The HIV Frontiers Program:
Bringing curative interventions for HIV disease to all parts of the world

Introduction

The HIV Frontiers Program was conceived during the summer of 2018 and approved by the Bill & Melinda Gates Foundation for its first four-year funding cycle (of $108M) in May 2019. Its primary goal is to deliver curative interventions for HIV to those in need in resource-limited parts of the world, where "cure" implies sustained antiretroviral therapy (ART)-free viral suppression and "those in need" are primarily individuals who, for whatever reason, cannot access or sustain a continuous regime of suppressive ART. The effort, in other words, is meant to be a complement to – and not a replacement of – ART. At the level of the individual, sustained ART-free viral suppression should predictably enhance and/or maintain health; at the population level, it should also reduce the frequency of transmission and, hence, the incidence of disease.

From the outset, it was clear that successful introduction of such a curative intervention will be confronted by the following challenges:

- The intervention will have to be one that can be delivered (ideally as a "single shot) in a manner that is safe, effective, affordable, and accessible in situations wherein medical care and infrastructure are largely lacking and/or not utilized by all in need. Translated to a target product profile (TPP), this means that the curative intervention will have to be one that is delivered *in vivo* by a viral or non-viral vector to long-lived cells in the body (*e.g.,* hematopoietic stem cells, or HSCs), modifying them in such a manner as to keep rebound-competent HIV genomes at bay. To address the technical aspects of such targeting and editing, a tactical decision was accordingly made to start with genetic modification of HSCs for the treatment of sickle cell disease (SCD), for which defined modifications have been shown to provide clinical benefit.
- Development of an analogous curative intervention for HIV will be dependent upon knowledge of the biology of the rebound-competent reservoir of HIV (*i.e.,* virus that persists in the presence of ART and that must thereafter be suppressed when ART is discontinued).
- Given the highly aspirational nature of the strategy, the program will best be served by the creation of strategic partnerships, bringing in those from multiple complementary disciplines to share the risk, inform progress, and contribute resources.

When the HIV Frontiers Program was launched, there was little financial incentive for biopharma to tackle these challenges: the R&D pathway to create such cures is long and treacherous and, even if successful, reimbursement may not be available at the end of the day. Yet, in the case of HIV, even though other funding bodies (*e.g.,* PEPFAR, UNAIDS, etc.) have committed billions of dollars over the years to the provision of ART, these efforts are falling short: many individuals are unable to access and/or to remain on ART and, even if they can, current treatments are not curative. In the case of SCD, the situation is even more dire: there is no effective treatment for this disease and most of those afflicted endure a short and painful life.

This overview is designed to provide a high-level description of the Program, one that will hopefully foster additional conversation and detailed exploration. For a more extensive description of the Program, see McCune et al., Human Gene Therapy, 2021.

Overview of Program

What does the cure for HIV and SCD look like, and how do we get there?

Given the continued high rate of transmission of HIV amongst young adults in resource-limited parts of the world as well as a "youth bulge" that is expected to occur in these regions in the coming decade (see

Ndung'u et al., Nature, 2018), it is conceivable that the HIV pandemic will continue unabated, particularly if more resources for ART and medical infrastructure are not brought to bear. Modeling this projection under various scenarios and using data from sub-Saharan Africa, it is evident that – under a pessimistic (but also realistic) assumption that there is no increase in ART coverage beyond that found in 2015, poor penetration of long-acting pre-exposure prophylaxis, no increase in condom usage, and no effective vaccine – the incidence of HIV infection will remain largely unchanged. In such a scenario, the introduction of a curative intervention that requires a single administration, that maintains viral suppression and prevents transmission, and that does so in 10% of the population per year starting in 2040 would have a dramatic effect on the incidence of HIV infection. Importantly, the gains evidenced by such an intervention are lost if it does not also prevent infection upon re-exposure to virus (see Beacroft et al., Global Health Research and Policy, 2019).

Putting this together, the aspirational **target product profile** for an HIV cure would be a single shot of a viral or non-viral vector that targets and edits long-lived cells of the body to generate an antiviral effect that safely suppresses the circulating viral load for a period of three years AND that prevents infection upon re-exposure (see Lewin et al., Lancet HIV, 2021 and Peluso et al., EBioMedicine, 2019).

To accomplish this goal, the HIV Frontiers Program has focused investments to answer fundamental questions in four major categories:

- **Design** – The exact mechanism(s) of action by which sustained ART-free suppression of HIV can be achieved.
- **Durability** (targeting and editing) – The way in which such mechanism(s) are introduced into long-lived cells in the body.
- **Detection** – The methods used to detect biomarkers of the rebound competent reservoir of HIV that can be used to empower clinical trials and to monitor success.
- **Distribution** – The approaches taken to build the capability and capacity to scale curative interventions in resource-limited parts of the world.

These overarching questions have been translated into a foundation-approved strategy with six bodies of work (Figure 1):

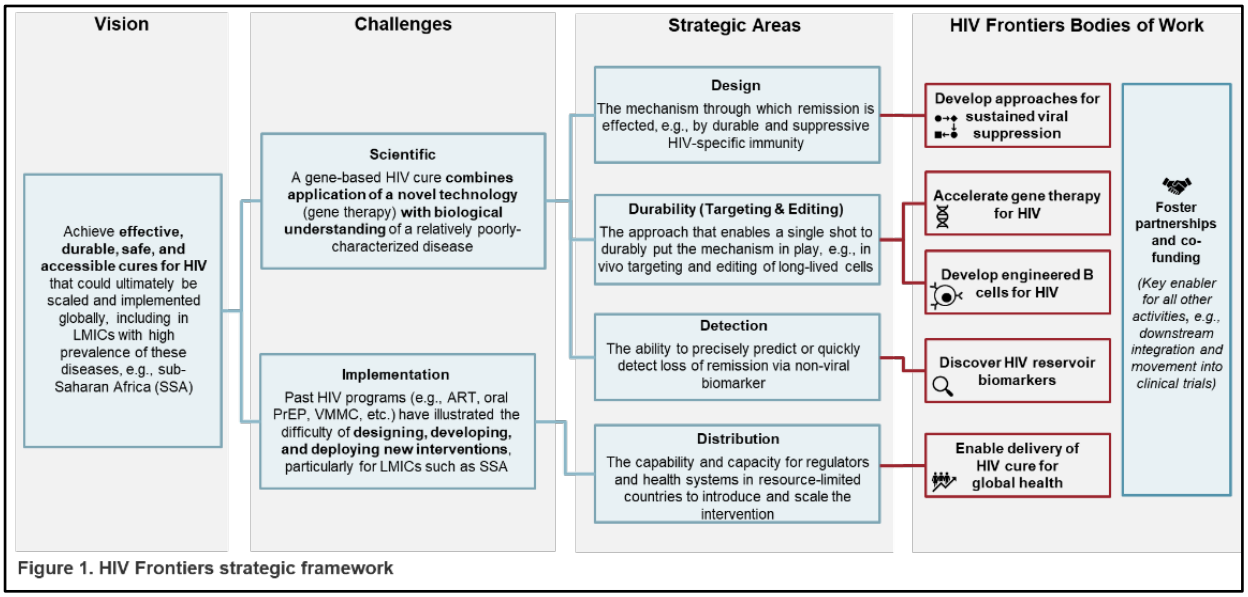

Figure 1. HIV Frontiers strategic framework

Progress to Date

Since the "design" of a curative intervention for HIV is yet unclear, a tactical decision was made (in 2019) to first focus on targeting and editing of hematopoietic stem cells (HSCs) *in vivo* for the prevention of sickle cell disease (SCD), for which clinical benefit has already been provided by *ex vivo* genetic

manipulation of HSCs. With a reasonably high degree of confidence, work leading to such an intervention *in vivo* should then be directly transferrable to *in vivo* targeting of HSCs and/or other long-lived cells in the body (*e.g.,* memory B cells, T stem central memory cells) for the purpose of an HIV cure, once we know better how to do that. Additionally, considerable progress has been made over the past several years in the design of "therapeutic vaccines" that might be delivered in a single shot to effect durable remission of HIV disease.

Given the four-year time frame of this initial period, the Program has also actively pursued the formation of critical **partnerships** to broaden input of expertise and of resources, including:

- A 50:50 formal collaboration with the NIH (including the OD, NIAID, NHLBI, and DPSCI) on *in vivo* genetic cures for HIV and SCD (see Cohen et al., Science 2019).
- Program-related equity and/or grant investments with several biotechnology companies, including BioNTech (to work on interventions that result in durable ART-free remission of HIV disease and therapeutic mRNA/LNP T cell vaccines against HIV), Immunocore (to develop compositions capable of HIV reservoir reduction for HIV cure), Vir Biotechnology (to develop "vaccinal" antibodies that result in durable ART-free remission of HIV disease), Ensoma (to develop helper dependent adenovirus vectors for *in vivo* HSC targeting in the context of HIV and SCD cure), CRISPR Therapeutics (to develop approaches to target and edit HSCs *in vivo* for the cure of HIV disease), Emmune (to develop a nonviral approach for *in vivo* expression of eCD4-Ig for HIV cure), and Addition (to develop a nonviral approach for *in vivo* expression of an HIV Env antagonist for HIV cure (see also press releases from BioNTech, Immunocore, Vir Biotechnology, and Ensoma).
- A formal investment in the multinational company, Novartis, to stand up a dedicated team of 23 scientists at the Novartis BioMedical Institutes of Research to focus on *in vivo* genetic cures for SCD and, ultimately, HIV disease (see press release from Novartis and McCune et al., Molecular Therapy, 2021).
- Multiple investments (>40 totaling more than $50M) with academic labs and small- to mid-cap biotechnology companies to test the ability of various viral and non-viral vectors to target HSCs *in vivo*.
- Establishment of a $46M, nine-team, 30-lab, four-continent effort ("the HIV Reservoirs Consortium") to better understand the biology of the rebound competent reservoir of HIV so that biomarkers of it can be defined, optimized, standardized, and used to create point-of-care and in-home diagnostics, both to inform the discovery of curative interventions of HIV and to enable detection of viral rebound, should the interventions fail.
- Establishment of a public-private partnership called HCAAP (the HIV Cure Africa Acceleration Partnership) to engage key stakeholders in sub-Saharan Africa to accelerate the design, social acceptance, and rapid adoption of "single-shot" curative interventions for HIV and sickle cell disease (Dybul et al., Lancet HIV, 2021).

These partnerships now form a unique and enabling foundation, with expertise spanning the spectrum of biomedicine from basic research to commercialization.

In sum, the intent of the HIV Frontiers Program is to discover and develop curative interventions for both HIV and sickle cell disease that are safe, effective, durable, affordable, and accessible to all of those in need, wherever they may be. Though this aspirational effort has progressed more quickly than originally imagined, it will only move forward with dedicated scientific focus, partnership with both the established R&D community (including the NIH and global health companies) as well as key stakeholders at every level of the health care matrix (including payers, ministries of health, regulatory agencies, local health care and faith communities, and - not least - patients and their families), and collaborative efforts that coalesce the requisite complementary strengths and resources (see McCune et al., Molecular Therapy, 2021).