

# Making Gene Therapy Accessible

In the 1990s, even as AIDS deaths plummeted in the United States, they were climbing in Africa. It took nearly a decade for much-needed but expensive HIV therapies to be made accessible in poorer countries; this shaped the course of the global HIV pandemic, which is now firmly centered in sub-Saharan Africa. COVID-19 and monkeypox vaccines have shown similar patterns, with access heavily skewed toward patients in high-income countries while the citizens of low- and middle-income countries (LMICs) wait. Gene therapy is poised to follow this well-worn path unless there are fundamental changes in the way this technology is supported and delivered.

By altering genetic material in cells, gene therapies create permanent changes that can result in lifelong cures for diseases. As of August 2022, more than 2,000 gene therapies were in development, with approximately 1,000 active clinical trials globally. However, this rapid rise in gene therapy research is not evenly distributed around the world. Less than 5% of clinical trials were recruiting participants in LMICs (not including China), with only four trials in all of Africa.

Gene therapy is widely perceived as an intervention only for the rich, and it's no mystery why: Zynteglo, a gene therapy for the blood disorder beta thalassemia, will soon reach the US market with a \$2.8 million price tag for a one-time infusion. Beyond the cost, these treatments also require sophisticated equipment, expert personnel, and a highly developed regulatory

environment. However, in addition to beta thalassemia, gene therapy can treat sickle cell disease, hemophilia, and (in the future) HIV—conditions where most of the affected individuals live in LMICs.

Do low-income countries really lack the capacity to deliver such treatments? In the early 2000s, funders, pharmaceutical companies, and governments of donor countries who were reluctant to provide antiretroviral therapies (ART)—a highly effective HIV treatment—to LMICs contended that ART was too expensive and too complex for developing countries' limited health infrastructures. But advocates persevered, and by 2020, 19 million people in Africa were benefiting from these life-saving drugs.

As gene therapies make it possible to move beyond managing diseases such as HIV to functional cures, there is an imperative to ensure such transformative treatments are available in LMICs with the highest burden of disease. The key will be to set up policies now so gene therapies are developed through a collaborative process, thereby creating the infrastructure and support systems to address multiple diseases—rather than the single-target approach of traditional global health initiatives.

## Building crosscutting platforms

Programs targeting single diseases, although successful in the past, fall short of what is needed now. The donors and multilateral organizations that fund a large portion of the health budgets for many LMICs often focus on specific diseases (e.g., the Global Fund to Fight AIDS, Tuberculosis,

and Malaria), leading to what are called vertical programs, with short- and medium-term objectives. Such programs helped reduce new HIV infections globally by more than one-third between 2000 and 2015 and prevented an estimated 54 million tuberculosis (TB) deaths worldwide from 2000 to 2017. Despite their successes, however, vertical programs have been criticized for creating parallel systems for funding and management, failing to strengthen broader health systems, and distorting national priorities by focusing on the narrow objectives and metrics set by funders.

More recently, organizations making investments to address HIV, TB, and malaria have recognized the need to focus on efforts that strengthen health systems more broadly. The US President's Emergency Plan for AIDS Relief (PEPFAR) was originally conceived as a vertical program to specifically address prevention and treatment of HIV/AIDS. Yet since 2009, PEPFAR has explicitly made long-term investments in strengthening health systems by training clinical and managerial personnel, constructing buildings and purchasing instruments for laboratories,

organizations, and community health workers expanded their activities to include COVID-19 testing and vaccination efforts. Still, these positive gains in addressing other diseases are considered secondary to PEPFAR's mission. Applying the organization's funding framework to gene therapies would be problematic, drawing the same criticisms that plague vertical programs.

Instead, it's time to widen the scope of intervention so that a general platform for gene therapy can be developed in LMICs to address multiple disease areas. This can lower overall costs, bring benefits into broader health systems, and better reflect each country's specific health priorities. Rather than being an afterthought or a spillover effect, multiuse design should be core to the original funding plan of gene therapies.

This is the approach the Bill & Melinda Gates Foundation has begun to take, despite a history of funding siloed vertical programs. The foundation's HIV Frontiers Program was started in 2019 under the leadership of Joseph "Mike" McCune, who has been researching HIV since the 1980s. Through his work to develop a single-

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developing supply chains and regulatory agencies, and designing health information systems. In LMICs around the world, the PEPFAR program has trained 290,000 health care workers in HIV care and other health services and supported more than 3,000 laboratories and 70,000 health clinics.

With these broader investments, PEPFAR's funding has had spillover effects beyond HIV treatment. Expanded infrastructure and increases in the number of trained clinicians have improved outcomes for a variety of diseases. A recent analysis showed countries that received PEPFAR funding saw a 25% reduction in maternal mortality, a 35% reduction in child mortality, and significant increases in childhood vaccination rates. PEPFAR has also helped train a generation of local scientists, whose research has fueled advancements in the understanding of the origins of diseases and led to breakthroughs in pharmaceutical and diagnostic discovery. This combination of infrastructure and expertise developed by PEPFAR has served as the backbone of the COVID-19 response in some African countries, where clinics, partnerships with community

shot gene therapy for HIV, McCune and his colleagues realized that a gene therapy cure for HIV would likely rely on similar technologies being developed to cure sickle cell disease (SCD). Recognizing the power of the gene therapy platform to address multiple disease areas that have not traditionally been addressed together, McCune broadened the mandate of the HIV Frontiers Program to include sickle cell and other disease areas.

Taking advantage of similarities in the underlying gene therapy science for curing HIV and SCD provides several benefits. Current gene therapy procedures involve removing a patient's cells, making a genetic change, and safely reintroducing cells back into the patient. The procedures require similar equipment and staff with similar training. Thus, offering multiple therapies in one location could save money and enable the treatment of various conditions in addition to HIV and SCD, including beta thalassemia and some cancers.

To realize the full benefit of such crosscutting investments in new gene therapies technology and facilities, the regulatory guidelines and laws that ensure quality and safety must be developed for gene therapy

as a *platform* rather than specifically for any one disease or condition. Likewise, community engagement efforts should abandon a siloed approach and focus on education and outreach that apply to multiple disease areas. Although the patients who will benefit from each individual therapy may be different, the other stakeholders—clinicians, politicians, advocates, and community leaders—are often the same people, with similar questions and concerns.

Low- and middle-income countries' own public health priorities do not always align with the funding objectives of external partners, but a coordinated approach will allow for better balancing of these interests. In particular, coordination will ensure that funding allocated toward the most prominent disease areas, such as HIV, will also impact other disease areas, such as SCD, which have struggled for funding. By focusing on commonalities, including the need for robust infrastructure, a well-trained workforce, and access to technology, the health needs of local communities, as well as the goals of funders, can be achieved.

### **Collaborative assessments to guide funding**

Formalizing collaboration across multiple disease areas, as exemplified by the Gates Foundation's HIV Frontiers Program, is crucial for improving access to gene therapies and other resource-intensive and innovative technologies. Another vital step in this direction would be expanding PEPFAR's remit to include using the program's existing infrastructure for HIV treatment to administer hydroxyurea, the inexpensive, standard-of-care treatment for SCD. However, doing so would require not only a shift in mindset, but also a change in how donors identify priorities and assess performance.

Ideally, determining the infrastructure investments that serve multiple health needs would occur prior to funding. This process would include identifying and coordinating among key stakeholders—including patients, clinicians, and technology developers from both high-income countries and LMICs—who would convene to determine what infrastructure is needed and how it can best be utilized across multiple diseases. This initial assessment should be led jointly by both the funder (e.g., PEPFAR) and the recipient (e.g., an LMIC's health ministry) to account for the needs of both.

Conducting and evaluating such assessments successfully requires a great deal of specialized knowledge and expertise, but models exist. The Global Gene Therapy Initiative (GGTI) was formed in 2020 as an alliance of clinicians, scientists, engineers, advocates, and community members to catalyze the development and implementation of gene therapies for diseases that disproportionately impact LMICs. With its

comprehensive understanding of rapidly advancing gene therapy technologies, changing regulatory landscapes, and diverse community perspectives, a group like GGTI could create, complete, or evaluate assessments, helping to ensure the long-term sustainability of infrastructure and maximize its impact.

To create new assessments for funding health care technologies in LMICs, how success is currently measured—and who does the measuring—will need to change. Gauging long-term effectiveness of crosscutting platforms is difficult because their impact is spread across multiple disease areas, types of infrastructure (e.g. hospitals and regulations), and timescales. A solution to this evaluation problem could include handing the process over to LMICs. Historically, funders have set the criteria for evaluating short- and long-term objectives of vertical health programs. But since multiuse infrastructure is designed to strengthen health systems, better align with country needs, and go beyond single diseases, LMICs themselves are best positioned to evaluate success and take timely and targeted steps to improve health and economic outcomes based on their findings.

### **Leveraging the moment**

As the prevalence of noncommunicable diseases in LMICs continues to rise, public health experts are calling for HIV-focused infrastructure to be leveraged to provide a wider range of health care services. And while the health care delivery system has been instrumental in addressing the COVID-19 pandemic, it's clear that LMICs need stronger and more agile systems that serve a range of different testing, manufacturing, and treatment functions, especially during public health crises.

As the global pandemic has catalyzed new conversations around infrastructure development in LMICs, gene therapy offers a case study for testing alternative funding and delivery models. It is also an opportunity to build equity and self-determination into the model of international funding by making it a more collaborative process. The resources required to build gene therapy capacity in LMICs will be significant, but if they are used to prioritize long-term success and stronger health systems, the health and economic benefits of this transformative technology could change many millions of lives.

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