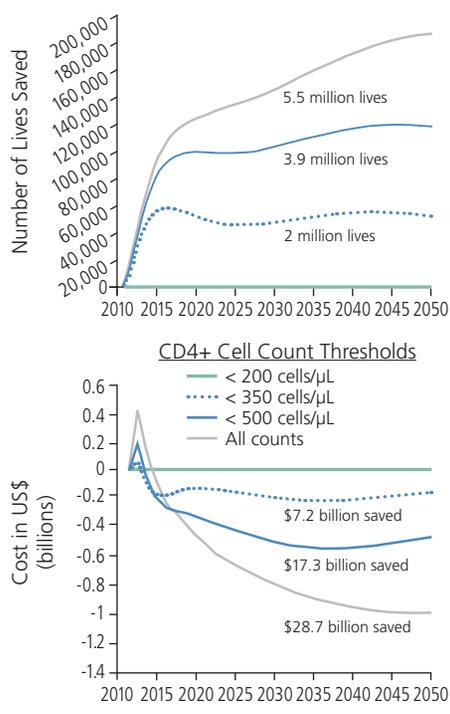


Figure 5. Estimate of lives saved by starting antiretroviral therapy at varying CD4+ cell count thresholds in South Africa (top). Costs associated with starting antiretroviral therapy at these thresholds, along with the cumulative cost savings over time (bottom). Adapted from Granich et al.¹⁵

antiretroviral therapy), and the only one with an interdisciplinary program dedicated exclusively to HIV. In other Canadian provinces, HIV care tends to be diluted within the health care system, and as a likely result, some provinces have seen an increase in new diagnoses of HIV.¹⁴ Thus, the success of treatment-as-prevention programs is not only dependent on having the tools available but also on working hard to bring those tools to people in need, who often cannot effectively access the services themselves.

Cost?

Granich and colleagues recently analyzed the cost and cost-effectiveness of starting antiretroviral treatment at various CD4+ cell count thresholds or at HIV diagnosis in South Africa.¹⁵ As shown in Figure 5, raising the CD4+ cell count threshold for starting antiretroviral treatment is associated with millions of additional lives saved. Although expansion of treatment comes at an initial cost, over time it becomes

a cost-saving endeavor. The conclusion that beckons is that there is no good reason for us not to bring more HIV-infected individuals into treatment and care—treatment as prevention saves lives and saves money.

Summary

Efforts toward the treatment and prevention of HIV infection are associated with the greatest preventive benefit from a societal perspective when the investment in improving care is focused on treating those who need it, who are relatively easy to define, and who are highly motivated to achieve their individual health goals.

There is an opportunity to optimize the health outcomes of antiretroviral therapy through focused HIV treatment-as-prevention programs. The question is whether there is the will, focus, and commitment to do it. A unique opportunity will be missed if it is not done.

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Thank You ZATA Donors and Art Buyers

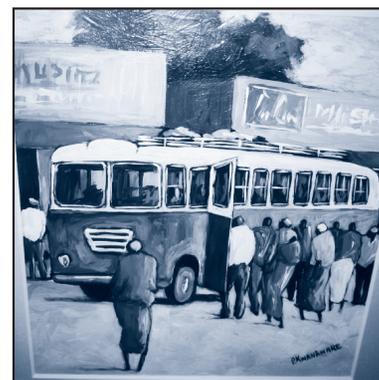


The Zimbabwe AIDS Treatment Project (ZATA) was established in 2004 to raise funds to support the University of Zimbabwe AIDS Research Centre (*photograph*) through the sale of original paintings, sculptures, and other artwork from talented Zimbabwe artists. ZATA was fortunate in being able to draw on the expertise of its Board and Advisory Board comprised of HIV/AIDS experts in both the United States and Zimbabwe—Drs Robert Schooley, Constance Benson, Thomas Campbell, James Hakim, and Margaret Borok-Williams—to name but a few.

of dollars of beautiful artwork at IAS–USA presentations and workshops held in 2004 and 2005 in New York, Washington, DC, and San Francisco. Because of these and other auctions and sales throughout the United States, ZATA funds began to grow steadily. We are pleased to inform our IAS–USA friends that after 9 years of fundraising, ZATA has sent almost *a quarter of a million US dollars* to Zimbabwe, including support for talented artists who would otherwise never find an audience for their work, funds for HIV/AIDS medications and medications to treat opportunistic diseases, pharmacy and nursing salary support, funds for a clean-water well to prevent cholera, and educational support for AIDS orphans through Nancy Padian, PhD, and the University of California San Francisco.

The ZATA Board thanks the IAS–USA for being there with us at the beginning and for supporting our mission by allowing the sale of ZATA artwork at their course sites. ZATA also welcomes IAS–USA audiences, supporters, and contributors to visit www.zataport.org to view and select original artwork for purchase or to make a donation to allow ZATA to continue to support the AIDS Research Centre for many years to come. The ZATA website also has information about a Zimbabwe Art and Sculpture Auction on October 19, 2013, at the Dairy Arts Center in Boulder, Colorado, for our local friends.

Sincerely,
Jane Oppenheim
President
ZATA Project Board



Original oil painting by artist Peter Kwangware