Compromised

Lessons learned from the AIDS epidemic

An essay by Matthew Thomas

Out of Africa

On the 5th of June 1981, the CDC's journal *Morbidity and Mortality Weekly Report* published a small article by doctors working in Los Angeles. They wrote of five strange, yet seemingly related cases of young, gay men being diagnosed with *Pneumocystis carinii* pneumonia, a rare and opportunistic infection that is commonly seen in people with compromised immune systems (1). In less than one thousand words, these authors unwittingly announced the beginning of the HIV epidemic, which ran rampant across the world in the latter half of the twentieth century, killing millions and whose effects are still keenly felt today. And yet, this was far from the true beginning of the crisis. Far away in time and space from 1980s Los Angeles, hunters in Cameroon caught and slaughtered a chimpanzee and were exposed to its blood which bore the Simian Immunodeficiency Virus. The infection spread locally at first, but was transported down the Sangha river system to the bustling metropolis of Kinshasa, where it circulated undetected for decades (2).

Where the COVID-19 pandemic has been rapid in onset and conquered the world in under a year, HIV spread far more slowly owing to its long asymptomatic period. Moreover, HIV patients present with a wide array of symptoms causing the early epidemic to go unnoticed. Nevertheless, we do know that HIV was circulating at this time. Remarkably, patient biopsies taken in this period were preserved and modern analysis allows us to amplify viral genetic material in these samples to see whether HIV is present (3). Indeed, such experiments have revealed a number of positive samples from this era of HIV prehistory, including one case in the United Kingdom and another in the United States. We now understand that the rise of cities in the region facilitated the spread of HIV prior to the advent of the AIDS epidemic, acting as an incubator in which HIV passed from host to host before its exponential boom in the latter half of the century (4).

While HIV multiplied unabated, the Congo saw seismic political change in gaining its independence from Belgium. In this period of instability left by the collapse of colonial rule, the United Nations recruited French speaking experts to help build a new Congolese administration. In total 4,500 technical advisors came from the Caribbean island nation of Haiti and in the intervening years some must have caught HIV and brought it home with them across the sea (5). We now know that in the following years, HIV was spreading in Haiti, because doctors in Port au Prince were reporting numerous cases of the very rare skin cancer, Kaposi's sarcoma. A month after cases of *pneumocystis carinii* in homosexual males was published in *Morbidity and Mortality Weekly,* the same journal reported 26 cases of Kaposi's sarcoma, all in gay men. A number of these patients were also suffering from severe infections. The authors of this report noted that this was highly unusual, and that no correlation between sexuality and Kaposi's sarcoma was known, but that opportunistic infections were seemingly on the rise, particularly in the gay community (6). In July of 1982, similar constellations of rare infections and Kaposi's sarcoma were being reported in Haitian patients in America. This was no longer an unusual coincidence, but a frightening pattern whose cause was unknown (7).

Knowledge of this novel disease was not confined to doctors and academics for long. The New York Times soon reported on what was being called "*Gay Related Immunodeficiency",* the disease was seemingly confined to homosexual men and was spreading in the United States. Sexual contact was likely to be involved, as was drug use, but no definitive cause was understood. Moreover, patients were being affected by rare and unusual diseases, some of which, such as cryptosporidiosis, were more akin to what vets would treat than doctors (8). By September of 1982, the CDC had settled on the name Acquired Immunodeficiency Syndrome (AIDS) and had received report of 593 cases. Of these patients, 243 had died (9). The next year, the world finally learned of the cause of these clearly related yet distinctly strange illnesses, a new virus. French virologist Françoise Barré-Sinoussi and her colleagues, working in the Pasteur Institute in Paris were the first to identify it. They took a lymph node sample from a patient suffering with symptoms of AIDS

and grew the cells for a fortnight. They wagered that the virus causing AIDS was related to a family of recently discovered Retroviruses and it was infecting special cells of the immune system called T-cells. They found that the cells they were growing showed Reverse transcriptase activity. This was the smoking gun that there really was a new retrovirus involved in causing AIDS (10). But what is reverse transcriptase? And what does this have to do with AIDS' role in shutting down the immune system?

The smoking gun

Any biology undergraduate will tell you that the "central dogma of molecular biology" is that DNA makes RNA makes protein. Essentially, all of our genes are written in DNA, an elaborate code that acts as a template to make all of the various thousands of proteins that build and maintain a human. DNA is a fantastic storage system for genetic information, but it can't act alone. And so, when a gene is turned on, our cells make a copy of the DNA using its cousin molecule RNA. RNA then acts as the template for the synthesis of proteins. Retroviruses don't care what biology undergraduates think. Their genes are written in RNA, and when they invade our cells, they copy their genes into DNA in a process completely opposite to how our cells work. They do this with a very unique enzyme called Reverse transcriptase, so the French scientists finding reverse transcriptase activity in their patient's cells was the tell-tale sign that AIDS was caused by a retrovirus.

We now know how it is that HIV infects our cells. Like all viruses, HIV latches onto proteins on the surface of our cells and uses them to get inside. HIV uses the protein CD4 to enter cells. CD4 is found on the surface of a number of cells in our immune systems but is most important as a co-receptor in Helper T-cells. When a bug enters our body, it quickly sets alarm bells ringing in the innate immune system. These cells engulf the invading pathogen and break it down into small fragments that the immune system can learn to recognise. These fragments are presented to naïve helper T-cells, and CD4 allows the helper T-cells to recognise the fragment as foreign. The helper T-cells are now able to activate other immune cells such as those that make antibodies to stop the pathogen (11). If any step in this process is disrupted, a fully-fledged immune response cannot be mounted against the invader, with dire consequences. Soon after someone is exposed to HIV, the virus spreads to the lymphoid organs, where immune cells congregate. Here, the virus spreads from CD4+ cell to CD4+ cell exponentially until eventually, the immune system slows its spread. This phase may last years, but is invariably transient, and eventually the virus will begin to spread again, decimating the CD4+ Helper T-cell population, causing progressive weakening of the immune system (12).

Don't die of ignorance

"Great uncertainties, great foreboding" reads the New York Times January 1986 article "*AIDS IN THE FUTURE: EXPERTS SAY DEATHS WILL CLIMB SHARPLY*". Philip Bofey put to words the anxieties of a generation, that no one knew how many were infected, how many of these would develop AIDS and whether anything could be done to curb the spread of a frightening disease for which there was no treatment, no vaccine, no cure. He reported that the head of the National Institute of Allergy and Infectious Diseases, a name now so familiar to us, Dr Anthony Fauci, believed that up to a million Americans were infected and that number could double within the decade should no progress be made. Indeed, in the intervening period between HIV's discovery and Fauci's interview precious little progress had been made. In 1984, US president Reagan's Secretary for Health and Human services Margaret Heckler had announced the cause of AIDS had been discovered and that a vaccine was only years away (13). A year later, when asked to answer

US government spending on the burgeoning crisis, President Reagan resisted calls from scientists for greater funding citing "budgetary constraints" (14).

Across the Atlantic, the British tabloid press, far from taking a compassionate stance on the growing crisis, instead chose hysterics and to stigmatise AIDS sufferers. Headlines read "AIDS PUBLIC ENEMY NUMBER ONE" , "THE GAY BACKLASH; landlords are worried about contamination" and "1-in-4 LONDON GAYS HAS THE AIDS VIRUS". Not to be perturbed by alarmism, Diana Princess of Wales opened the UK's first AIDS ward in Middlesex hospital and, remarkably for the time, didn't wear gloves. Her gesture was one of kindness and was exceptionally important in changing public perceptions of those living, and dying, with HIV- that they could be touched without fear of infection (15). That same year, then health secretary Norman Fowler launched a major public health campaign aiming to ease the spread of the virus, which was predicted to kill 4,000 Britons in the next four years. Leaflets were distributed to 23 million households and a television advertisement voiced by John Hurt was aired in which a large black tombstone engraved with the word "AIDS" topples over, and flowers are flung onto it. Fowler believed, given the lack of available treatments, public education was "the only vaccine we [had]" (16).

A stark warning from the UK government. Millions of leaflets bearing information about AIDS were delivered across Great Britain.

Achilles' heel

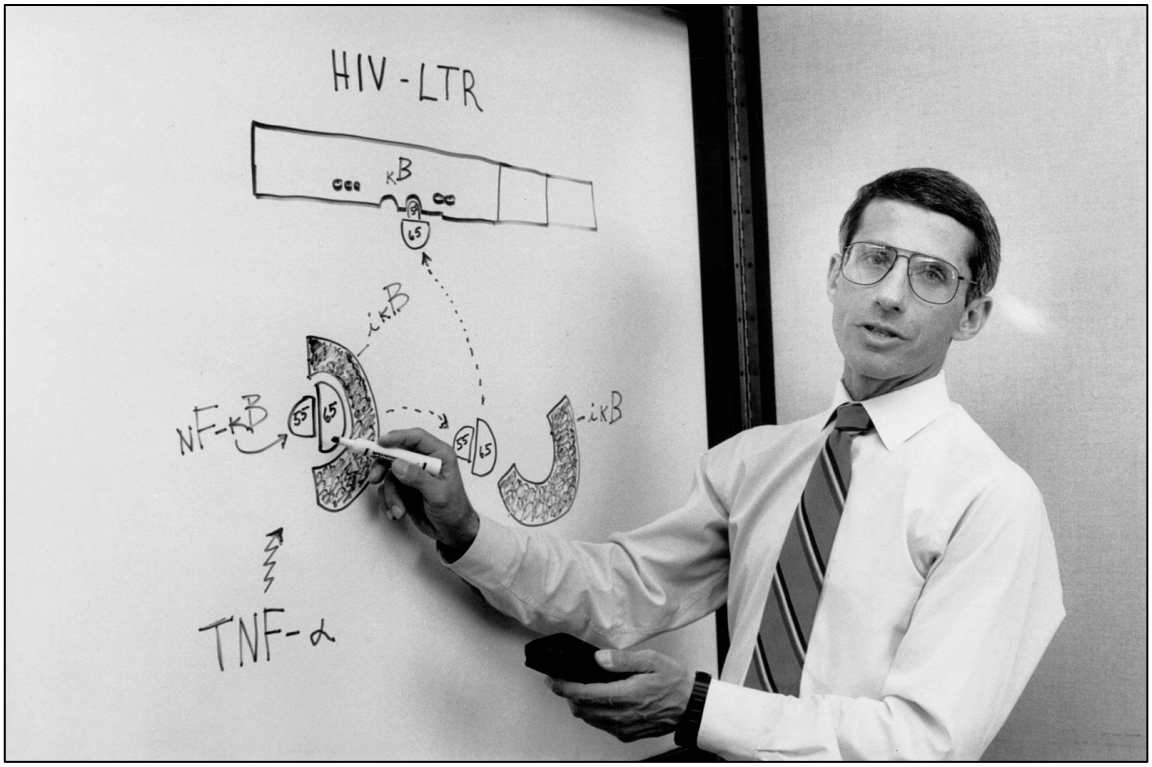
In July 1987, Margaret Fischl and her colleagues published their phase III clinical trial of the new drug Azidothymidine, more commonly called AZT, in the New England Journal of Medicine. The drug was designed to inhibit reverse transcriptase, and it showed striking results. In patients treated with a placebo, 19 had sadly died during the trial. Of those treated with AZT, only 1 had succumbed to their illness. The patients in the study all suffered from AIDS, and to be included had to have opportunistic infections. After six weeks on AZT, no participant had any such infection. It halted the fall in CD4+ T-cells too, and those on AZT saw their helper T-cell counts *increase*. The authors of the study stopped the trial early. The positive effects of AZT were too obvious and it would have been unethical to continue letting patients take a placebo (17).

AZT took advantage of the quirk in HIV biochemistry that its discoverers had noted several years earlier: reverse transcriptase. As before, reverse transcriptase is the enzyme HIV uses to transform its genes from RNA to DNA. Once in DNA form, the genes are actually spliced into the host's chromosomes, effectively turning immune cells into HIV factories. This is enormously destructive to infected cells. Churning out HIV virions can kill them directly, and more importantly, reverse transcriptase being not particularly good at its job, frequently produces DNA copies that are incomplete. This viral DNA drives nearby immune cells into a destructive inflammatory response that is responsible for the majority of CD4+ cell death in HIV infection (12).

The designers of AZT knew this however, and they understood that reverse transcriptase was unusual in yet another way: it incorporated bases into DNA that would prevent any more DNA being synthesised. DNA is made of individual bases that are chemically linked to each other end on end in a phosphodiester bond. These special bonds are formed when the OH end of one base reacts with the OH of the next . AZT, from a chemical perspective, looks a lot like any other DNA base, except it doesn't have an -OH group at one end. When reverse transcriptase foolishly adds it into the DNA strand that it's making, no more bases can be added, because it lacks the -OH to form the crucial phosphodiester link (18). DNA synthesis grinds to a halt and HIV replication is severely impeded. We now know that HIV eventually mutates to be resistant to AZT. It has harsh side effects and its expensive (19). But in the late 1980s, faced with near guaranteed death, it was a godsend for HIV patients.

Dragging heels

"Anthony Fauci, you are a murderer" opens Larry Kamer's 1988 open letter. In the final years of the decade, AIDS activists grew increasingly resentful of the sluggish process of drug approval which inhibited their access to new medicines. In October of the same year, AIDS activists descended upon the FDA headquarters and the National Institute of Health in the States. In the wake of AZT's approval, further trials were testing its efficacy in tandem with other antivirals. And yet, many HIV sufferers were turned away because they had or were using, other experimental drugs. The activists, desperate for any chance to save their lives, were pitted against scientists anxious to preserve the integrity of their studies. What seemed to be an unstoppable force met an unmovable object. Rather than turn a blind eye to the protester's grievances however, Dr Fauci decided to meet with leaders of the protest and consider their perspective, as opposed to many scientists at the time, who would rather have preserved the status quo (20).



A familiar face. Dr Anthony Fauci demonstrates HIV immunology, 1990.

Drug development is slow, costly, and beset by rigid regulatory hurdles which must be overcome prior to a therapy's final approval. It can take over a decade for a new medicine to go from a scientist's bench to a patient's bedside. And many AIDS patients had far less than decades of life left, should no new treatment be found. A compromise was struck called parallel track in which AIDS suffers would be able to access new medications prior to their full regulatory approval once they'd been demonstrated to be safe in phase I clinical trials. Fauci was instrumental in developing this program, which he announced without prior warning, much to the consternation of his colleagues in the FDA. Parallel track brought with it the benefit of potentially helping the very sick, for whom there was no other hope while also allowing clinical trials to be conducted without confounding factors such as patients previously being treated with experimental antivirals. In July of 1989, pressure was on to allow early access to the dideoxyinosine, another reverse transcriptase inhibitor. A meeting between the drug's manufacturer Bristol-Myers, the FDA, NIH and community activists had arrived at a remarkable compromise, the drug was to be made available for anyone for whom there were no further options (21).

Conspiracy and Quackery

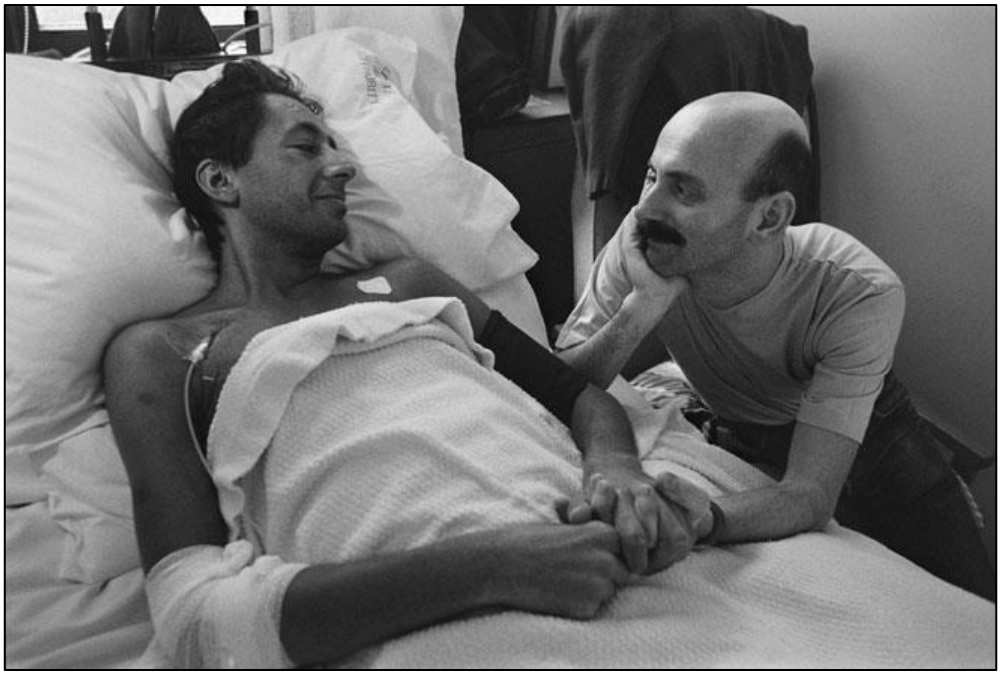
Through the 1970s, Peter Duesberg had been a respected biochemist researching genes that, when mutated, drive the development of cancer. In 1987, however, he began to focus instead on the cause of AIDS. His article "Retroviruses as carcinogens and pathogens: Expectations and reality" concludes the "AIDS virus is not sufficient to cause AIDS". His belief was that HIV was essentially harmless, and while commonly found in AIDS patients, was not causing their immunodeficiency (22). Despite being contrary to established scientific consensus, his ideas, like the malignancies he was once celebrated for studying, began to spread. Soon, others were taking

up the cause of AIDS denialism, with soon-before struck off Doctor Robert Willner pricking himself with a syringe of blood taken from a man he claimed was HIV positive. He did this at a press conference, which he claimed was not to promote his book "Deadly Deception: The Proof that SEX and HIV Absolutely DO NOT CAUSE AIDS". Too often, we are complacent in the face of conspiracy and scientific denialism. Indeed, many high profile scientists including Nobel prize winner Walter Gilbert, came to Duesberg's defence (23). Many didn't defend his stances *per se*, but his right to question. And indeed, science is founded in scepticism, and dissent must be tolerated and embraced. However, dissent in the face of overwhelming evidence is futile. What's more, when there are lives at stake, denial of evidence based medicine is a menace, which is exactly what became of Duesberg's grotesque contrarianism and ignorance, which was so artfully disguised as science.

The prestigious scientific journal *Nature* is famous for publishing brilliant, insightful, and novel research. On the 6th of July 2000, however, it published scientific insights that had been common knowledge for the better part of a decade; "*HIV causes AIDS. Curbing the spread of this virus must remain the first step towards eliminating this devastating disease"* (24). This short document was signed by 5,000 doctors and scientists and was endorsed by respected institutions such as the Royal Society, Pasteur Institute, and US National Academy of Sciences. This seemingly redundant declaration, however, was very pointed in its aim. South African President Thabo Mbeki was sympathetic to AIDS denialists, his advisory panel on the topic filled with dissenters including Duesberg. A year before, under pressure to provide AZT for the increasing population of HIV positive South Africans, Mbeki had announced the drugs were harmful and wouldn't be provided to those who needed them. His government restricted the distribution of Nevirapine, a drug that prevents the transmission of HIV from pregnant mothers to their unborn babies (25). The implications of this decision are staggering. It is estimated that the use of antiretroviral drugs would have prevented 343,000 deaths between 1997 and 2007. 35,000 babies were born with HIV who needn't have (26). Words fail me in attempting to convey the scale of this tragedy. It's an enormous and irreversible loss of humanity, whose victim's lives were every bit as meaningful as yours or mine.

We'll always be together, however far it seems

In 1987 an enormous patchwork quilt was displayed on the National Mall of Washington DC. Each panel, 3 feet by 6, represented an individual who had died from AIDS. The quilt grew year on year and by 1996, on its final outing, it had grown to cover the entire Mall (27). Each panel is digitised and freely accessible at aidsmemorial.org. It speaks to a human tragedy which statistics fail to convey. Some panels are elaborately decorated while others simply bear names and small messages from loved ones such as *we miss you, remember me,* and *together in electric dreams*. Another particular poignant description of the impact and cost of the crisis is Gideon Mendel's photographic work *The Ward*, which captures the experiences of AIDS patients in London's Middlesex hospital in an era prior to effective medicines. The photos, remarkably candid and warm, depict the end of life care AIDS patients received. They show attentive doctors and nurses, loving family members and lovers embracing. Mendel notes that all of the patients photographed died soon after he had finished shooting. It is all too easy to become lost in a world of abstraction when confronting the enormity of the AIDS crisis but seeing artworks such as these are tremendously impactful in a manner that is difficult to affect otherwise. In seeing the statistics of the great number who lost their lives to AIDS, it is all too easy to remember each of that number had friends, families and aspirations that can never be realised. A life full of meaning cut short.



"André with his partner" . Mendel's work illustrates the AIDS crisis in a touching manner, provoking us to consider the human cost on an individual and emotional basis.

Towards a cure

Timothy Ray Brown was a university student when he received his HIV diagnosis. By his time however, it was no longer a death sentence, and he was able to start on AZT and a year later, protease inhibitors. Highly active retroviral therapy allowed him to live a perfectly average life for an ensuing decade before inexplicable bouts of exhaustion forced him to see a doctor. Initially, it was suspected Timothy had anaemia, a pathological lack of oxygen carrying red blood cells. When treatment for anaemia failed, he was sent to an oncologist, who made the diagnosis of acute myeloid leukaemia. Brown embarked on four gruelling rounds of chemotherapy, during which he developed a severe infection and had to be put into an induced coma. Before he concluded his chemo, Brown's oncologist took a sample of his bone marrow to see if he had any matches, in case he needed a transplant.

Brown, however, was satisfied that his chemo would suffice. Bone marrow transplants after all, aren't trivial procedures and carry a hefty risk of death. Brown's oncologist was keen however, to find a donor with a rare genetic mutation called *CCR5δ32*, which confers carriers with resistance to HIV infection. Those carrying the mutation don't express the protein CCR5 on their CD4+ T-cells, therefore blocking the virus from wreaking havoc on the immune system. Brown remained hesitant, despite a suitable match being located. His hand was forced however, when his leukaemia recurred. At his doctor's behest, Brown ceased taking his anti-retroviral medications the day of his transplant. After three months, no HIV could be detected in his body (28). Brown remains the first of only two people ever cured of HIV.

While the therapy that has cured these patients is remarkable, it will also never be a viable solution for eradicating the virus worldwide. Nevertheless, it's a fantastic achievement and gives us a glimpse into a future where HIV might be an unpleasant memory. Far from fantasy, however, scientists are driving efforts into developing a feasible, scalable, and affordable cure. A significant barrier in this effort is the presence of "latent" virus infected cells. As before, HIV inserts its own genetic code into our chromosomes. In the case of people on effective treatments, the virus lives

on, not as infectious particles roaming through our blood seeking out immune cells to infect, but lies in wait in the form of DNA, waiting for its opportunity to re-emerge. A novel strategy to cure HIV takes this into consideration in a wonderfully counterintuitive way: we turn the virus back on. Once the viral DNA begins to churn out new HIV virions, we can train the immune system to ruthlessly clear cells hosting the virus. The proposal is called *shock and kill*. This is far from being realised at present. HIV manipulates the cells it infects to its own ends, particular in the regulation of cell death. For *shock and kill* to become viable, drugs which inhibit HIV's control over infected cells will also need to be identified (29). For now, *shock and kill* remains in its infancy. But watch this space! The rise of immunotherapies has made remarkable inroads in cancers previously intractable to treatment. Perhaps in years to come, they will make waves in the world of HIV therapy.

Epilogue

On the 12th of January 2020, the World Health Organisation published a situation report outlining the outbreak of a novel beta-Coronavirus in China. With only 41 cases having been confirmed at the time, the evidence suggested that the virus was likely not easily transmissible from person-to-person. It all seems like a distant memory now (31). US author Mark Twain once remarked that "no occurrence is sole and solitary but merely a repetition of a thing which has happened before"- and so it is apt to ask ourselves this; faced with a new viral outbreak, have we learned our lessons from the AIDS crisis? In many respects no, we have not.

October last, the editors of the *New England Journal of Medicine* published a remarkable editorial urging US readers to vote President Trumps' administration out of office. They noted that at time of writing, the US death rate was 50 times greater than that of Japan's- despite the latter's vulnerable ageing population. The authors attribute America's abysmal handling of the pandemic to its leadership, which neglected to adequately test, isolate, and quarantine potential cases. Restrictions were lifted too soon, before the disease was adequately controlled, and the wearing of masks was politicised (32). Parallels may easily be drawn between the disinterested response of the Reagan administration to AIDS, and the neglectful approach taken by Trump *et al.* last year. Furthermore, the editors noted that COVID19 has affected ethnic minority communities disproportionately, exacerbating existing inequality. Of course, we cannot forget AIDS was once referred to as 4 H disease, for the four communities it seemed originally to target- homosexuals, Haitians, haemophiliacs, and heroin addicts. All vulnerable and marginalised communities *prior* to AIDS.

Just as with HIV, we have seen COVID19 bring with it a toxic wave of overt prejudice against those, some foolishly blame for the spread of the virus. We saw this with the British press denigrating AIDS victims, and we see it again- in the rise in anti-Asian hate crimes, which can be in part attributed to some politicians referring to COVID19 as "the China virus" or "Kung Flu". Childish name calling is only one element of this bigotry, as we have seen a distressing increase in overt physical violence against Asians not only in the USA, but in Ireland, too (33)(34).

Conspiracy theories proliferate in times of fear and uncertainty. With the rise of social media, they can spread faster, and to more people, than they could before. Unfounded conspiracies abound regarding COVID19. They are often nonsensical and contradictory, ranging from there being no virus, to the virus being man-made in some Chinese laboratory, to it being harmless and little more than a common cold. Some profess that masks, rather than being the lifesaving intervention we know them to be-are a means of controlling the populace, and that the vaccine will microchip us, so that some global elite can track our every move. We shouldn't be complacent when faced with this sort of quackery, however- for it has real world implications. Vaccine hesitancy will cost lives

if vulnerable people are convinced by anti-vaccine rhetoric. Lest we forgot all those lives lost in South Africa.

Progress in HIV and COVID have come at the behest of science. From the recognition that the clusters of pneumonia cases in central China were in fact a novel Coronavirus, we have seen scientists across the world working tirelessly to sequence its genome, to develop sensitive tests to identify the sick, and to track the emergence of new variants. The jewel in the crown, has of course been the breath taking brevity in which safe and effective vaccines have been developed. It's a testament to the utility and brilliance of basic research that such fantastic interventions can be developed at such short notice, though it should be borne in mind that these vaccines build on the work of decades of basic research in messenger RNA technology, and adenovirus vaccine vectors.

It was a bitterly cold morning, and I was waiting for the 46E to arrive and whisk me away to college. A new ad displayed in the bus stop caught my eye. A dapper chap stares directly into the camera and emblazoned below his face are the words "EFFECTIVE TREATMENT MEANS YOU CAN'T PASS ON HIV TO PARTNERS". Gone are the days of the ads my parents watched, with the great black tombstone and the stark warning of death. And yet, we have a ways to go. Writing in *Nature Reviews Microbiology* in 2013, Françoise Barré-Sinoussi and colleagues recount the various triumphs scientific research has yielded in HIV, from our understanding of the virus's biochemistry to the development of effective treatments that have changed it from a mortal threat to a chronic illness. Nevertheless, they also recall the challenges that remain including disappointing vaccine trials and the fact that 34 million people still live with the virus (30).

While HIV and COVID19 may still be considered works in progress -we can rest assured that scientists work best when there are problems to solve. And we can marvel nonetheless at the work already done. It's hard to disagree with novelist Kurt Vonnegut's assessment, that science really is magic that works.

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