Published: September 2018

A history and analysis of a scientific controversy: When is the optimal point to start antiretroviral treatment?

Nathan Geffen - Visiting researcher, Centre for Social Science Research, University of Cape Town.

Most HIV scientists will remember the destructive and unnecessary debate about the cause of AIDS during the era of President Thabo Mbeki. The debate shed little light on how science is conducted: nearly all scientists understood that HIV is the cause of AIDS and that antiretrovirals (ARVs) are an effective treatment. Mbeki's support for denialism is what gave the debate its oxygen in South Africa. When Mbeki went, AIDS denialism disappeared into the margins.

There have been numerous papers and books on South Africa's catastrophic era of AIDS denialism, including by this author. The "when-to-start ARVs" debate in our view is, at least from a science perspective, much more interesting but much less known and written about. It offers a fascinating look at how scientific disagreements between reasonable people, who are experts in the field, work, and how consensus evolves as evidence accumulates. This is why Marcus Low, and I decided to write the history of the when-to-start debate.

When to start antiretroviral treatment?

For nearly three decades, since the publication of the results of the first ARV trial in 1987 (1), HIV clinicians, scientists and activists have debated when to start. Guidelines changed back and forth, reflecting changes in expert opinion and new scientific developments.

Many people in the 1990s and early 2000s were reluctant to endorse early treatment because of the surprising results of the Concorde trial (2). This trial of AZT monotherapy, conducted from 1988 to 1992, showed no benefit to starting early. Patients who started AZT before becoming sick no longer had a treatment option when they developed AIDS because they were resistant to AZT.

With dual and then triple-drug therapy, the resistance concerns decreased, though not entirely. Toxicity and adherence worries remained, although slowly but surely ARV regimens were improving to the point where taking one, two or three pills once or twice a day with minimal side-effects became the norm.

The HPTN 052 study, whose results were presented in 2011, showed that antiretrovirals prevented people transmitting HIV to their sexual partners (3). Many scientists saw this as the basis for encouraging everyone with HIV to start treatment, but others were more cautious, wanting evidence that early treatment would offer clinical benefits. Observational data suggested there was a benefit, but it was not sufficiently convincing for many, and what the data was showing, as well as its quality, was contested. There were also concerns that starting treatment early would be costly and therefore benefit had to be shown unequivocally before it became public health policy.

The scientific method in practice

The scientific method is often idealised as a series of carefully carried out experiments that falsify and refine hypotheses; gradually, but linearly, our knowledge increases. In practice, it is a lot messier: Studies give conflicting results; Some critical studies are delayed because of costs or politics, or simply because they take a long time; Answers to vital questions remain uncertain. Clinicians therefore had to decide with their patients when to start treatment, and guideline writers had to make recommendations on when to start, with life-changing consequences, especially for patients using public health systems.

When important data is lacking, we tend to rely on what is called expert opinion. However, experts reach different conclusions based on their underlying beliefs on the answers to these and other difficult questions: Is a plausible biological explanation sufficient to determine a guideline?; What about observational data?; Alternatively, do we always need a clinical trial to answer questions about a treatment intervention?; Can we change policy based on what models predict?

Many readers of this journal will be aware of the 2008 model by Granich et al. (4), developed by SACEMA's Brian Williams. It is quite possibly the most cited epidemiological model ever (over 1,860 citations as of 16 August according to Google Scholar). Its influence has been considerable. It showed that a universal test-and-treat approach could practically eradicate the HIV epidemic. The paper's authors convinced many that treatment policy should change because of the model's results. Nonetheless, for many scientists, a model was not enough. HPTN 052 swayed more scientists over to the start immediately position, however, the question of when-to-start did not reach consensus until the results of a randomised clinical trial, the START trial (5), became available in 2015.

So the questions of when to start ART was only definitively answered in 2015. Finally, consensus was reached that if one has HIV, one should ideally start treatment as soon as possible after diagnosis.

In conclusion, we hope that our paper in the South African Journal of HIV Medicine (6) that is summarised above, will provide an example of historical importance of the scientific method in practice to philosophers of science, with all its warts and imperfections, but also its ultimate success.

Nathan Geffen *- Visiting researcher, Centre for Social Science Research, University of Cape Town. Research interests: human rights aspects of HIV and TB, as well as modelling HIV.* *nathangeffen@gmail.com*

References:

1. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of Patients with AIDS and AIDS-related complex. N Engl J Med. 1987;317(4):185–191.
2. Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Lancet. 1994;343(8902):871–881.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
4. 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(9657):48–57.
5. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807.
6. Geffen, N; Low, MO. When to start antiretroviral treatment? A history and analysis of a scientific controversy. Southern African Journal of HIV Medicine, (S.l.), (18), 1-8 Dec. 2017. ISSN 2078-6751.