

WHITEPAPER

## **Global Access to Human Gene Therapy: Lessons Learned from HIV**



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The global rollout of HIV programs for the prevention and treatment with antiretroviral therapy (ART) is one of the most impressive and important achievements in the history of public health, saving in the range of 20 million lives.

The success was largely driven by the creation of national systems for the purchase and distribution of life-long therapy. The US President's Emergency Plan for AIDS Relief (PEPFAR), the largest international health initiative in history for a single disease, created the momentum and, in the early going, provided the lion's share of external financial and technical resources. The Global Fund to Fight AIDS TB and Malaria (the Global Fund), an innovative public-private partnership, marshalled financial resources from around the world, but also helped to bring together key UN agencies, e.g. UNAIDS and WHO, in a coordinated approach to support national responses.

In retrospect it all looks so easy. But success was not a foregone conclusion. There were many forces at play that could have – and almost did – derail the whole enterprise. HIV was devastating many parts of the world – in particular Sub-Saharan Africa. In the hardest hit countries, approximately one-third of the adult population was infected. Life expectancy had dropped by a decade. As excitement, and some funding, and well intentioned efforts are underway to advance certain gene therapies in Africa and beyond, e.g. CRISPR and CAR-T, for Sickle Cell Disease (SCD), HIV and potentially cancer, it might be useful to consider key lessons learned.

## Leadership at All Levels is Key

When President Bush launched PEPFAR, there were more than 100 “Presidential Initiatives.” It would have gone the well-worn path of most, lingering in the background to be strangled in the crib by US government departments and agencies that have honed skills over decades to demolish anything they see as a threat to their supremacy. President Bush had to be personally engaged in the first five years to ensure PEPFAR overcame countless bureaucratic hurdles until it, itself, became entrenched in the system. Fortunately, there was strong, bipartisan Congressional support and leadership, thwarting the tried and true method of Government departments and agencies to go to Congress to slow or kill the initiatives of the head of their own branch of Government. That combination of Presidential and bipartisan Congressional leadership – which has lasted nearly 20 years – was the central key to the durability of PEPFAR.

In a similar way, the UN agencies with a stake in HIV, and to a lesser degree malaria and tuberculosis, had their knives out and tried hard to shred the Global Fund before it was created. However, as PEPFAR was President Bush's idea and passion, the Global Fund was Secretary General Kofi Anan's brainchild. As President Bush made clear to his team, Kofi made clear that continued efforts to undermine the Global Fund by the heads of the agencies he led would lead to shortened tenures.

While we tend to focus on global leaders, they could do nothing without the strong leadership in countries, starting with the heads of state and government. In many lower- and middle-income countries, the authority of the top is definitive. The leaders who embraced the international efforts and, effectively, rammed them through their own bureaucracies, rapidly scaled up programs. Some,

like President Mogae of Botswana, had a head start. He had already led an effort to provide ART. President Museveni of Uganda also had a focus on HIV. Others, e.g. Presidents Kagame, Kibaki and then Kenyatta, Kikwete, Pohamba, Prime Minister Meles, His Majesty King Mswati III and others moved quickly.

While some had strong Ministers and leadership teams, others had to push everything through directly and with deep personal engagement.

The lesson is clear. Without leadership from the top, rapid advancement is not going to happen.

### **Lead with People and Communities**

Leadership from the top levels of government goes only so far. And science goes only so far. In the research and public health community we sometimes have an over self-confidence – and perhaps a touch of self-importance and self-righteousness - that if the science is there, political leadership should be there and people and communities should simply accept and do what we say. While that might be true for some people, perhaps even most, levels of trust and belief in science can be highly variable and in no small part related to your heritage and community. The current experience with COVID-19 vaccine hesitancy in the USA and many other parts of the world, including Africa, has starkly demonstrated that fact.

It is not all wackos, uneducated and anti-science nuts either. There are many communities who have good reason to mistrust government authorities. And those with poor access to, or who have been treated poorly by, the health system, are not often willing to simply follow what they are told to do.

In Africa, this history of colonization and often experiences with corruption, e.g. the need to pay health professionals on the side for services that should be provided for free, can lead to hesitancy. There is also a long history of campaigns, e.g. malaria elimination, that begin with great energy and enthusiasm

When PEPFAR began, I very naively assumed programs would be set up quickly, lines would form and we would roll on easily. We quickly encountered widespread fears that ART was a CIA plot to sterilize the continent (a fear that often accompanies vaccine campaigns), that we were bringing Western values regarding HIV prevention and medicine in the usual colonial way, that it would all fade in time, in particular if there when there was a new US President. The fact that HIV was linked to “sex, drugs and rock and roll” led to strong pushback in generally socially conservative religious and traditional medicine communities. We did not realize that many Africans, including heads of state, seek traditional before or alongside “Western” medicine.

On the treatment side, because of hesitancy, the people most likely to come to ART clinics were deathly ill. Word quickly spread that people went to clinics still alive, were given ART and died soon after. So the ART must have killed them.

That is just a snapshot of the many deep and complicated social and cultural issues that needed to be overcome.

ART – and forms of prevention, e.g. condoms, female condoms, voluntary medical male circumcision – were complicated enough. Gene therapy is another ballgame. Like HIV, there had been resistance to vaccines and other medical interventions with deeply held beliefs that “outsiders” try

to sterilize Africans to wipe out the continent. Given history, such beliefs are understandable. If that were a problem for ART, imagine introducing a product that is gene therapy for humans. In fact, when it was proposed to study gene modified mosquitos to prevent malaria, only a few African countries accepted. Many African countries have strict policies against genetically modified food products. Those responses to gene modified food and mosquitoes provide some indication of the hurdles gene modification of human cells could pose.

While many researchers in Africa are interested in studying gene therapy and are supportive of it – as was the case with ART - that does not mean there is broad support beyond them. Identifying communities where resistance could exist, e.g. through market research and human centered design, is essential to build support long before a product is introduced.

### **Start Where You Can Start**

In global health and development, there is often a tendency to push for immediate access for everyone and the financial and other resources needed to provide it. That is the ideal. And we need advocates to push for that to give policy makers the room to act. But we live in the real world. As a concrete example, when President Bush made the historic commitment of \$15 billion over 5 years, there was a loud cry for \$5 billion per year. Had we done that, the program would have collapsed in less than 2 years. We knew from Botswana and nearly every public health intervention in history – including ART in the USA - that it takes time to build capacity including training, supply chain, awareness and acceptance, etc. If we had requested, and Congress allocated \$5 billion per year, by the end of year 2 there would have been billions unspent and a catastrophic loss of confidence. One only need compare the trajectories of the Millennium Challenge Corporation and PEPFAR to see the reality.

Instead, using historical global health efforts as a guide, PEPFAR projected a scale-up and met every key target on time and on budget. That created the foundation of confidence that has driven the nearly 20 years of bipartisan support for the program. In fact, the final budget request was \$6.5 billion (approximately the same level as every year since then) and, because of increases to the Global Fund by Congress, the total for 5 years was more than \$18 billion.

Be aggressive and push as hard as possible. But for long term sustainability, start where you can start.

### **Integrate, Integrate, Integrate**

PEPFAR demonstrated that, at the beginning, to build a program, dedicated and very focused resources are required. But as foundational systems are built, for sustainability, it is essential that services become part of the health system as much as possible, including integrating community systems as part of the health system.

## **Humility and a Sense of Humor**

Somehow, with very limited data and huge programmatic and financial assumptions, PEPFAR met all of its key targets on time and on budget. That is not common among Government programs. And the key ingredients of the original plan are still in place. But as then General Eisenhower said: “Plans are worthless, but planning is everything.” Listening, adjusting with the data, following the lead of those on the ground are indispensable. That requires a profound sense of humility and a sense of humor, perhaps the two most important ingredients of success.

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