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Overlapping Impacts of HIV/COVID-19 Pandemic on HIV Vaccine Development

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ABSTRACT

The quest for a safe and effective HIV vaccine holds life-saving potential for people globally. Interestingly, the HIV/COVID-19 overlapping pandemic have impacted each other in diverse ways, some being advantageous, while others detrimental. On one hand, the HIV platforms for development of rapid test kits, neutralizing antibodies, vaccine development and trials, collaboration and mobilization etc. has proved very helpful and a promising template for the development of interventions for the COVID-19 pandemic; while on the other hand, a number of ongoing HIV vaccine safety and efficacy trials are being abridged, stopped or suspended amidst the Coronavirus Disease-19 (COVID-19) crisis. The COVID-19 outbreak that begun in Wuhan, megacity of China late December, 2019, has spread to 220 countries and territories, with more than 36 million total confirmed cases and 1,057,505 total deaths globally as at 08 October, 2020 and still counting. Currently, no approved vaccines exist to prevent infection with the novel Coronavirus, however, the impact of the pandemic has been enormous with devastating effects on the global health and economy, with many countries introducing stringent response measures to de-escalate the spread of the virus. Recruiting and retaining volunteers for HIV vaccine trials this period has become very challenging due to a lot of factors including fear of potential exposure to the new coronavirus, ethical issues and safety concerns amongst others. The protection and safety of participants and clinic staff remain a priority for HIV vaccine investigators worldwide. They are at the moment making conscious efforts to execute measures necessary to prevent potential exposure and transmission of COVID-19 among study participants and clinic staff in various study sites. This review takes a look at the overlapping impacts of the HIV/COVID-19 pandemic on HIV vaccine development.

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Introduction

Human immunodeficiency virus (HIV) infection remains one of the largest pandemics in the world with 0.8% global prevalence in 2018. According to the World Health Organization (WHO), an estimated 37.9 million people are living with HIV in 2018, with the sub Saharan Africa region being the most affected (25.7 million), follow ed by the South-East Asia (3.8 million), America (3.5 million), Europe (2.5 million), Western Pacific (1.9 million), Eastern Mediterranean and others (0.5 million). About 21.7 million people accessed antiretroviral therapy, 1.8 million people became newly infected and an estimated 770,000 people died from AIDS-related illnesses in 2018 [1-5].

While virologists and vaccine developers are racing to find safe and effective vaccines for the prevention of the HIV/AIDS pandemic that have bedeviled humanity for decades now since 1981, cases of atypical pneumonia among persons who had either visited or had consumed food from the live animal market in Wuhan City, in the Republic of China was reported to the World Health

Organization (WHO) in December, 2019. Since then, cases have been exported to other Chinese cities, as well as internationally. On January 7, 2020 the WHO announced that they had identified a new virus responsible for the atypical pneumonia. The Severe Acute Respiratory Syndrome Virus- Coronavirus-2 (SARS-CoV-2) as it is now known is an enveloped non-segmented positive sense single-stranded RNA virus in the Coronaviridae family, which also includes SARS and MERS. As the virus continued to spread globally like a wide fire, the WHO eventually declared the coronavirus outbreak a pandemic officially on March 11 2020 [6-11].

Currently, the virus has spread to about 220 countries and territories, with more than 19 million total confirmed cases and still counting. Currently, no approved vaccines exist to prevent infection with the novel Coronavirus [12-14], however, the impact of the pandemic has been enormous with devastating effects on the global health and economy, with many countries introducing stringent response measures aimed to stop the rapid spread of the virus. These include: travel restrictions, closure of borders, schools, religious gatherings and businesses and asking people to stay home amongst others [6, 15].

Furthermore, since the fight against the pandemic started, thousands of healthcare professionals have been exposed and infected, with many paying the ultimate price with their lives in a bid to provide healthcare services to COVID-19 patients. Currently, many are either in quarantine or isolation. Still, many are working in fear of the virus and under poor conditions, without adequate protection or life insurance. At the onset of the pandemic, wild conspiracy theories about Bill Gates and the new coronavirus emerged online. Perpetrators of the conspiracy theories have accused Bill Gates of creating the virus himself, had it patented and seeking to use Coronavirus vaccine as a gambit to monitor and control people through an injected microchip or quantum-dot spy software. The Gates conspiracy theories are part of an ocean of misinformation on COVID-19 that is spreading online. These false claims have gone viral and have resulted in several anti-coronavirus vaccine protest rallies, as well as destruction of 5G phone masts in different parts of the world following a conspiracy theory that linked 5G radiation to the coronavirus. Amidst misinformation, disinformation, fear of the Coronavirus and associated global crises, a number of ongoing HIV vaccine and immunotherapy efficacy trials are being paused or curtailed. The HIV Vaccines Trial Network (HVTN) on Monday 24 March, 2020, officially announced that several of its large-scale safety and efficacy trials would be shortened, paused or postponed and since then, a number of other study investigators have made similar decisions [16-21]. Recruiting and retaining volunteers for HIV vaccine trials have thus become very challenging this period. The COVID-19 era has generated a lot of fears, fake news and conspiracy theories that is likely to impact negatively on the success of recruitment and continuous participation of volunteers for the HIV vaccine clinical trial. To this end, this review takes a look at the overlapping impacts of HIV/COVID-19 pandemic on HIV vaccine development.

Search for A Safe and Effective HIV Vaccine

A safe, potent and accessible vaccine is ultimately required to complement and enhance the effectiveness of existing prevention strategies to control the HIV/AIDS pandemic globally. While vaccination is the most effective medical intervention ever recorded in human history; vaccine research, development and production is a financially demanding and huge task requiring months to several years of pre-clinical and clinical trials before advancing to the licensure stage. The World Health Organization (WHO) criteria for candidate vaccine evaluation and prioritization include: safety profile (25 points), potential for efficacy (25 points), vaccine stability (10 points), vaccine implementation (15 points) and vaccine availability (25 points) [22-24].

The pre-clinical development stage involves research in the laboratory using tissue culture and animals. This is targeted at identifying vaccine candidate antigens, creation of vaccine concept, evaluation of vaccine potency in test tubes and animals and the manufacture of the vaccine. This then progresses to the clinical development stage which is composed of three clinical trial phases. This is when the vaccine is first tested in humans. Clinical trials are built on rigorous ethical principles of informed consent from volunteers, with emphasis on vaccine safety as well as efficacy before presentation for licensing [23]. When candidate vaccines make it to human clinical trials, they first go through Phase 1 trials primarily to test the vaccine's safety, determine dosages and identify any potential side effects in a small number of people (1-100 volunteers). Phase 2 trials further explore safety and start to investigate efficacy on larger groups (100-1000 volunteers). The final stage, Phase 3 trial, which few vaccines ever make it to, involves a much larger number of people (1000-10000 volunteers), to confirm and assess the effectiveness of the vaccine and test whether there are any rare side effects that only show up in large groups [25]. So far, the National Institute of Health (NIH) has evaluated 23 candidates and 10 adjuvants in 49 Phase I and Phase II clinical trials to determine the safety of HIV vaccine candidates and their effect on the human system [26-30].

Developing an effective HIV vaccine is not an easy task. One approach to a preventive HIV vaccine involves trying to elicit broadly neutralizing antibodies in healthy people. Some people with HIV infection make antibodies that can neutralize multiple HIV strains. Not only are the antibodies directed against their own virus strain, but also against different subtypes of HIV that circulate worldwide. These broadly neutralizing HIV antibodies (bnAbs) bind to structures on the surface of the virus which barely change and are identical in different viral strains. Dubbed "spikes," these sugar and protein complexes are the only surface structures that stem from the HIV virus itself and can be attacked by the immune system via antibodies. Scientists have studied these antibodies to find clues about how they bind to the virus and neutralize it. Due to their broad impact, these antibodies constitute a promising cornerstone for the development of an effective vaccine against HIV in the future [31-35].

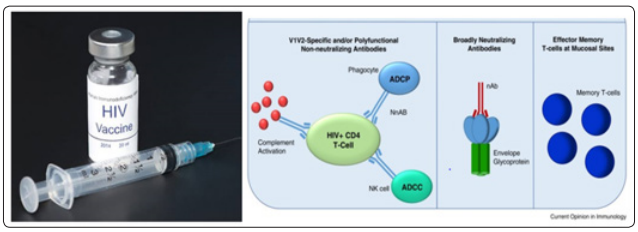

Figure 1: Potential Correlates of Protection for the New HIV Vaccine Studies

In 2016, scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID) identified an epitope (Called the HIV fusion peptide, it's part of the HIV surface receptor that helps the virus enter a person's cells) that's thought to be similar across most HIV strains. The research team engineered proteins called immunogens that were designed to activate an immune response against the HIV fusion peptide based on its known structure. The team tested which immunogens most effectively elicited HIV-

neutralizing antibodies to the fusion peptide. The best immunogen consisted of eight amino acids of the fusion peptide bonded to a carrier protein often used to boost the immune response. To improve their results, the team paired this immunogen with a replica of the HIV spike. They tested several vaccine regimens in mice and analyzed the antibodies generated. Antibodies prompted by the vaccines attached to the HIV fusion peptide and neutralized up to 31% of viruses in a panel of 208 HIV strains from around the world. The researchers used the lessons learned from these experiments and tested modified vaccine regimens in guinea pigs and monkeys. These animals also formed broadly neutralizing antibodies that were active against dozens of HIV strains. These findings in mice, guinea pigs, and monkeys show that the vaccine regimen can work in several species. The scientists are now working to improve the regimen and test it further in monkeys. A small study of the new HIV vaccine was anticipated to commence in late 2019. NIH scientists have used their detailed knowledge of the structure of HIV to find an unusual site of vulnerability on the virus and design a novel and potentially powerful vaccine [36-38]. This elegant study and others represent a potentially important step forward in the ongoing quest to develop a safe and effective HIV vaccine.

Challenges Facing HIV Vaccine Development

HIV infection involves an 'arms race' between the immune system and a virus that is always one step ahead of it. Developing an effective and safe HIV vaccine has been a global public health necessity, but so far, researchers are yet to have a breakthrough in this regard. Identified hurdles over the past 30 years include: 1) The tremendous genetic variability of HIV: There are many different strains of the virus with amazing ability to rapidly mutate, 2) The HIV envelope is coated with host derived sugars (Glycan shielding) that the human immune system cannot recognize as foreign, 3) Lack of reliable immune correlates, 4) Absence of a good animal model in which to test HIV vaccines. It is not possible to test a vaccine in humans without testing it first in animals. The immune systems of small animals like mice, rabbits, and guinea pigs are too different from the human immune system to be helpful. Rhesus monkeys are primates whose immune system is much closer to that of humans, but HIV cannot infect or replicate in monkeys, unless it is genetically modified, 5) Associated risk of working with HIV in the laboratory due to its infectious nature. This limits the number of laboratories that can work on HIV. The above and many more explain the disappointments and failures recorded by past HIV vaccine clinical trials [39,40].

Impacts of COVID-19 Pandemic on HIV Vaccine Trials

The novel coronavirus (SARS-CoV-2) has been reported to be highly infectious and transmissible [16]. Human-to-human transmission of SARS-CoV-2 is mainly through respiratory droplets from infected individuals, contact with contaminated objects and surfaces and social activities like hand-shaking and hugging [6]. The virus is spread in droplets or droplet nuclei released from the nose and mouth of an infected person when they sneeze or cough. Once the virus becomes airborne, it may remain suspended in the air for up to 8 hours depending on the prevailing environmental conditions such as temperature and relative humidity [41]. As of October 08, 2020, the COVID-19 virus has spread to 220 countries and territories, with 36,265,982 total confirmed cases and 1,057505 total deaths globally (Figure 2). The top 14 most hit countries as indicated by Johns Hopkins University Center for Systems Science and Engineering [12] are: US (7,560,010), India (6,835,655), Brazil (5,000,694), Russia (1,253,603), Colombia (877,684), Argentina (840,915), Spain (835,901), Peru (835,662), Mexico (799,188), France (711,642), South Africa (685,155), United Kingdom (546,959), Iran (488,236) and Chile (476,016).

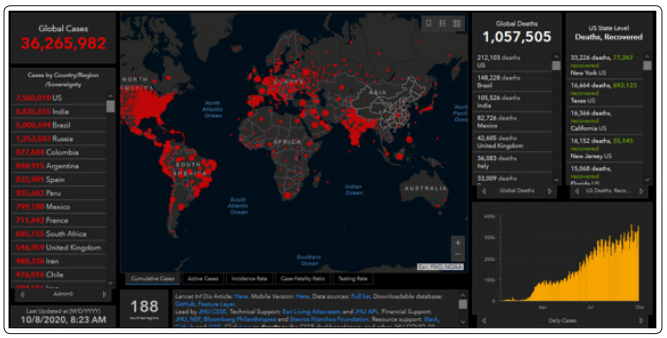

Figure 2: COVID-19 Global Cases by JHU-CSSE as of October 08, 2020

As indicated above, the United States of America has been far hit by the COVID-19 pandemic than other countries. The virus has continued to threaten efforts to address existing health challenges, including the HIV/AIDS epidemic. Last year, before the emergence of the novel virus, the United States of America commenced implementing "*Ending the HIV Epidemic - EHE*", *a plan for America* to significantly reduce new HIV infections through a combination of diagnostic, treatment, and preventive efforts. At the moment, the US economy, health system and workforce needed to address the HIV epidemic are being stretched thin to confront this new coronavirus crisis [15, 42]. Immunocompromised individuals, including those living with HIV are at greater risk of the COVID-19 pandemic. Other factors compounding the risk of serious illness from COVID-19 among people living with HIV, even those with controlled HIV through treatment, are higher rates of certain comorbidities including hypertension, diabetes, cardiovascular disease, pulmonary disease, liver disease and renal failure, than in the population overall. Also, lop-sided numbers of people living with HIV are in the South where COVID-19 death rates are trending higher and health systems are strained to provide even basic care. This situation is further complicated as with HIV, not everyone with COVID-19 displays symptoms right away, or at all. Worst still, major HIV vaccine trials that were initiated before this time have been being shortened, paused or postponed amidst the COVID-19 pandemic due to fears of potential risk of exposure to the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) among study participants and clinic staff: First, is a multi-million dollars HIV vaccine trial (HVTN 702- Uhambo), led by Dr. Larry Corey (the principal investigator) formerly launched by HIV Vaccine Trials Network (HVTN) in October 2016 in South Africa. This trial aimed at testing the safety and efficacy of a new version of a candidate vaccine (ALVAC-HIV + subtype C gp120/MF59 studied in the landmark RV144 clinical trial in Thailand with 31% effectiveness (a phase IIb and III trial) has been abruptly stopped two years before it was scheduled to end. The trial was supposed to last until July 2022, but on 23 January, 2020 an independent monitoring board announced that it was "futile" to continue". Following this development, the United States National Institutes of Health officially announced the termination of the HVTN 702 clinical trial on Tuesday February 4th 2020 at Geneva [42-48]. Although no evidence exists that the vaccine caused harm, as happened in a different large HIV vaccine study that was abruptly halted in 2007, the reason for the sudden termination of the vaccine trial may not be unconnected to the risk of COVID-19 transmission among study participants and clinic staff. While vaccination was terminated in February 2020,

participant follow-up will continue at the 14 trial sites for the next one year. The leadership of the Uhambo study has empowered each participating site to implement measures aligned to guidance from the local public health authorities and Ethics Committees. This includes expanding visit windows, delaying visits and/or conducting some visit procedures remotely.

The second, is the Mosaico clinical trials (HVTN 706/HPX3002) initiated in Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain and the United States involving about 3,800 participants at 57 trial sites. The Mosaico is testing an investigational mosaic based vaccine regimen, the same as that of Imbokodo, with the goal of determining if it is effective in preventing HIV infection in HIV negative men who have sex with men (MSM) and transgender individuals aged 18-60 years. With the emergence of the COVID-19 pandemic, the leadership of the Mosaico study temporarily paused all new screening, enrollment, and vaccination visits to ensure the health and safety of study participants and clinic staff. The Pause, has however been reassessed and lifted. Results are expected in 2023. Janseen (the developer of this vaccine) is currently leveraging on the HIV vaccine platform for the development COVID-19 vaccine. The third, is the twin Antibody Mediated Prevention (AMP) clinical trials (HVTN 703/HPTN 081, HVTN 704/HPTN 085). One study involves women in African countries including Kenya, Malawi, Mozambique, Tanzania, Zimbabwe and South Africa; the other involve men and transgender individuals in 11 countries including Switzerland, Botswana, Peru, Brazil and the United States of America. The two studies were launched in April, 2016 and results are expected later this year (2020). The AMP is testing whether a broadly neutralizing antibody called VRC01 can prevent HIV acquisition in people [49-53]. A total of 4,625 participants have so far been enrolled for the study, however, with the emergence of the highly dreaded Coronavirus, the leadership of the AMP studies has been forced to discontinue all further infusions in the interest of participants and clinic staff safety. Never-the-less, participant follow-up continues, utilizing remote or in-person visits as feasible. The good news here, according to the investigators, was that the data accrued on infusions already administered are sufficient to achieve the study objectives.

The last, but not the least is the Imbokodo clinical studies (HVTN 705/HPX2008) initiated in some African countries mainly Malawi, Mozambique, South Africa, Zambia, and Zimbabwe in November, 2017. The Imbokodo is testing an investigational vaccine regimen based on mosaic immunogens – vaccine components comprising elements from multiple HIV variants – designed to offer protection against a variety of global HIV strains. The study enrolled 2,600 HIV-negative sub-Saharan African women aged 18-35 years with the goal of determining if the vaccine regimen is effective in preventing HIV infection. The study has since completed enrollment on May 28, 2019, and now continues in follow-up. Despite considerable investment in prevention during the trial, there was still an HIV incidence of around 4% per year among the women in the trial. To ensure the health and safety of study participants and clinic staff as the COVID-19 continue to escalate globally, the leadership of the Imbokodo study has issued guidance that is specific to the particular circumstances of participating countries and study sites. Where appropriate, this guidance may include temporarily pausing vaccinations. Results are expected in 2021 [54, 55].

The above reports and many more, clearly indicate that the search for the development of a safe and effective HIV vaccine has been negatively impacted by many challenges including the emergence of the COVID-19 pandemic. Though the HIV vaccine trial in southern Africa was not successful, it is a "wake up call" for virologists and vaccine developers. To this end, the World Health Organization (WHO), the HIV Vaccine Trial Network (HVTN) and other important stakeholders must reiterate their commitments in monitoring and ameliorating the impact of COVID-19 on the conduct of the early and large-scale HIV vaccine clinical trials, with emphasis on the safety of all study participants and clinic staff. Worthy of note is the fact that the COVID-19 pandemic can be leveraged upon to promote HIV vaccine development. This is based on the fact that the COVID-19 pandemic has to a great extent reawaken the government and other funding agencies to the need to equip hospitals and research laboratories to facilitate viral studies. Greater breakthroughs are expected if these opportunities are leveraged upon.

Benefits of HIV on COVID-19 Pandemic

The rapid advances in response to and containment of the COVID-19 pandemic have leveraged on lessons learnt from the HIV pandemic. Researches on intervention have successfully used the HIV platforms as templates. Examples of such areas include:

1. Strategies for isolation and manufacture of neutralizing antibodies which has entered already into the clinical trial stage [56].
2. Protocols for combination antiviral therapy [57].
3. Rapid point-of-care testing methods/protocols especially for low and middle-income countries [58].
4. Novel vaccine platforms which includes nucleic acid-based vaccines such as DNA, RNA and live vectors. Some of this approaches have already entered into 2nd and others 3rd clinical stage trial [59].
5. Conversely, many of the equipment and infrastructure that where purchased under the pressure of the COVID-19 pandemic has potentials of being of great advantage to viral research generally. This is evident by the fact that a large population of companies that had never been into viral research and manufacturing have as a matter of necessity reorient their focus and are now seriously involved in it. This has to a large extent also opened up opportunities for inter- disciplinary research.
6. Though there are grave short term impacts of COVID-19 on HIV research and services such as the halting or slowing down of almost all clinical trials globally, transformative advances being achieved in the response to COVID-19, could be leveraged upon through strong collaborations to achieve great research and intervention outputs in the nearest future [60,61].

Recommendations

In line with the guidelines laid down by the WHO and HVTN, we therefore make the following recommendations to reduce the risk of transmission of COVID-19 among study participants and clinic staff in ongoing HIV vaccine trials:

Limit Facility Risk

- Points of entry should be limited and visitors properly managed.
- Everyone entering the facility should be screened for COVID-19 symptoms. A health worker should always be stationed at the entrance of the facility, to check participant's temperature (using infrared thermometer), disinfect their hands (using alcohol-based sanitizer) and to ask them about their symptoms and document the same.
- Volunteers should be attended to individually and as soon

as they arrive.
- Clinic waiting time and contact time between study participants and clinic staff should be reduced to the barest minimum.
- Those with a scheduled appointment should contact the site before visiting if they develop any complication or suffer any adverse effect.
- Sufficient ventilation in the facility must be ensured.
- Potentially contaminated surfaces should be disinfected before starting any procedure.
- Medical devices/equipment must be sterilized before use.
- High level environmental sanitation must be ensured in the facility.
- Medical wastes including used vaccine vials must be properly decontaminated and disposed-off.
- Entrance into the vaccination area should be restricted.
- The facility should have a robust surveillance system for effective infection control and prevention.
- Surveillance data should be readily made available for continuous quality improvement.
- Incidence should be acted upon, documented and reported immediately.
- Training and re-training should be provided for infection control and prevention personnel.
- The safety officer must ensure frequent monitoring of adherence to safety practices.

Protect Self and Others
- Physical contacts should be minimized. Instead telephone calls and scheduled virtual visits should be encouraged.
- Barriers should be installed to limit physical contact with study participants at triage.
- Clinic staff must be provided with adequate Personal Protection Equipment (PPE) before attending to study participants.
- Hand and respiratory hygiene must be practiced at all times.
- Aerosol generating procedures should be minimized as much as possible.
- Use of respirators for aerosol generating procedures should be prioritized.
- Spatial separation (Social distancing) in the waiting or working area should be observed.
- Safe vaccination procedures must be ensured.
- The temperatures of the clinic staff and participants must be monitored always upon entering the clinic.
- Mass screening of clinic staff with asymptomatic infection must be carried out periodically [62-64].

Conclusion

The protection and safety of participants and clinic staff must remain a priority for HIV vaccine investigators. They must make conscious efforts to implement measures necessary to prevent the potential exposure and transmission of COVID-19 among study participants and clinic staff in various study sites. All preventive measures should align with the recommendations and guidance from the local public health authorities and Institutional Health Research and Ethics Committees. Despite drawbacks, virologists and vaccine developers must not relent in their quest for a safe and effective HIV vaccine, rather they should redouble their efforts and build on past lessons. The scientific integrity of each clinical trial must not be compromised for economic gains. The World Health Organization with other stakeholders must continue to monitor the impact of COVID-19 on the conduct of the early and large-scale clinical trials globally. Although developing an effective HIV vaccine is not an easy task, a break-through in the field of HIV vaccine research and development amidst the COVID-19 pandemic will definitely revolutionize HIV infection control and prevention globally. There is therefore an urgent need to bring together researchers from different disciplines, institutes and continents in new collaborations through which knowledge can be exchanged and new research ideas in the field of HIV vaccine and vaccinology can be generated and investigated. Bringing new researchers into this field, and progressing the careers of early career researchers is a potentially important step forward in the ongoing quest to develop a safe and effective HIV vaccine amidst the COVID-19 pandemic.

Competing Interests

The authors have declared that no competing interests exist.

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