The evolution of HIV treatments: From antiretroviral therapy to vaccines, where we are today and what’s next.
Introduction

The challenges in treating and preventing HIV, and subsequently AIDS, lies in its heterogeneity.

This disease characteristic makes an integrated response more difficult, creating further hurdles in getting closer to a more comprehensive, evidence-based response. In 1984, when HIV was identified as the cause of AIDS, U.S. officials declared there would be a vaccine in two years. More than 35 years later, vaccine clinical trials remain ongoing. 1

To help accelerate innovation and solutions, many groups and organisations have set ambitious targets, including UNAIDS 90:90:90 agenda as outlined below: 2

- By 2020, 90 percent of all people living with HIV will know their HIV status
- By 2020, 90 percent of all people with diagnosed HIV infection will receive sustained antiretroviral therapy
- By 2020, 90 percent of all people receiving antiretroviral therapy will have viral suppression

At the end of 2019

81 percent of people living with HIV knew their status
67 percent of all people living with antiretroviral therapy
Only 59 percent of people living with HIV have undetectable levels of the virus

80m people are living with HIV - a number that has tripled since 2010

Considerations for patient-centricity when designing trials for people at-risk or living with HIV

References
Globally, great strides have been made in HIV testing and treatment. At the end of 2019, 81 percent of people living with HIV knew their status, and an estimated 25.4 million of the 38.0 million people living with HIV — a number that has more than tripled since 2010.1

While the latest numbers reported show substantial progress, as 2021 approaches, there remains a long journey ahead to achieving this global target. Part of this delay stems from the HIV epidemic varying by region and country, and, thereby, necessitating a different emphasis in different geographies.

However, the central tenets of the response to HIV remain the same in any comprehensive response irrespective of geography. If we were to consider the 90:90:90 as the framework for progress, we might simplistically say that the main challenges are the diagnosis of HIV infection and the provision of treatment. Yet, it is not that straightforward. On a global level, other factors play a significant role including political commitment (such as self-replenishing funding); access to quality health services (traditional health services are not reaching many key populations at risk, e.g. sex workers, LGBTQIA community, and intravenous drug users, etc.); stigma and discrimination; social exclusion; uninterrupted access to treatment; and new technologies and innovations.

While each of these factors remain central to ensuring a comprehensive and impactful response, in this whitepaper, we will discuss the latter — new technologies and innovations in the context of the history and recent innovations that are leading to better tolerated and more affordable treatments, specifically pre-exposure prophylaxis (PrEP). In addition, we will discuss continued needs and challenges facing clinical research, solutions to managing infectious diseases clinical trials and a path forward for the decade ahead. It is acknowledged that only a vaccine will end AIDS and with more than twenty HIV vaccine clinical trials ongoing and some very recent learnings from innovative vaccine approaches in the quest for a SARS-CoV-2 vaccine (e.g. mRNA technology) the HIV vaccine environment looks more promising than ever before.

Advances in research have highlighted the false dichotomy between prevention and treatment in the area of infectious diseases, emphasising the need for a combination of interventions to decrease new infection rates. So, why do we need to keep focusing on novel and innovative treatments?

Treatment has many benefits as part of a comprehensive package of evidence-based interventions. First, it prevents HIV-related illnesses for the individual and averting AIDS-related deaths. For example, before antiretroviral treatment availability, life expectancy for a person living with HIV was reduced by approximately 12.5 years. Now, this same individual will have near-normal life expectancy. Second, treatment prevents transmission through the reduction of viral load, and, additionally, some newer antiretrovirals have high efficacy for primary prevention. Lastly, treatments have health and economic benefits in terms of averting new infections. Add in other impacts – such as labour productivity, orphan care, impact on communities and more – and these gains grow even more.

PrEP: A transformative treatment, yet barriers remain

PrEP, as one of the more recent developments, has the potential to prevent HIV transmission through the pre-emptive use of antiretroviral treatment in HIV-negative individuals considered at substantial risk of acquiring the virus (more than three per 100 people, in the years where PrEP was not available). In fact, a 2019 study by the Centers for Disease Control and Prevention (CDC) examined the impact of targeted outreach to Men Who Have Sex With Men (MSM) about PrEP, with PrEP awareness increasing from 60 to 90 percent from 2014 to 2017.2 Yet, despite increases in PrEP use, significant barriers to increasing PrEP among those at substantial risk for HIV remain. For many groups at risk of acquiring HIV, lack of access to appropriate health services is an issue, as is the stigma associated with sexual risk.

Additional barriers to usage include difficulty adhering to daily oral regimens and apprehension of side effects. Some solutions to these barriers are showing progress, including promising data from the HIV Prevention Trials Network 083 study on the long-acting injectable integrase inhibitor cabotegravir.3 The study also reported high adherence to the regimen, showing that it could be a safe and effective alternative for those who find taking a daily pill challenging.4
A decade of PrEP

For HIV-uninfected patients, PrEP using antiretroviral medications is an evidence-based way to prevent new infections among those at greatest risk. Shown to reduce the risk for HIV infection by greater than 90 percent, PrEP changed the course of prevention strategies for acquiring HIV. From oral pills to injectables, the evolution of PrEP is depicted in the timeline below.

Sources:
Despite the efficacy of PrEP, ending the HIV epidemic requires a preventive HIV vaccine. According to one prediction, the added benefit of an HIV vaccine could mean that incident cases globally from 2015 to 2035 could decline by as much as 49 million. A vaccine can reach populations at risk where PrEP may not be approved, affordable and easily accessible. Further, it could potentially help those struggling with adherence to daily oral medications or scheduling regular injections.

Lifelong antiretroviral treatment comes at a significant cost, particularly for low-income countries. Add to this the spread of drug-resistant strains and the cost increases, as do the treatment failures.

Yet, the journey to developing a safe and effective HIV vaccine has been fraught with challenges and failures. The virus’s highly variable nature — along with its ability to target and impair important host immune cells, to integrate into the host genome early in infection, and to then establish latency — has increased the complexity of developing vaccines. Further, as there is no known natural protective immunity in humans, there are no immune correlates to guide vaccine creation.

However, over the past decade, advances in scientific knowledge and new technologies have led to some successes and has helped frame the research agenda around HIV vaccine research. There have been many stop-starts, too many to include but some are worth noting in terms of the contributions they have made, one way or another. The RV144 study, which recruited over 16,000 participants in Thailand in 2003, with follow up for three years, was published in the New England Journal of Medicine (2009), and was the first time an HIV vaccine showed some level of protection, and offered the promise that a preventive vaccine was possible. Building on the scientific knowledge from RV144, researchers moved forward with developing vaccines for other studies, including in Sub-Saharan Africa to adapt to regional strains. One such trial was the Uhambo trial in South Africa. The Uhambo trial was halted in early 2020 due to lack of efficacy, so while these initially promising vaccines have not been found to greatly reduce risk, similar efficacy studies are still ongoing.

Other approaches, such as the Imbokodo trial (2017), are evaluating “mosaic”-based vaccine regimens, which use mosaic immunogens (delivered through a viral vector comprised of an inactivated common cold virus) — molecules that are capable of inducing an immune response to a wide variety of strains of HIV. This Phase IIb proof of concept study enrolled women aged 18-35 years of age in five countries across Sub-Saharan Africa, a region where more women than men are becoming newly infected with HIV. In fact, according to an UNAIDS report, in Sub-Saharan Africa, young women and adolescent girls accounted for one in four new infections in 2019, despite making up about 10 percent of the total population.

Looking forward, other innovative approaches to vaccines are garnering attention.

Still, in the preclinical phase, a new investigational vaccine from Moderna administers messenger RNA (mRNA). As we are all now aware, this same technique has shown very promising interim results against SARS-CoV-2, after recent Phase III studies showed its ability to promote the production of neutralizing antibodies and T-cell responses. Using this same technology for a HIV vaccine, this strategy “injests” instructions for making viral proteins to stimulate an immune response rather than using the traditional approach of administering a viral vector to deliver HIV proteins.

2015–2035 possible decline of 49 million

Other vaccine trials, such as PrEPVacc (to be launched in 2021 in Mozambique; South Africa; Tanzania; and Uganda), will be a combination efficacy study comparing two experimental vaccine regimens with placebo, with a concurrent open-label randomised PrEP arm.

The early positive results of Imbokodo have led to Mosaico, a Phase III trial, which began enrolling MSM and transgender people in Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain and the United States in 2019. Mosaico is testing a similar mosaic vaccine regimen with an added protein, aimed at Clade B, a strain often found in North America and Europe. Other vaccine trials, such as PrEPVacc (to be launched in 2021 in Mozambique; South Africa; Tanzania; and Uganda), will be a combination efficacy study comparing two experimental vaccine regimens with placebo, with a concurrent open-label randomised PrEP arm.

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The COVID-19 effect on HIV

When new viruses present themselves in our population, such as HIV, uncertainties arise from epidemiology to clinical presentation. Over the decades, the HIV/AIDS pandemic has taught us many lessons, providing an opportunity to apply these learnings to the current COVID-19 pandemic.

Reducing new HIV infections has required a combination of interventions, along with the inclusion of affected communities in the planning and implementation of clinical research and patient care. Through HIV, the healthcare industry learned that accurate and timely information is needed to enable and guide interventions. Investment into research for HIV treatments not only led to major decreases in new infections, but also a better quality of life and lower mortality for people living with HIV – without a vaccine. Moreover, HIV has shown that the timing of an intervention during the disease life cycle is critical to a therapy’s impact.

Further, HIV illustrated that collaboration between researchers and the community was more than feasible – it improved the scientific process. For example, advocates pressured scientists to act quickly, transparently, and to clearly communicate scientific rationale, resulting in shorter timelines for scientific investigation, regulatory review and implementation of effective interventions.

Like HIV, initial COVID-19 prevention measures were behavioural, and combating this virus will require nonpharmacologic public health strategies, even after effective therapies or vaccines are identified. Similarly, early intervention will be key to preventing the spread of COVID-19, as well as disease progression. Therefore, a combination of strategies for preventing and treating COVID-19, could include pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and vaccines.

COVID-19 clinical trials should be well coordinated and implemented, with results being clearly and objectively analysed and interpreted. As solutions develop to the COVID-19 pandemic, sponsors should consider a coordinated effort to ensure diversity is represented in clinical trials. Additionally, trials should not be solely focused on evaluating either medical therapies or behavioural interventions, since testing, social distancing measures, the use of masks, and the use of preventive or therapeutic therapies all have social and behavioural components. As such, clinical and public health efforts will require strategic and multidisciplinary teams.

Considerations for HIV clinical trials amid a pandemic

Like many other therapeutic areas, ongoing clinical trials with patients at risk, or living with HIV, have felt the disruptions caused by the pandemic. Therefore, sponsors should implement new strategies to manage these clinical trials and to reduce the risk of infection to trial participants and staff – such as only conducting visits in-person when absolutely necessary, with the remainder being conducted through remote means. Moreover, incorporating decentralised elements – such as home health care or using alternative site solutions – into a trial can ensure uninterrupted access to HIV treatments and services, while further reducing contact with clinics.

Sources:


Next steps in clinical research to address today’s challenges

As research into newer treatments and vaccines, and as PrEP evolves, more attention needs to be given to engaging relevant at risk groups in research strategies and agendas to ensure adequate representation, not only in the dialogue around access and accessibility, but also in clinical trials and other research interventions. Clinical trial design, research approaches and surveillance, which consider and account for the needs of people living with HIV, and those substantially at risk of acquiring it, is a worthwhile endeavour. Many tens of thousands of research participants are needed to continue to drive this agenda.

With increasingly efficacious prevention options, future clinical trial designs are becoming more complex. As such, developing innovative strategies to engage participants in research at the outset, and to support their adherence and ongoing participation is key. Suspicion of clinical research, the pharmaceutical industry and healthcare providers requires focused approaches to encourage and sustain participation. Leveraging newer tools and approaches in clinical research may be particularly beneficial in engaging participants in clinical trials. Incorporating digital health technologies, such as wearables, in addition to decentralised and virtual trial approaches, including home care options, can increase patient engagement and retention in trials.

“...The use of these prevention measures, which can reduce HIV incidence among trial participants, may also impact the assessment of vaccine.”

Exploring clinical trial models from agile to decentralised

The evolving HIV prevention landscape can challenge the design of vaccine efficacy trials. Sponsors will need to consider the use of active controls, study populations, standards of prevention, primary or surrogate endpoints and biomarkers, as well as flexible or adaptive, trial designs.

For example, many trials include an HIV prevention package that may include risk reduction counselling, free condoms, sexually transmitted infection testing and treatment, and education around and access to oral PrEP. Yet, the use of these prevention measures, which can reduce HIV incidence among trial participants, may also impact the assessment of vaccine efficacy. Therefore, clinical trials become a balancing act between the ethics of providing participants HIV prevention and enabling an adequate efficacy trial. Further, designs must reflect the diverse cultural, lifestyle and biological circumstances that influence individual decision-making around the use of HIV prevention strategies, which may change over the course of a trial. Agile trial designs can impact clinical operations with regard to enhancing recruitment and the informed consent process. Community and the participant’s awareness, input, education and attitudes toward such a design will need to be confirmed. In addition, recruiting a wide network of sites will be required to ensure a trial enrols inclusive, diverse patient population. Moreover, regulatory challenges include having a precise statistical analysis plan that would be prepared either prior to the trial, such as by including a protocol for approval, or during the study, which would entail defining specific activities, such as interim analyses and other changes.

In addition, sponsors should consider decentralised alternatives to the traditional site model. Incorporating home healthcare services — where nurses can conduct site visits within a patient’s home — into protocols has many benefits including reducing patient burden (decreasing travel issues), increasing patient retention (mindful of stigmas in participation) and keeping trials running during emergency situations (pandemic-related travel disruptions). Additionally, sponsors can employ technologies, such as telemedicine, to reach patients.

Other considerations include protocols that don’t require on-site monitoring. Instead, remote monitoring can allow clinical research associates to review clinical trial materials, such as source documents, reducing travel.

Home healthcare:

- Technology
- Telemedicine

Reducing patient burden
Increase patient retention
Keep trials running during emergency situations

We have already seen much progress in these approaches during the last ten months, not only with respect to trial participants but also in relation to study staff and teams leveraging technology to reduce contact and interactions with sites.
Digital health technologies

Within the context of HIV clinical trials, digital health technologies are being used to measure adherence to antiretroviral therapies. Some examples include programmes in South African and other Sub-Saharan countries to engage women in HIV prevention treatment using text messaging for interventions. Despite successes in the use of digital health as interventions, in some settings, patients may have limited access to new technologies, and, as a result, challenges remain in bringing innovative approaches to HIV prevention in areas with some of the greatest needs.

When designing digital health interventions, sponsors will need to develop solutions that are engaging, age-appropriate and take advantage of technologies that are already embedded in these individual’s lives. As such, wide-scale adoption of smartphone technology has led to its popularity as a platform for delivering adherence interventions targeting PrEP. One example currently in clinical trials is P3 (Prepared, Protected, emPowered), an interactive smartphone app that utilises game mechanics and social networking features to improve PrEP adherence, retention in PrEP clinical care, and PrEP persistence among young MSM and young trans women who have sex with men, ages 16-24.

Further, smartphone interventions can address issues that often impede engagement with in-person interventions such as transportation logistics, stigma and confidentiality. Some examples include apps for locating HIV testing services, web-based programmes for counselling and gamification to educate about HIV risk. Other trends include the use of social network sites and wearables for real-time assessment and feedback. Ultimately, digital health technologies bring the opportunity to facilitate large-scale dissemination of information and effective delivery of tools to help promote and maintain behavioural modification.
Considerations for patient-centricity when designing trials for people at-risk or living with HIV

People at risk for or living with HIV face the challenges of stigma and discrimination, both of which are known to negatively affect quality of life, as well as treatment outcomes. Therefore, sponsors will need to be aware of the societal stigma associated with HIV, including participation in HIV clinical trials. As such, sponsors will need to provide sensitivity training to staff and sites. For example, rather than providing smartphones for collecting patient diaries, sponsors may consider BYOD (bring your own device) to reduce stigmas, as patients may be questioned about why and how they received new devices.

ICON uses a hybrid approach with the combination of three critical elements: Home Health Care (HHC) services, virtual visits, and implementing an end-to-end participant engagement platform to promote study compliance. Through its In-Home & Alternative Site Solutions, ICON can deploy specially trained nurses/teams to conduct certain visits in the participant’s home. These services reduce travel burden on participants and their families, whilst home visits offered outside normal business hours to accommodate participants’ schedules facilitate better compliance.

Virtual visits using telemedicine allow the investigator to observe the participant, instruct them to complete assessments and record their observations. ICON partners with technology vendors to provide telemedicine and end-to-end data capture. Participant communication and education is key. Providing a Study App with notifications, reminders and surveys allows for communication and remote data collection directly from the participant, thus the investigator and study team are not waiting for a participant to attend an on-site visit for data collection or download. Having the participant app provided via an end-to-end digital tool, allows the participant to have one access point for recording data. Combining this with the deployment of eConsent through ICON’s FIRECREST portal eases the burden on both participants and study teams,

The HIV care and prevention continua and eHealth interventions

Testing
- Home text kit with video instructions and modules for partner communication
- App-synced home text kit to trigger counselling support by phone
- App-based product ordering, scheduling and reminder support

HIV - Negative
- Interactive web-based game to engage and educate adolescents
- Culturally appropriate stories and scenarios presented by app
- Empowering social media group to reduce risk behaviours, improve mental health and social support

HIV - Positive
- Web-based content presented in diverse formats, including messaging boards, games, peer support, and trained counselling
- Web-based program for adolescents in outpatient substance abuse treatment to learn about preventing secondary transmission

Education
- Web-based modular content originally developed for in-person counselling
- Journaling of risk behaviours and substance use in app with individualised response messaging
- App notification reinforcing safer sex if smartphone geolocator near gay venues or use opens sexual networking app

Behavioral change
- Tailored messaging and navigation of local services
- Promotion of local testing and primary care resources using sexual networking apps in areas with no physical venues for MSM

Linkage to care
- Smartphone app to identify local resources for culturally appropriate HIV care for African-American MSM
- Home HIV testing with web-based counselling and proactive support for locating treatment options

HIV care
- Monitoring of recent sexual behaviours with tailored response messaging
- Video vignettes using social thinking and social-cognitive theories to support condom use, serostatus disclosure

Care support
- Self-care app using social networking, games and adherence support
- Home-based self-care program to address psychosocial impact of HIV
- Self-care app for adherence, mental health, suitable appointments
- Smartphone game to improve ART adherence for young patients

Primary care
- Web-based self care program to address psychosocial impact of HIV
- Self-care app for adherence, mental health, suitable appointments
- Smartphone game to improve ART adherence for young patients

HIV care
- Web-based self care program to address psychosocial impact of HIV
- Self-care app for adherence, mental health, suitable appointments
- Smartphone game to improve ART adherence for young patients

P/EP
- Self-care app using social networking, games and adherence support
2021 and beyond: A new outlook for HIV

As 2020 comes to an end, we have witnessed a shift from conventional antiretroviral therapy combinations (now more than 30 antiretroviral drugs) to new treatments on the horizon. Some of these exciting new investigational products include the use of broadly neutralising antibodies (bNAb) for HIV prevention and treatment, as well as gene-based treatments. The most advanced of these trials is evaluating whether giving HIV-negative people a bNAb, called VRC01, as an intravenous infusion every eight weeks is safe, tolerable and effective at preventing HIV. Novel bNAb, which are being optimised in the laboratory, have been proven to be more potent and broad-acting than PrEP. What’s more, they can potentially be administered by subcutaneous injection rather than intravenous infusion.

Another early phase technology, IGS-6307 Gilead, consists of an injection of small molecules that disrupt the function of HIV capsid protein, essential for multiple phases of the viral replication cycle. Results of this Phase Ib trial, published in Nature, demonstrated the potential of lenacapavir as a long-acting agent to treat or prevent infection with HIV.

IAVI (International AIDS Vaccine Initiative) continues to forge ahead with its work on HIV vaccines, having also expanded its scope to include other diseases. Acknowledging the complexity of finding a vaccine for HIV and the fact that traditional approaches to vaccine development have failed us to date, IAVI is now pursuing innovative strategies to design vaccine immunogens to activate both arms of the adaptive immune response (B-cell and T-cell immunogens) as well as investing in innovative HIV vaccine technologies - including one which, as outlined above, has gained public focus in recent weeks due to the emergence of some very promising SARS-CoV-2 vaccines - mRNA technology as well as the use of a replicating viral vector such as vesicular stomatitis virus (VSV). IAVI is currently working on a recombinant VSV vector incorporating an HIV Envelope gene, now being tested in preclinical studies, an approach which may also have therapeutic applications. The search continues.

Moreover, gene therapies on the horizon have the potential to change HIV treatments for people living with the virus, turning the current regimen of a daily cocktail of medications into a possible lifetime cure. For example, the University of Southern California and the Fred Hutchinson Cancer Center are working to engineer blood cells that confer immunity to HIV from a patient’s own stem cells. Equally exciting, researchers from Harvard University developed a dual CAR T-cell immunotherapy to not only target and eliminate HIV-infected cells, but also reproduce in the body to enable the patients to fight off the infection. These novel advanced therapies will call for innovative trial designs, which will require the necessary expertise to navigate regulatory bodies and optimise study protocols and operations.

Despite not reaching the ambitious 2020 goals set forth by 90-90-90, there remains great potential to get there in the near future. Over the course of the next decade, we will continue to witness more innovative treatments, from preventive to curative, as the HIV community works to reduce new HIV infections to a level where it is no longer considered a public health threat.

Further reading

Infectious Diseases
ICON has worked on over 250 infectious diseases clinical studies, including numerous HIV studies.
ICONplc.com/ID

Vaccines
ICON has led development of 17 vaccines resulting in FDA/EMA approval. We are currently working on a number of COVID-19 vaccine trials.
ICONplc.com/vaccines

Government & Public Health Services
ICON provides full-service clinical development and staffing services across multiple agencies in the U.S. Government and is a preferred BARDA partner. We have over 20 years of experience in Africa, across 27 African and Middle East countries
ICONplc.com/GPHS
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Advancing the future of global health

For over 30 years we have been at the forefront of preparing for, and fighting, global epidemics and pandemics.

Our clinical development expertise extends across basic, applied, and clinical infectious diseases biomedical research, and vaccines development and testing.

We have partnered with biopharmaceutical companies, US Federal agencies, non-government organisations and multinational public health organisations to deliver clinical trials that develop treatments and vaccines.

Our work is supporting the mission of improving global health, fighting pandemics such as HIV and COVID-19, and epidemics such Malaria, Ebola or Zika virus.

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ICON plc is a global provider of outsourced drug and device development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. The company specialises in the strategic development, management and analysis of programs that support clinical development - from compound selection to Phase I-IV clinical studies. With headquarters in Dublin, Ireland, ICON currently, operates from 94 locations in 40 countries. Further information is available at ICONplc.com/contact

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