HIV Treatment as Prevention
Building on the HIV Experience to Promote Healthcare Sustainability

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Executive Summary

"Insanity is doing the same thing over and over again and expecting different results"
-Albert Einstein

Following the discovery of combination antiretroviral therapy (cART) for HIV and AIDS, in part at St. Paul's Hospital and the University of British Columbia, the provincial government agreed to expeditiously implement cART free of charge in BC. Within a matter of months, morbidity and mortality were decreasing significantly; furthermore, at the same time new HIV infections were unexpectedly declining, while syphilis rates were increasing province-wide. Based on additional ecological and cohort studies we concluded that cART was exerting a previously unrecognized secondary role preventing HIV transmission. We coined the term "Treatment as Prevention" (TasP) to characterize the ability of cART to decrease morbidity, mortality, and secondarily HIV transmission. In 2006, we proposed that cART could stop HIV disease progression and also reduce HIV transmission by over 90%, and that this could serve as a new strategy for the control of HIV/AIDS based on the expansion of the access to cART under the banner of TasP. Eventually, we showed TasP to be successful within NIDA funded pilot studies in British Columbia. Eventually this was confirmed in a randomized controlled trial, HPTN 052, published in 2011 that showed that cART was over 95% effective in preventing sexual transmission of HIV.

We have worked with the United Nations AIDS Programme (UNAIDS) to help disseminate the success of TasP globally. Specifically, in collaboration with UNAIDS, we developed a new global target for HIV treatment based on the success of our TasP strategy, referred to as the 90-90-90 Target. The new target proposes that by 2020, 90% of all people living with HIV should know their HIV status; 90% of them should be receiving sustained antiretroviral therapy; and 90% of them should have achieved sustained viral suppression. UNAIDS modelling suggests that achieving these targets by 2020 will decrease AIDS incidence, AIDS related deaths and new HIV infections by 90% from 2010 levels by 2030. The 90-90-90 Target was formally endorsed at the 2014 UN General Assembly (UNGASS) by the United Nations Secretary General, Mr. Ban Ki-Moon, who put forward the 90-90-90 Target as the UN cornerstone for the post-2015 Millennium Development Goals agenda. Since then, the 90-90-90 Target was formally embraced by the US, Panama, Spain, France, Argentina, Sierra Leone, South Africa,

Brazil, India, China, Russia, among others. There is a growing sentiment that the 90-90-90 Target will be ratified as the new 2016 Sustainable Development Goal at the 2015 UNGASS.

More recently, it has become apparent that the strategy of Treatment as Prevention could be of value if applied to other contagious diseases, whether infectious or not. Our next immediate target is to export this strategy to the area of hepatitis C infection where this is particularly attractive given the emergence of the novel direct-acting agents, which makes treatment highly viable and extremely successful. We are currently finalizing details regarding the implementation of such a program, on a pilot basis, in the Downtown Eastside of Vancouver with the Ministry of Health. We are similarly exploring the use of this strategy to deal with conditions that are contagious -but not infectious- where the vector may be a form of "social contagion". As such we are exploring the use of the strategy within the framework of Addiction Medicine.

Of note, Treatment as Prevention has proven cost-saving, because it's effect on transmission acts as a multiplier in terms of return on the investment. This has led us to conceive a strategy of Treatment as Prevention driven targeted disease elimination to enhance healthcare sustainability.

Treatment of HIV/AIDS

While an outright cure or a preventive vaccine for HIV/AIDS remain elusive, remarkable advances in HIV treatment have been achieved over the past two decades. Most significant among these is the development of modern antiretroviral therapy.

Two international clinical trials presented at the 1996 International AIDS Conference in Vancouver, served as the cornerstone for the emergence of triple therapy regimens based on the use of two nucleosides plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (a.k.a. highly active antiretroviral therapy or HAART) as the new standard of care.[1,2,3] In each case, a novel triple therapy regimen used among treatment naive individuals fully suppressed HIV replication and, therefore, rendered the number of viral copies present in the patient's plasma undetectable. As a result, the CD4 cell counts recovered and the disease was placed into a long-term remission.

In the province of British Columbia (BC), within three years of the implementation of HAART, the BC Centre for Excellence in HIV/AIDS (BC-CfE) documented an 85% reduction in HIV/AIDS mortality among patients engaged in HAART. Similar results have been observed in other resource rich environments, and increasingly in resource-limited settings, where HAART has become available. The evolution of HAART, since 1996, has further led to an expansion in the life expectancy for HIV-positive individuals at age 20 to over 50 additional years as of the end of 2007, meaning that life expectancy of HIV infected individuals who access modern HAART is now approaching that of the general population.[4]

Treatment as Prevention

More recently, evidence has accumulated that the viral load suppression achieved by HAART has a marked impact on decreasing HIV transmission. Already in August 2006, we proposed that the expansion of HAART coverage to all those in medical need would represent a key strategy to dramatically curb HIV/AIDS morbidity and mortality,

as well as HIV transmission.[5] We further suggested that such a strategy would be potentially cost-averting.[6]

Evidence to support the impact of HAART on HIV transmission can be readily found in vertical transmission studies where it has led to the near complete prevention of transmission of HIV from the infected mother to the newborn. Similarly, among sero-discordant couples (one infected and one uninfected partner) transmission is a direct function of the level of plasma HIV viral load in the infected member of the couple: the more HIV is present in blood, the more virus is present in sexual fluids and, therefore, the greater the risk of HIV transmission.[7] HIV viral load in plasma and, consequently, in sexual fluids are effectively decreased to undetectable levels with HAART; thereby HAART dramatically reduces the risk of sexual HIV transmission. We have also shown that HAART can similarly prevent HIV transmission among injection drug users.[8] These results have now been independently validated within the ALIVE Cohort in the US.[9]

At the population level, we have documented that expansion of HAART uptake between 1996 and 2010 has been associated with a greater than 65% decrease in HIV new diagnoses in BC.[10] Of note, this has taken place against a background of stable or rising sexually and blood-borne infections in the province. As a result, the provincial government has committed to further expand outreach efforts to maximize HIV testing and facilitate HAART access in BC, this initiative is known as *Seek and Treat for Optimal Prevention of HIV/AIDS in BC (STOP HIV/AIDS in BC)*. It should be emphasized that the expansion of HAART in BC has been associated with marked decreases in morbidity and mortality (over 90% decreases from pre 1995 levels), and secondary decrease in HIV transmission (a 60% overall decrease, with over 90% decrease in IDUs, and over 90% decrease in Vertical Transmission).[11]

The BC-CfE's proposal in support of "Treatment as Prevention"[4] was initially regarded as controversial; however, this notion has gained the support of the international community, including the International AIDS Society, President Clinton in 2008, and Michel Sidibé, the Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), shortly thereafter. In January 2009, investigators based at the World Health Organization (WHO) AIDS program published a paper in *The Lancet*, which independently verified the potentially critical role of "Treatment as Prevention" in the control of the epidemic.[12]

More recently, HPTN 052 - a prospective randomized trial - provided definitive and compelling confirmatory evidence of the efficacy of "Treatment as Prevention" among sero-discordant couples.[13] HPTN 052 showed an impressive 96.3% decrease in the risk of HIV transmission with immediate HAART. Of note, immediate HAART was also associated with a 30% decrease in the combined endpoint of disease progression and death, and an 83% reduction in the incidence of extra-pulmonary tuberculosis.[11]

The latter results further galvanized international attention toward the key role of "Treatment as Prevention" for the control of the HIV epidemic. Indeed, US Secretary of State Hilary Clinton pledged the support of the US administration towards re-profiling PEPFAR efforts to emphasize the role of "Treatment as Prevention" and this was echoed by US President Obama during his speech on Dec 1,2011, and in Dec 23, 2011, Science Magazine named "Treatment as Prevention" as the scientific breakthrough of 2011.

It is clear that expanding access to HAART is highly effective in preventing morbidity and mortality among HIV-infected individuals, and secondarily it prevents HIV transmission.[14] The data is conclusive and compelling. The new WHO treatment guidelines released in July 2013 fully incorporated "Treatment as Prevention" as the new global standard of care, and thus markedly expanded HAART eligibility globally.[15]

More recently, at the suggestion of UNAIDS, the United Nations endorsed the '90-90-90' target as a new post 2015 antiretroviral target to be achieved by 2020.[16] The target calls for 90% of people living with HIV knowing their HIV status, 90% of them receiving sustained ART, and 90% of them maintaining an undetectable viral load. Meeting the proposed target would ensure that by 2020, at least 73% of all people living with HIV worldwide will be virally suppressed; a nearly three-fold increase over current rough estimates of global viral suppression. This will "maximize the effectiveness of existing tools by 2020 to virtually eliminate (defined as a ≥90% decrease below 2010 levels) progression to AIDS, premature death and HIV transmission, and thereby transform the HIV/AIDS pandemic into a low level sporadic endemic by 2030."

The challenge remains to secure the necessary political will to meet the 90-90-90 global target by 2020, as the cornerstone of the global control of HIV transmission and AIDS. An AIDS & HIV-free generation is within reach, however, this will not be attained if we fail to fully capitalize on the promise of "Treatment as Prevention".

Treatment as Prevention as a framework for healthcare sustainability

Over the last decade, it has become clear that Treatment as Prevention offers a roadmap for the implementation of therapeutic/management strategies that could specifically address high-burden diseases with the ultimate goal of dramatically decreasing their burden in society. This is readily apparent for infectious diseases where treatment of the index case has a direct benefit in terms of reducing morbidity and mortality and secondarily, a multiplier effect due to decreasing transmission. In that context, we have initiated work with the support of the Minister of Health in British Columbia to develop a Treatment as Prevention framework for viral hepatitis. In the case of hepatitis C, this has been made possible by the recent development of safer, simpler, and better-tolerated regimens that are interferon-and ribavirin-free. A significant component of the strategy, however, pertains to the accessibility of the direct-acting agents-based therapies to harder-to-reach populations who are overrepresented in terms of the core transmitters for hepatitis C. Furthermore, given the fact that hepatitis cure is associated with no residual immunity, it becomes critical that this issue be approached on a programmatic basis to ensure that appropriate strategies are deployed so that the impact of the program is optimized. This will require a great deal of coordination between services, as well as ongoing monitoring and evaluation.

Other potential targets in the realm of infectious diseases would include hepatitis B or tuberculosis. Indeed the Treatment as Prevention strategy, as currently conceived for HIV, could be safely described as a spin-off of the early efforts from the STOP/TB campaign.

Perhaps, less apparent, is the fact that this strategy could be adapted to address the societal impact of other potentially communicable diseases of non-infectious etiology. In this case, we propose that disease that are amenable to a social contagion phenomenon such as addiction, tobacco-related diseases, obesity-related conditions, etc, could be potential targets for a similar kind of intervention.

Treatment as Prevention would therefore open a door to the development of disease-specific targeted and opportunistic disease elimination strategies. This would aim to decrease the combined burden of selected diseases, in terms of morbidity, mortality, and transmission, by a given factor of 80% or 90%. The strategy would be opportunistic in that it would specifically target diseases where there is an underutilized

therapeutic/management approach that is known to be effective but not yet fully optimized. We propose that given the commonalities of the monitoring, evaluation, and implementation of these programs, it would be highly efficient to bring these initiatives together under a disease elimination strategy that would aim to promote healthcare sustainability through the aggressive optimization of therapeutic/management strategies.

[1] *Carpenter et al. JAMA, 1996*
[2] *Gulick et al. NEJM, 1997*
[3] *Montaner et al. JAMA, 1998*
[4] *Samji et al. PLoS ONE 2013*
[5] *Montaner et al. Lancet, 2006*
[6] *Lima et al. JID, 2008*
[7] *Quinn et al. NEJM, 2000*
[8] *Wood et al, British Medical Journal, 2009*
[9] *Kirk et al, CROI, 2011*
[10] *Montaner et al, Lancet, 2010*
[11] *Montaner et al, PLOS One 2014*
[12] *Granich et al, The Lancet, 2009*
[13] *Cohen et al, NEJM, 2011*
[14] *Lima et al, Lancet HIV 2015 (in press)*
[15] *WHO presentation at TasP, 2013 www.treatmentaspreventionworkshop.org*
[16] *http://www.unaids.org/en/resources/documents/2014/90-90-90*