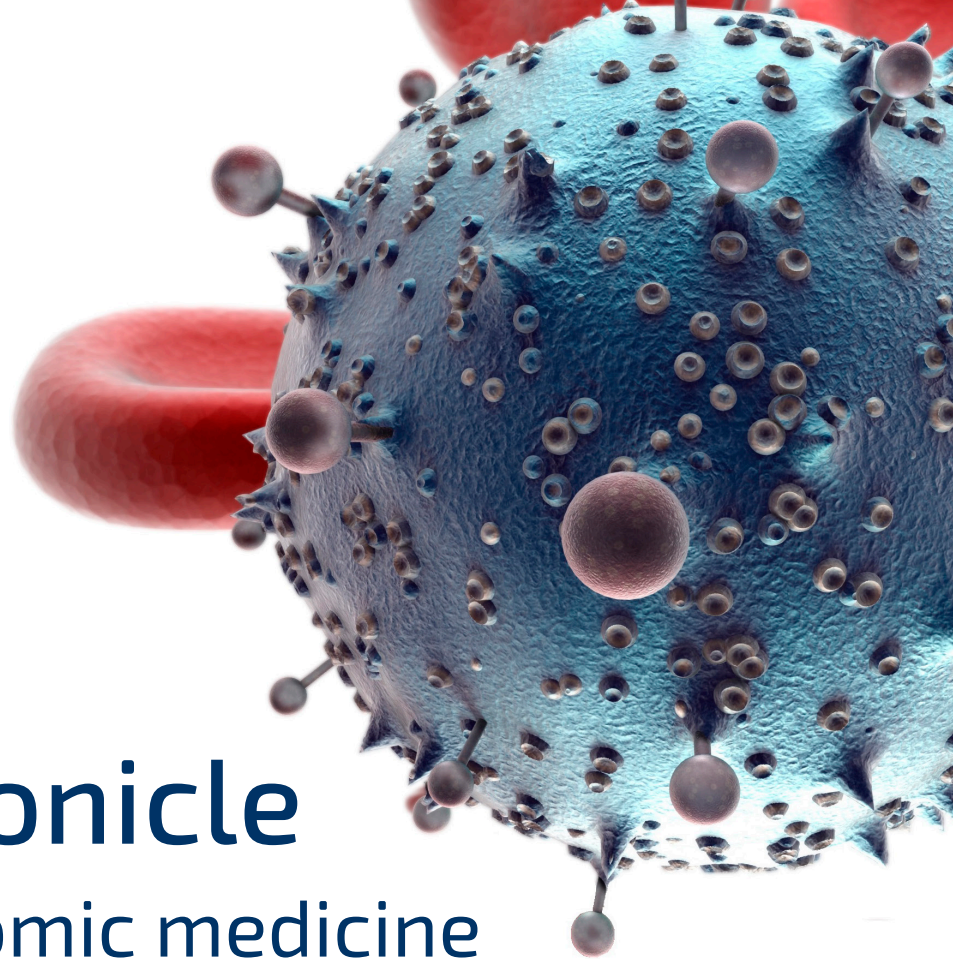




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HIV/AIDS Chronicle

A case study in genomic medicine

The transformation of this disease from death sentence to manageable condition is one of the best-personalized medicine stories ever seen and one of the world's best examples of the power of genomics.

A virus is born

The origin of HIV/AIDS can be traced to Sub-Saharan Africa sometime around the turn of the 20th century. On June 5, 1981 the AIDS 'epidemic' officially began when the US Centres for Disease Control and Prevention reported unusual clusters of a distinct strain of pneumonia—Pneumocystis pneumonia called PCP pneumonia—in homosexual men in Southern California. Over the next 18 months health authorities realized that nearly half of the people being diagnosed with PCP pneumonia were not homosexual men. The same opportunistic infections were also observed among hemophiliacs, heterosexual intravenous drug users, and Haitian immigrants. By August 1982, the disease had been named Acquired Immune Deficiency Syndrome (AIDS), and human immunodeficiency virus (HIV) was identified as the cause.

Fast-forward ten years and we were confronted with a vicious, widespread disease tearing through communities and responsible for a death every day in the province of British Columbia. These were the darkest days for Drs. Michael O'Shaughnessy, Julio Montaner and Richard Harrigan, when treatments were simply non-existent and the virus was spreading rampantly. In 1992 the newly established BC Centre for Excellence in HIV/AIDS (BC-CfE) could only offer, at best, end-of-life care. Within the communities most affected by the disease— particularly Vancouver's large and politically active gay population—there was a great deal of activism and pressure to develop drugs that worked. And while these voices were heard, at this time there was no clarity around how to find an effective treatment for the disease.

During this time, PCP pneumonia and blindness resulting from Cytomegalovirus retinitis (CMV retinitis) were often precursors of death. "Hundreds of people were dying a year and the big question was how to get palliative care wards open," says Dr. Harrigan, currently the Director of the Laboratory Program at the BC-CfE. And then things got even worse. The first promising drug that had been developed—azidothymidine or AZT—seemed to have little to no impact when prescribed as mono-therapy to HIV patients, and in some cases made the virus worse through severe side effects. Even though large-scale drug trials were underway, the effects were limited and the disease was spreading. Something had to be done.

Imagine if the study of genomics was available in the 1980s and early 1990s. Imagine what could have been done. Imagine what we can do now.



Dr. Michael O'Shaughnessy



Dr. Julio Montaner



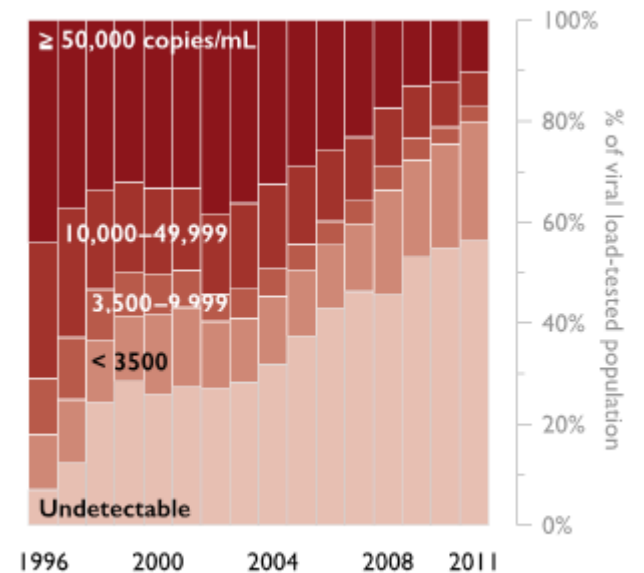
Dr. Richard Harrigan

Seeing the virus through the trees

With clinical trials ongoing throughout North America and Europe, the first genetic test was developed to examine quantitative amounts of HIV RNA in the bloodstream. Lacking the sophisticated genetic testing we have today, it was difficult for scientists to determine how “much” infection people were carrying. The big breakthrough came when researchers realized the virus was being produced continuously and at very high levels—there were hundreds of thousands of copies of the virus in just 1mL of blood.

Other studies determined that tracking both the amount of virus in CD4, a type of white blood cell that fights infection, and viral load were both good predictors as to how long someone would take to transition from HIV infection to AIDS. From 1993-1995 scientists from the BC-CFE pioneered use of the quantitative Polymerase Chain Reaction (PCR) assay to measure HIV viral load as a primary outcome measure in clinical trials. This showed the drugs worked to reduce the amount of virus and that two drugs were better than one.

Plasma HIV-RNA Levels in BC



Nosyk et al. Lancet Infect Dis, 2014

A light in the dark

This early trial demonstrated that AZT did in fact reduce the amount of virus in people by about 50% in the short term and, more importantly, it also demonstrated that triple drug combinations worked better than double and generated a bigger and more sustained reduction in the viral load. This new understanding of infection time and disease progression began to shed light on who to treat—with the limited tools available—most urgently. The BC-CfE was one of the test sites for the first randomized trial of triple drug-therapy.

The effects of these two drugs provided a small crack that began to shed light on this huge problem. More than a decade after HIV first appeared in North America, two drug therapies, AZT and saquinavir (marketed as Fortovase) began to offer hope, while ineffective therapies were terminated early and often, in order to preserve resources for continued research.

And along came Julio

The BC-CfE was not set up solely as a clinical trials network site and patient care centre: it was also intended to monitor the province's drug therapy guidelines. Because the disease was concentrated in the neighborhood core around St. Paul's Hospital, and there was a huge amount of fear around the disease, all of the information for drug utilization and purchases was centralized through the Centre.

Dr. Julio Montaner, then Director of Clinical Activities, took over as head of the BC-CfE in 1996. In a Vancouver Sun interview (November 30, 2013), he spoke of those early days:

The concentrated streaming of AIDS patients to one Vancouver hospital created a pressurized environment that transformed the Catholic-run hospital, and gave rise to a unique opportunity for study and research.

"At first our staff resented the actions of the other hospitals. But it turned out to be a good thing. It further focused our resolve, our intent, our attention. So HIV became an area of intense focus for us and led to very dramatic discoveries," said Montaner.

"It would be easy to write the history as if we were heroes and everyone else were villains. The truth is, we didn't know what was happening. There was fear. There was concern. A lot of hesitation. For us it was a matter of urgency because it was something that was happening in our own midst. The epicentre of HIV-AIDS was in the West End. We couldn't walk away from our neighbours."

Using a BC-based model, that of the BC Cancer Agency, the BC-CfE's vision was to monitor treatment on a province-wide basis and analyze outcomes through a central lens.

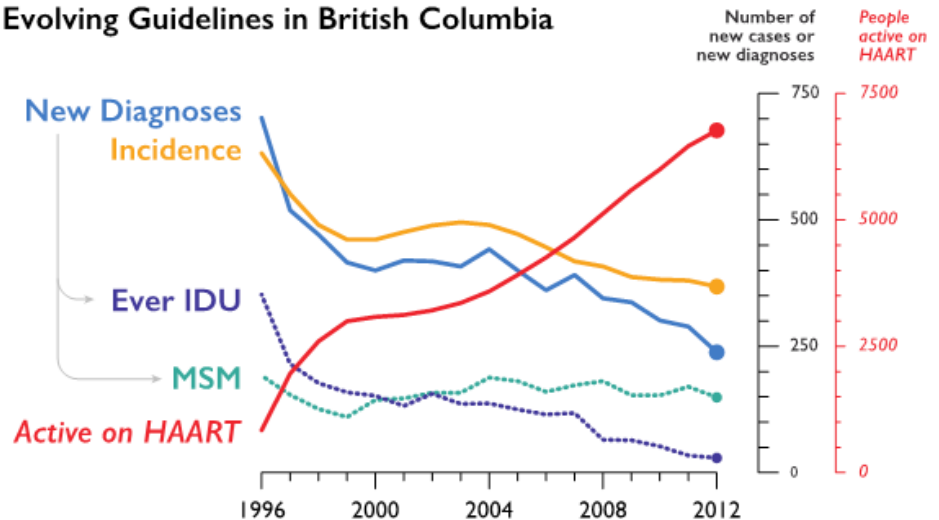


Dr. Montaner and a student examine an AIDS patient in the 1990s

Combination drug therapy and genetic technology

1996 was “the watershed year” for HIV treatment. Vancouver hosted the International AIDS conference where BC-CfE investigators under the leadership of Dr Julio Montaner reported the success of using multiple antiretroviral drugs to control HIV infection. This approach using multiple drugs that act on different viral targets is known as highly active antiretroviral therapy (HAART). HAART decreases the patient’s total burden of HIV, maintains function of the immune system, and significantly decreases opportunistic infections that often lead to death. Dr. Montaner implemented new standards of care incorporating routine genetic viral load monitoring and triple drug therapies were also unveiled. The vital link between a reduced viral load and dramatically improved outcomes had been made, and BC became the first Canadian province to adopt triple drug therapy (the “cocktail”) and routine viral load testing for all eligible patients in a publicly funded plan and immediately saw dramatically reduced HIV and AIDS related morbidity and mortality.

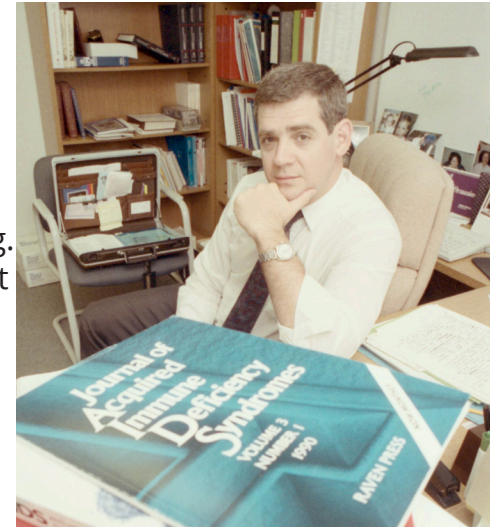
Figure 1. Increasing HAART Coverage Within Evolving Guidelines in British Columbia



Montaner et al. PLoS One, 2014.

The series of combination drugs has a two-fold effect: patients could do better for longer and in a more tolerable regimen, and while the chance of a virus mutating was high, it was less likely to resist a combination.

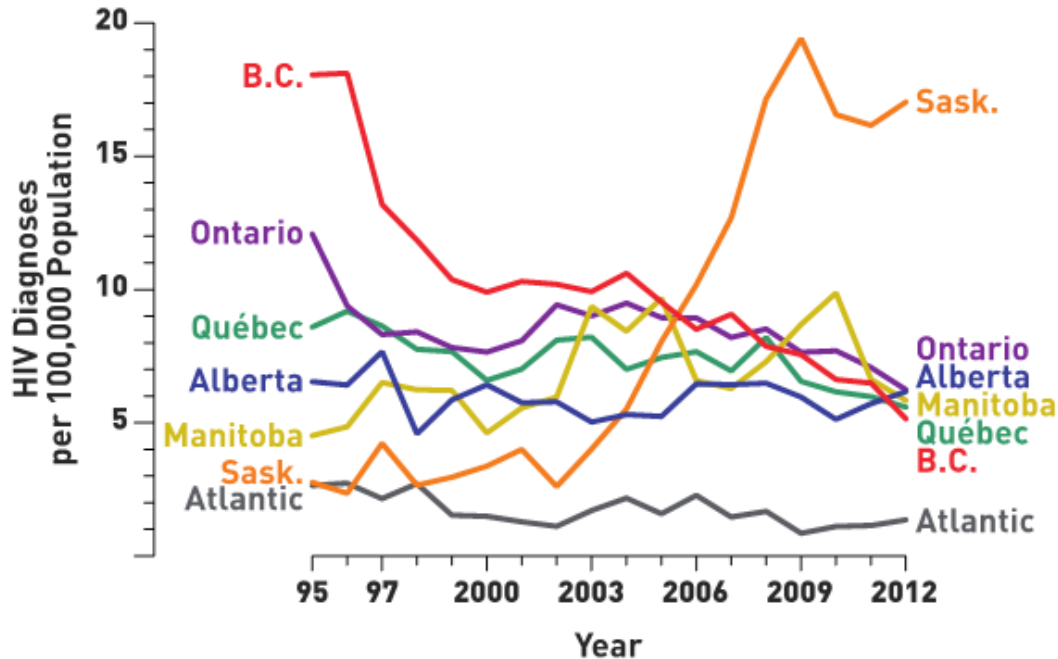
Early viral analysis was done using basic PCR analysis, and only monitored the amount of RNA in the virus. Behind the scenes it was constantly changing. This chess game between mutating virus and combination drug therapy went on long enough so there was time to move from short-term clinical trials to find basic solutions to a whole treatment management paradigm. The BC-CfE treatment guidelines changed and the bulk of patients were receiving triple therapy. Within one year the number of deaths dropped by half- a huge morale boost for public health and the community. In 1998, the BC-CfE was the again the pioneer, making HIV drug resistance a routine part of monitoring in Canada.



Dr. Montaner and early AIDS research

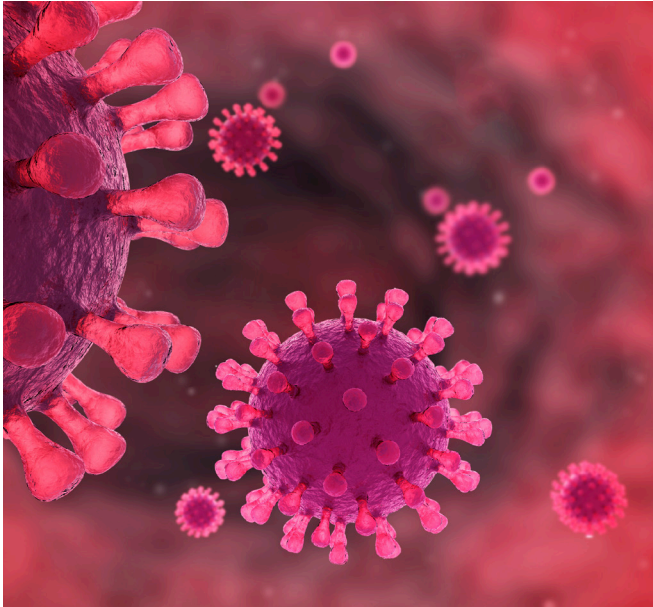
The turning point

Individualized monitoring of the HIV/AIDS virus through quantitative PCR and/or sequencing became standard clinical practice at the BC-CfE towards the end of 1990s. No other area of medicine was looking at DNA analysis or quantitative information on this scale, and it became apparent to researchers that they needed databases that linked genotypes to the virus (to phenotypes) and to link phenotypes to clinical outcomes. The BC-CfE played a significant role in demonstrating that this information could be clinically useful, creating a biobank of over 400,000 samples, linking information about the patient, the virus and the outcomes.



Combatting side effects with viral and genomic markers

The new millennium saw even more advances in HIV/AIDS treatment. In 2000 the BC-CfE became the first group to use therapeutic drug monitoring of antiretroviral drugs for HIV infection in Canada. By 2002 the BC-CfE's research laboratory had refined techniques to measure the amount and impact of different levels of adherence to HIV therapies.



Side effects had always been a major difficulty for patients, but genetic markers were now able to offer insight into reactions to the drug. In 2002 an Australian scientist, Dr. Simon Mallal, published a seminal research article on HIV adaptation to HLA-restricted immune responses in *Science*, which has spawned the use of population studies to examine host-pathogen adaptation. Dr. Mallal's work also confirmed that a particular genomic marker makes a person susceptible to the severe side effects from some HIV/AIDS drug therapy.

In Vancouver, because all HIV/AIDS patient care was centralized through the Centre, the test was available to all HIV positive individuals and physicians could prescribe appropriately. All virology testing was done at St. Paul's Hospital, meaning that all a physician needed to do was call and request an analysis of the sample (which was already there).

Personalized Patient Genomics, Personalized Pathogen Genomics of the Next Generation

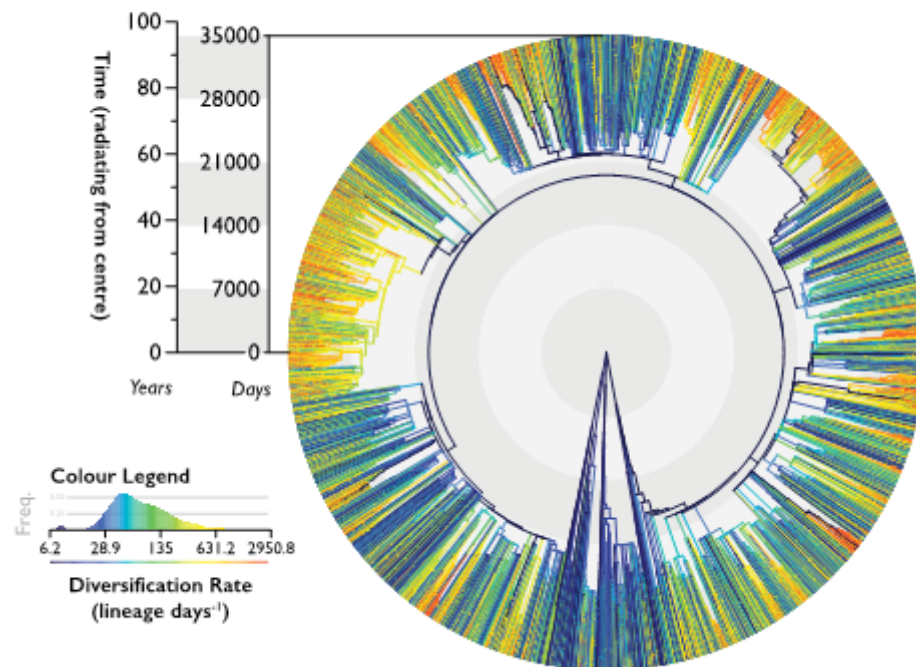
In the latter half of the decade, researchers took full advantage of the most up-to-date and modern “Next Generation” sequencing methods. These methods allowed for the most powerful analysis of human cells and viral cells available at the time: they made the genome available for deep research. In 2005 the BC-CfE’s research lab demonstrated the effect of impact of human and virus genetics in the response to HAART treatments.

Large-scale analysis of thousands of patients was linked to virus sequences and began to characterize whether or not individuals would respond to therapies. Patients were being offered treatment options and could play a role in choosing their ideal therapy. The study of the human genome and the viral genome began to offer insight into potential landmarks on the genome and more information on host and pathogen interaction. While an HIV particle is only 0.0001mm in size, the implication of every genetic discovery about the virus is globally significant.

Genetic testing of the HIV virus had revealed that there were two main strains of the disease each targeting different cell types called CCR5 or CXCR4. A new drug therapy was developed that exploited genetic duplicates – the new drug only affected CCR5 cell. It also became obvious that a test for genetic characteristics related to drug therapy responsiveness would be useful in day-to-day patient care. One laboratory in the US could perform this test but it took a month and cost thousands. By 2007 the BC-CfE’s research laboratory introduced widespread human pharmacogenetic testing for treatment side effects into routine clinical practice.

In 2012, the BC-CfE developed a new metric called the Programmatic Compliance Score (PCS) to help identify individuals who are at a high risk of mortality as a result of improper disease management in the beginning of treatment. Through validation of the metric, researchers found adherence to HIV treatment guidelines significantly increases survival.

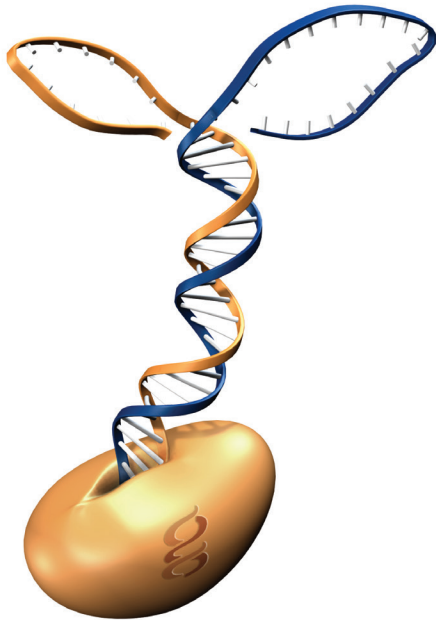
Most likely phylogeny and diversification rate of British Columbia HIV



Joy et al. Presented at CROI, Boston, USA, 2014.

Personalized Patient Genomics, Personalized Pathogen Genomics of the Next Generation (Continued)

In 2013 Genome BC and Genome Canada announced a new \$5 million HIV/AIDS research project to be led by Dr. Harrigan and Dr. Montaner of the BC-CFE. The project aims to develop an improved HIV drug-resistance test, real-time drug resistance surveillance, and better methods for personalizing treatment of HIV based on each patient's unique DNA. This funding now means that cutting-edge Next Gen sequencing can be applied



on an even larger scale. Analysis related to tracking how HIV/AIDS flows around the population is ongoing: a person with a low viral load is much less likely to pass it along, which falls into the Treatment as Prevention plan. However, with the variability of the virus, there are times when people are less well or populations are not receiving correct treatment. The sequence of the virus offers information about what has gone on with new infections. This work is done on a daily, real-time basis and instances of drug-resistant viruses are recorded immediately.

The cumulative impact of this work has meant a huge increase in life expectancy for people with HIV/AIDS. Where an AIDS diagnosis once meant five to six months to live, it now means that a person at age 20, with medication and management, will live to an average age of 73 years. Because of the fewer cases of new infection less treatment is required and thus fewer healthcare dollars are being spent on drug therapy and care. The instance of mother to child transmission is also now next to none, in the past 10 years in BC only two children were born HIV positive.

The transformation of this disease from death sentence to manageable condition is one of the best-personalized medicine stories ever seen and one of the world's best examples of the power of genomics.

Thanks to the study of genomics, we now know each patient and their disease have a unique genetic and molecular makeup. The genetic variants among individuals affect if and how they develop disease and how they respond to treatments. These differences are the basis of the personalized medicine (also known as genomic, individualized, molecular, targeted, predictive or stratified medicine) approach.

In the past, patients with the same disease were managed the same way, using the one size fits all or disease-centred approach. This resulted in more than 50 per cent of patients responding poorly to initial therapies and many suffering from adverse drug reactions, as were frequently seen in the early years of HIV/AIDS treatment. And while disease-centred care is still the standard treatment for most conditions, genomics is changing this situation.

The research and clinical care performed in the laboratory at the BC-CfE includes the genomic analysis of both the patient and the virus, which helps inform drug therapy treatment guidelines for physicians. The research done in the laboratory is translated in real time to patients thanks to a sophisticated centralized database and strong network of physicians in B.C. The early understanding of phenotypic information and the centralized database enabled access for the BC-CfE to one of the best cohorts in the world. The simultaneous analysis of both patient and disease genomes, coupled with major technological leaps in the last decade, cracked the HIV/AIDS conundrum wide open, saving countless lives, and tens of millions of health care dollars. While an HIV particle is only 0.0001mm in size, the implication of every genetic discovery about the virus is globally significant.

This application of genomic medicine to healthcare is growing in scope every year. There are enormous implications to research and treatment for cancer, rare genetic diseases are now being unraveled, infectious diseases like hepatitis and public health epidemics now have new tools. The iceberg is becoming more and more visible.

Imagine if the study of genomics was available in the 1980s and early 1990s. Imagine what could have been done. Imagine what we can do now.



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Genomic medicine now plays an important role across the entire clinical continuum from risk assessment in healthy individuals to genome-guided treatment in patients with complex diseases.

Genomic medicine tools are crossing over into clinical application where they have the potential to markedly alter the clinical care of patients.

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