Published: September 2015

Ending AIDS

Brian Williams - Epidemiologist affiliated to SACEMA.

Triple-combination anti-retroviral therapy (CART) for HIV is the Lazarus Drug—people at deaths door pick up their beds and walk. But as the world embraces immediate treatment for HIV the game is not over: stigma and discrimination persist; drug procurement, supply and delivery are failing in many countries; ways must be found to ensure adherence with treatment to keep people alive, minimize resistance and stop transmission; thirty million people will need treatment for the next half-century or until a cure is found. This is an auspicious time to review a few of the many studies that have accumulated over the last fifteen years in support of providing treatment for people infected with HIV as early and as soon as possible.

In 1984 Brazil was the first country to make anti-retroviral treatment (ART) for HIV available in the public sector starting with mono-, dual- and then triple- therapy. In 1984 25% of AIDS patients developed tuberculosis (TB) and 73% of AIDS patients died; by the year 2000 TB incidence had fallen by 88% and mortality by 96% (1) (demonstrating the power and efficacy of CART.

In 2000 the ZVITAMBO trial of Vitamin A supplementation for mothers and babies was carried out in Harare, Zimbabwe before ART became available in the public sector. In HIV-positive women with $CD4^+$ cell counts below 50/µL the annual mortality was 45%, 129 times that in HIV-negative women. But even in women with a $CD4^+$ cell count of 1,000/µL the annual mortality was still 3.9 times greater than in HIV-negative women (2) suggesting that early ART would have a significant impact on mortality even among women with high $CD4^+$ cell counts. In the same study the mortality in babies born with HIV was 0.5% per week in the first week of life rising to 4.3% per week in the 13th week of life and falling back to 0.5% per week in the 36th week of life; at week 36 the cumulative mortality was 49% in babies born with HIV compared to 1.9% in babies born without HIV (3). This highlighted the importance of starting all HIV-positive pregnant women on ART as soon as possible to keep them alive and to stop vertical transmission and, if their babies are born with HIV or acquire it during labour and delivery or through breast feeding, ensuring that their babies start treatment as soon as possible.

In 2002 the Department of Health and Human Services (DHHS) in the United States, drawing on data from the Multicenter AIDS Cohort Study (MACS), published the first formal attempt to use immunological markers to decide on the timing of treatment initiation. To ensure that people whose chance of developing an AIDS related condition within three years was greater than 10% they recommended ART to anyone with a $CD4^+$ cell count below 500/µL or a viral load above 10,000/mL (4); 90% of people living with HIV in South Africa at that time would have been eligible for treatment (5).

In 2007 the AIDS Therapy Evaluation Project, Netherlands (ATHENA) study, a seven year observational cohort, demonstrated the rate and extent of immune recovery in people on ART (6). At the start of treatment $CD4^+$ cell counts increased at an average rate of 271/µL/year to a steady state of 371/µL above the value at the start of treatment. The important and unexpected observation was that the increase was independent of the cell count at which treatment was started; the higher the $CD4^+$ cell count at treatment initiation the higher the asymptotic $CD4^+$ cell count and, by implication, the better the immune recovery.

In 2008 an analysis of data from the Abbott M97-720 trial (7), in which people were followed up for seven years, demonstrated the effectiveness of CART. With good treatment and high levels of compliance viral loads fell by about 100 times after one month and 10 thousand times after one year (7). While the benefit to individual patients of early ART was already clear, this showed that patients on ART could achieve levels of viral load suppression that would almost certainly render them uninfectious to others. The bad news was that while viraemia could be reduced to about 10/mL, even the best treatment did not eliminate the virus completely so that CART is not a cure.

In 2009 and 2010 the evidence for the effectiveness of treatment as prevention followed quickly with several studies of the relationship between viral load and transmission (8-10). A subsequent analysis (11) showed that transmission saturates at a viral load of about 10k/mL and declines linearly with viral load below 10k/mL; reducing viral load from a mean of about 100k/mL to 100/mL would reduce transmission by about 99%.

In 2010 an important study on drug resistance was published using data from the British Columbia Drug Treatment Program (12). In the early 2000s rates of acquired drug resistance were increasing in

many places (13,14). As expected people on mono-therapy were very likely to develop drug resistance and dual therapy was not sufficient to contain this. By 1996 the incidence of acquired resistance in Vancouver was 20%/year; by 2008, as more people on CART had fully suppressed viraemia, the incidence of acquired resistance had fallen to 2%/year (12).

In 2010 there was still some concern that while CART had clear health benefits for infected people and would significantly reduce both transmission and drug-resistance, there was a need to demonstrate these effects directly in interventions at a population level (15). In 2011 the first large randomized controlled trial of the impact of CART on transmission, HPTN-052, was published (16). This showed that CART could be used to reduce transmission among discordant couples by about 96% providing definitive confirmation that CART could be used to stop transmission and confirming the earlier conclusions based on indirect, but solid, scientific evidence.

In 2013 a study carried out in South Africa showed that a similar impact could be obtained in a public-health setting and not only under trial conditions (17). In the Hlabisa district of KwaZulu-Natal, comparing communities with different levels of ART coverage, the incidence of HIV fell by about 1% for every 1% increase in the coverage of ART (17).

While the impact of CART both in preserving the health of infected people and in reducing transmission to uninfected people is clear, there is still some concern about the affordability of ending AIDS. The cost of CART in 2000 was of the order of US$10k *per annum* which, with about 30 million people infected with HIV, would imply an annual cost of US$300 billion a year for drugs alone. Fortunately the cost of CART has fallen to about US$100 to US$200 *per annum* in low and middle income countries (18) so that the drug costs of putting all infected people on ART would only amount to about US$3 billion to US$6 billion *per annum*. Even allowing for the additional costs of care and support for people on CART this would be affordable in most countries and with international support in all countries (19).

Now, in June 2015, three important results have been obtained. The first is from the Strategic Timing of Anti-retroviral Therapy (START) trial comparing the outcomes for people who started treatment when their $CD4^+$ cell count was greater than 500/µL with people who started treatment when their viral load was between 350/µL and 500/µL (20). The trial was stopped early when it became clear that mortality in the delayed treatment arm was 3.3 (1.8–5.9) times greater than in the early treatment arm confirming the analysis of mortality in the ZVITAMBO trial (2). The second, an elegant analysis of data from Vancouver, has shown that not only does early treatment save lives and reduce transmission, but leads to better viral load suppression, no increase in loss to follow-up, lower rates of drug resistance, and fewer AIDS defining illnesses (21). The third is the announcement that Cuba has become the first country in the world to eliminate mother-to-child transmission of both HIV and syphilis (22).

These clear and definitive scientific results, accumulated over 15 years, provide overwhelming evidence that immediate treatment for HIV, as soon as possible after a person becomes infected, is in the best interests of individual patients and will, if delivered effectively, lead to the elimination of HIV as a public health threat. In the words of Michel Sidibé, Executive Director of UNAIDS 'Every person living with HIV should have immediate access to life-saving ART … Delaying access to HIV treatment under any pretext is denying the right to health' (20). The human rights implications are clear (23).

Ten years ago Julio Montaner, who more than anyone has driven the early treatment agenda, wrote (24): 'The present approach to the management of HIV/AIDS is … not sustainable [or] acceptable if we hope to control the … HIV …pandemic. A prevention-centred approach to the use of HAART [highly active anti-retroviral therapy] … will be challenging and … need careful consideration of … emerging ethical issues. However, expanded free access to HAART … provides a … means to [control] the HIV pandemic'. Based on hard science and the overwhelming evidence that we can stop AIDS, the need now is to muster the political will and the financial resources to rid the world of the scourge of AIDS once and for all.

Brian Williams - *Epidemiologist affiliated to SACEMA. Area of research interest: mathematical biology.* *williamsbg@me.com*

References:

1. Anonymous. HIV, TB and ART in Brazil: Data available from present author on request. http://www.aids.gov.br/ Accessed 29 July 2015
2. Williams BG, Hargrove JW, Humphrey JH. The benefits of early treatment for HIV. AIDS. 2010; 24: 1790-1.
3. Hargrove J. Personal communication. Data available from present author on request. 2015.
4. Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): DHHS; 2014.

5. Williams BG. Combination prevention for the elimination of HIV. arXiv 2013.
6. Gras L, Kesselring AM, Griffin JT, van Sighem AI, Fraser C, Ghani AC, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology. 2007; 45: 183-92.
7. Palmer S, Maldarelli F, Wiegand A, Bernstein B, Hanna GJ, Brun SC, et al. Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy. Proceedings of the National Academy of Sciences USA. 2008; 105: 3879-84.
8. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009; 23: 1397-404.
9. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010; 375: 2092-8.
10. Lingappa JR, Hughes JP, Wang RS, Baeten JM, Celum C, Gray GE, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. Plos One. 2010; 5: e12598.
11. Williams B, Lima V, Gouws E. Modelling the impact of antiretroviral therapy on the epidemic of HIV. Current HIV Research. 2011; 9: 367-82
12. Gill VS, Lima VD, Zhang W, Wynhoven B, Yip B, Hogg RS, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. Clinical Infectious Diseases. 2010; 50: 98-105.
13. Blower S, Ma L, Farmer P, Koenig S. Predicting the impact of antiretrovirals in resource-poor settings: preventing HIV infections whilst controlling drug resistance. Current Drug Targets: Infectious Disorders. 2003; 3: 345-53.
14. Blower SM, Aschenbach AN, Kahn JO. Predicting the transmission of drug-resistant HIV: comparing theory with data. The Lancet Infectious diseases. 2003; 3: 10-1.
15. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. Clincial Infectious Diseases. 2010; 50 Suppl 3: S85-95.
16. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. New England Journal of Medicine. 2011; 365: 493-505.
17. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013; 339: 966-71.
18. Williams BG, Gouws E. Ending AIDS in South Africa: How long will it take? How much will it cost. arXiv 2013.
19. Williams BG, Gouws E. Affordability, cost and cost-effectiveness of universal anti-retroviral therapy for HIV. arXiv 2012.
20. The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine. 2015. [epub ahead of print]
21. Lima V, Reuter A, Harrigan PR, Lourenco L, Chau W, Hull M, et al. Initiation of Antiretroviral Therapy at high CD4 cell counts is associated with positive treatment outcomes. AIDS. 2015. [epub ahead of print].
22. WHO. WHO validates elimination of mother to child transmission of HIV and syphilis in Cuba. [http://www.who.int/mediacentre/news/releases/2015/mtct-hiv-cuba/en/] Accessed 29 July 2015.
23. Kavanagh M, Cohn J, Mabote L, Meier BM, Williams B, Russell A, et al. Evolving Human Rights and the Science of Antiretroviral Medicine. Health Hum Rights. 2015; 17.
24. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet. 2006; 368: 531-6.