Are we standing in our own way on the path to a cure for HIV/AIDS

Although there are many reasons to celebrate the life-extending benefits from antiretroviral therapeutics (ART) for HIV/AIDS and the ability to chronically manage patients' disease for decades, the majority of people around the world living with the virus do not have access to ART and those that do, have over decades developed life-threatening side effects. Our inability to identify a cure to HIV lies not only in the as-of-yet failure of the medical research community to identify and develop appropriate means of ridding the body of the virus but also government and industrial policies that promote public opinion exclusively focused on chronic management scenarios instead of broadly exploring innovation for cure.

"An inconvenient truth"
(Davis Guggenheim)

There are approximately 37 million people living with HIV and 39 million have died of AIDS-related diseases since the start of the epidemic in 1981. As of March 2015, only 15 million people have access to treatments for HIV. It is estimated that one fifth of people infected with HIV in the USA have not been diagnosed and only half the patients with access to ART in the USA take prescribed medication. Durable suppression of HIV is only achieved in 25% of the patients who are linked to medical care and receiving ART. The etiologies for these statistics are hotly debated but as concerning as these numbers are, they are likely to be gross underestimates of the magnitude of the global epidemic. As the majority of Americans are not rountinely tested for HIV, the virus can go years without being diagnosed in an HIV positive person. With these statistics it is no wonder that every day an estimated 5,600 people globally become newly infected with the virus. Importantly, the statistics we are analysing are biased for populations who can or are willing to access HIV testing/treatment programs and where government policies or cultural beliefs allow the health status of individuals to be revealed.

Despite the research on HIV and AIDS from academic institutions, industry and advocacy groups and dedicated efforts of AIDS treatment activists that forced government policy for early and expanded access to experimental drugs, the medical community and society are struggling with the fact that we are barely managing the HIV epidemic and AIDS crisis. For years we have been locked into thinking of solutions in terms of a chronic disease with life-long treatment. The past 30 years in which anti retroviral drugs (ARV) have been identified and treatment modalities have been refined are remarkable in their success in prolonging the lives of people infected with HIV. These years also have the inconvenient truth that they reflect with one exception, the Berlin patient, failure to discover a cure or achieve sustained viral suppression without ever changing drug regimens.

Cocktails, cascades and a conundrum

At this time, decision makers speak of an 'HIV Care Continuum', underwritten as policy by a United States Federal initiative and supported by the Center for Disease Control (CDC) and the National Institutes of Health (NIH). This four-part recommendation includes comprehensive HIV testing and diagnosis, linking and maintaining all HIV positive individuals to a health-care provider, providing all HIV positive patients with life-long access to ART and ensuring that for each patient, viral loads remain suppressed. The impracticality of this management model as a solution to the global AIDS pandemic can be appreciated in both social and economic considerations. In fact, while the ink is still wet on the HIV Care Continuum initiative, we already know that its goals are not broadly achievable due to significant attrition from care and treatment dubbed as the 'care cascade'.

Two potential limitations of the new policy are the magnitude of chemical production that will be necessary to meet the global demand for ARV (i.e. how do we produce this quantity of chemistry, for that many people, for all years that their disease will need to be managed) and an inadequate mechanism in place that can ensure long term compliance (i.e. uninterrupted access to healthcare and ART to a diverse global community with disparate education, infrastructure, cultural and religious beliefs). The limitations of this model will be exacerbated by the recent announcement from the World Health Organization (WHO) that they have reversed their policy from one of 'don't treat with ART until individuals become significantly immune-compromised'

Dr. Harold Charles Smith

to advocating that 'everyone be given ART immediately after diagnosis'. The recommendations go further to include pre-exposure prophylactic ART treatment (PrEP) for HIV negative individuals who are at high risk of infection. We now are faced with the conundrum of an expanded and global epidemic with a need to supply ART and access to medical care for decades on a planetary scale. Given the improbability of this course of action, discovering a cure to HIV/AIDS has to become an overriding priority.

A challenge to the imagination for those who could make a difference

Key opinion leaders (KOLs) have in recent years said that they now "dare to imagine" a cure yet others say we cannot go there because 'there be dragons' in charting a course to cure, i.e. a cure is not possible. The HIV community is encouraged by talk about HIV eradication but are confused over the course that is being prescribed. The negative outlook toward curing HIV/AIDS actually has held back adequate funding for cure research by actively discouraging it for many years as 'intellectually unsound'. There is a peer review system comprised of experts from academia and industry that adjudicates and ranks research proposals submitted to government and private foundations. A majority of those who served in peer review have been in lockstep with the dogma that a cure was not possible and they put the 'thumbs down' on priority scores that determine grant funding for hypotheses for the eradication of HIV. Simply put, if one could not state a hypothesis for a cure, then specific research objectives could not be articulated in a funding proposal for testing opportunities to cure HIV. Eventually word got out and such ideas no longer were submitted for consideration or they were couched as being for therapy. In that way, KOL's and rank and file scientists themselves influenced capitalisation and development of new concepts. I hasten to add that in this era gone by, had academic scientists inadvertently found a cure to HIV, it is unlikely that they would have suppressed findings simply based on government or foundation funding priorities. But cure has the potential of being a disruptive technology for the pharmaceutical industry and Wall Street. So it is not clear how industries would manage the impact of a cure on sales of life-long ART that have held reliable billion dollar profits from the sales of so-called 'block buster' drugs.

"A rose by any other name would smell as sweet"

(William Shakespeare)

Many members of the drug discovery and drug development communities remain astonished by the about-face that is now referred to as 'cure research'. The past structure leaves many scientists uncomfortable with the direction for and implementation of this change in emphasis. The many

years of the chronic therapeutic management mindset has left the map for ideation with many information voids. The years required for exploration have been squandered. Confusion is a typical symptom of deep shock that may explain why eradication research has become mired in a debate over what the word 'cure' means? Recent media blitzes have tragically rushed to be first to proclaim (define) a cure that turned out not to be. Trying to define cure as what can or cannot be achieved has been distracting. We certainly will know a cure when we find the overt evidence in someone like the Berlin patient.

We have to accept and stop arguing about whether a cure can only be 'functional' (no replicating virus detectable but genetic analysis will demonstrate the presence of HIV genomes) or what most would understand to be an absolute cure (the complete elimination of HIV genetic material from the patient's body). Will a cure be achievable for everyone who has HIV or only possible for certain strains of the virus? Will a cure only be achievable for patients with particular genetic backgrounds? Can a cure be achieved that enables an ART-free future or will there be a remission period that requires maintenance boosts over time? While one might speculate about the answer to these questions, a cure in any form MUST be acceptable, no matter how limited.

Learning from the past but encumbered by it

Eradication of HIV and prevention of new infections with the use of an HIV vaccine is a logical and appealing cure strategy that has been evaluated for many years. In fact, this has been the only 'cure talk' that was tolerated before the recent glasnost on cure research. A vaccine strategy that is capable of neutralising one or multiple strains of HIV and does so for extended periods of time has not been achieved. Clearly there is precedent in other diseases that justifies continued pursuit of a broadly neutralising vaccine strategy. These endeavors have yielded a fascinating understanding of the acquired immune system relative to HIV that may yet triangulate investigators toward a curative vaccine strategy.

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Otherwise, cure research includes a reversal on the epidemic-long policy endorsed by government and industry to restrict innovation to new classes of drugs that interact with proteins and functions encoded solely by HIV. We know that HIV encoded functions must co-opt cellular and biochemical infrastructure and raw materials in order to replicate the virus. However, therapeutic strategies to thwart the virus by targeting pathways in the cell are discouraged and sidelined with speculation that they might be fraught with adverse effects. The development of many experimental ARV compounds has in fact been suspended by the systematic and industrial application of these criteria.

This position only makes sense if one chooses to ignore the fact that most FDA-approved ARVs can have serious side effects that will almost certainly manifest in chronically treated patients.

For decades the efficacy of a new drug candidate has been assessed pre-clinically by the ability of HIV to evolve drug resistance to it in the laboratory. This policy is based on the premise that if a drug is interacting with an important viral target, the virus will figure out a way to become drug-resistant. Said in a different way, all ARVs that have been brought to market are already known to select for minority subspecies of HIV and therefore they have anticipated 'use until dates' (i.e. not curative). The industry and venture capital firms demand this proof and failure to establish it evokes silence in the room.

These policies certainly will become fodder for future debates on how to eradicate HIV. Would a new drug that is curative be able to satisfy these criteria? The Berlin patient was cured of HIV while treating him for his cancer. Certainly cancer eradication is not without significant side effects and risks. One has to wonder whether taking a toxic drug for 6 months to a year might not be worth the potential of a life-long cure for HIV/AIDS? If the answer to this question is yes, then it evokes concern that the rubric we have been following for drug approval may be responsible for why a cure has never been found in the 30 years of ARV development?

Given the industry-wide position of 'well tolerated' new drugs, it is curious that there has been lightning-fast uptake of the concept known as 'shock and kill'. The premise is that viral reservoirs (cells infected by HIV but not shedding virus) are the major

reason why ART cannot eradicate HIV. In this strategy, viral reservoirs are forced to express HIV so that the body's inflammatory and immune responses can identify and eliminate them. The drugs being evaluated in clinical trials are known as histone deacetylase inhibitors (HDACi) and are a class of drugs that induce gene expression by changing the structure of human chromosomes. Although these drugs have clinical applications as mood stabilisers, anti-epileptics, anti inflammatory and anti-cancer treatments, they are fairly toxic, and their effect is not limited to viral genes. The use of HDACi treatment in HIV patients has been pushed through to clinical trails despite significant concern and skepticism in the scientific community. The public media has hastily portrayed HDACi as a 'cure' drug because in clinical trials it induced expression of HIV (viremia) from viral reservoirs in patients whose viral loads would have otherwise been suppressed by the ART they were receiving. Further studies will determine whether the activation of viral reservoirs with HDACi, or by any other means, will safely destroy all viral reservoirs, prevent the induced viremia from forming new reservoirs and provide, potentially in combination with ARV, a cure?

Links in the chain of responsibility

New findings from university and biotech labs have been largely portrayed as academic and ignored by the HIV media, KOLs and pharmaceutical industry. These new ideas are the background noise for a select cast of speakers invited to HIV conferences. Federal and foundation research grants are very difficult to get and typically only support incremental discoveries. Moreover, research universities, due to their non profit tax status and professed need to protect their intellectual freedom, largely do not see it as their responsibility to do more than basic science, patent their ideas and wait for an industrial partner. Faculty and their students are generally discouraged by institutional policy from participating in contract research for drug development and cannot participate in commercialisation. Venture capital will not invest in new ideas unless there is a clear path (flip) to an industrial partner. Consequently ideas for cure (and therapeutics) at an early stage of development and the biotech companies bold enough to push them forwards are struggling in a financial 'valley of death'. The HIV-positive population will continue to grow unless everyone takes responsibility for discovering a cure and the monopoly on resources is dispersed.

Timothy Ray Brown, the Berlin Patient, Speaks to the ACTG

"When you come to a fork in the road, take it"
(Yogi Berra)

It is essential that new research ideas and innovative approaches for cure are rapidly reviewed and diverse and divergent proposals become adequately funded so that they can be vetted, not lost in endless KOL debates in the media and at meetings on HIV/AIDS. Biotechnology needs to be preserved and the biotech industry should be facilitated under a mandate to bridge the valley of death for the development of ideas for eradication as a matter of government policy. Government relationship with the pharmaceutical industry and taxation policies need to change such that resource allocations are incentivised for the development of new ideas for eradication. Society should demand of governments, foundations and HIV advocacy groups to demonstrate the political will to create a new fund, one of military budget proportions, for the discovery of a cure(s) for HIV/AIDS so that we can truly win a global war on HIV rather than manage the engagement.

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