Next generation HIV vaccines and delivery methods
A promising approach to fight AIDS

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INTRODUCTION ON HIV & AIDS

After the first cases of Human Immunodeficiency Virus (HIV) were reported in 1981, the new disease was given a name: AIDS (Acquired Immune Deficiency Syndrome). The natural process of human immunodeficiency virus type 1 (HIV-1) infection is characterized by a high viral load, immune cell exhaustion, and immunodeficiency, leading eventually to the stage of acquired immunodeficiency syndrome (AIDS) and opportunistic infections [1].

Major advances in HIV-testing, treatment with life-saving anti-retroviral therapy (ART), which was introduced in 1995 and prevention including pre-exposure prophylaxis (PrEP) led to a decreasing incidence of AIDS-related morbidity and mortality in subjects living with HIV. Today, a person living with HIV can expect to die of old age from causes unrelated to HIV/AIDS but in 1985, a 25-year-old diagnosed with AIDS in the U.S. had a life expectancy of less than two years [2]. Unfortunately, despite the availability of these effective tools, the AIDS pandemic was still taking a life every minute in 2021, resulting in 650 000 AIDS-related deaths [3].

After 4 decades, HIV (AIDS) continues to be a major global public health issue, having claimed 40.1 million lives so far. In 2021, approximately 38.4 million people were living with HIV, 1.5 million people became newly infected and 650 000 people died from HIV-related causes [4].

HIV TRANSMISSION

Infections with HIV mostly occur during sexual contact across mucosal surfaces or sharing needles, syringes, or other drug injection devices. Importantly, the virus can also be transmitted from mother to child during pregnancy, birth, or breastfeeding. Luckily, advances in HIV prevention and treatment have made this type of transmission less common [6].

Usually, the efficiency of sexual virus transmission that accounts for more than 80% of all HIV-1 infections is surprisingly poor (1 per 1000 sexual contacts) Possible explanations are protective effects of the mucosal layer, limited target cell availability, or elimination of HIV-1 by innate immunity factors. But once an infection has been established, it leads to the continuous and efficient replication of the virus and loss of CD4 T cells in the infected host [7,8], allowing the progression of other infectious diseases, including those caused by potentially oncogenic viruses (HBV, HCV, HPV, EBV) [9].

HIV & CANCER

Today, substantial evidence associates HIV-induced immuno-deficiency with an elevated risk of many specific (mostly viral) cancer types. This increased risk of developing cancer is driven by immunosuppression, decreased cancer surveillance, persistent co-infection with oncogenic viruses and HIV viremia [10].

Compared to women without HIV, women living with HIV have six times more risk of cervical cancer and an estimated 5% of all cervical cancer cases are attributable to HIV. This higher risk is manifested throughout the lifecycle starting with an increased risk of acquiring Human Papilloma Virus (HPV) infection, more rapid progression to cancer, lower chances of regression of pre-cancer lesions and higher rates of recurrence following treatment [11-13].

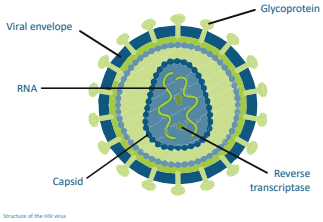
Women living with HIV are 6x more likely to develop cervical cancer than women without HIV[11]

HIV is also linked with liver cancer. About 1 in 10 HIV patients have a Hepatitis B co-infection and even about 1 in 5 have a Hepatitis C co-infection. Chronic HBV infection affects 5-20 % of people living with HIV and the progression of chronic HBV to cirrhosis, end-stage liver disease or hepatocellular carcinoma is more rapid in persons with HBV/HIV coinfection than in persons with chronic HBV infection [14].

The increased cancer risk caused by HBV and HPV can be addressed by improving global access and uptake of antiretroviral therapy, HPV and HBV vaccination, screening for Hepatitis B and C infection and optimized cancer screening programs [10].

HIV VACCINES

As virus integration occurs early on in infection, before a protective antibody or T cell response can occur, generation of protective antibodies before HIV-1 transmission is required to achieve protection [15]. Over the years, the greatest challenge in developing an effective HIV vaccine has been the high rate of mutation and recombination during viral replication [16].



Beside high viral mutation and recombination rates, extraordinary worldwide genetic diversity is yet another hurdle to the development of a vaccine.

HIV is composed of 4 groups: M (main), O (outlier), N (non-M/non-O), and P (pending). Group M is further subdivided into 9 subtypes/clades denoted by the letters A, B, C, D, F, G, H, J, and K [16].

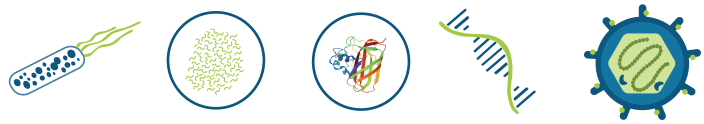
The difficulty of developing a universal vaccine is further compounded by the fact that 10–20% of HIV infected people in several parts of Africa, are infected with two or more viral variants (subtypes and recombinant forms) that circulate in these regions [16].

40 YEARS OF HIV VACCINE DEVELOPMENT

Soon after the isolation and identification of the HIV virus in in the eighties, the first clinical trials were started to test protein-based vaccine candidates. Multiple paths to HIV vaccine development have been explored to date, yet no effective HIV vaccine is available. In October 2022, Mosaico, a Phase 3 trial of Janssen's experimental HIV vaccine using an adenovirus serotype 26-mosaic-based vector (Ad26.Mos4.HIV), came to an end. Despite the fact that the vaccination regimen's safety was unaffected, the Mosaico review of the data to date revealed that the regimen did not provide HIV protection, and the trial is not anticipated to reach its primary aim [17]. Today many researchers believe an effective HIV vaccine will need to introduce broadly neutralizing antibodies against the virus [2].

Broadly neutralizing antibodies (bnAbs) are antibodies capable of neutralizing the majority of strains of a given highly antigenically variable pathogen.

Traditional types of vaccines include live-attenuated, inactivated, and replication-defective pathogens as well as subunit and conjugate vaccines [18].



Live-attenuated vaccine | Inactivated virus | Subunit, recombinant, polysaccharide and conjugate vaccines | mRNA vaccines | Viral vector vaccines

The development of both live-attenuated and inactivated vaccines requires large-scale growth of the pathogen posing a biosafety risk.

Sub-unit vaccines have favorable safety profiles and eliminate the need to culture or grow live pathogen, but often require booster immunizations as well as adjuvants.

To combat outbreaks requiring the rapid development of vaccines or difficult to manufacture antigens, new technologies such as viral vector and nucleic acid vaccines are needed [18].

mRNA VACCINES

Major innovations in RNA stabilization, biology, and delivery systems allowed mRNA-based vaccination to become a promising platform in vaccine development for the prevention, control, and treatment of infection and cancer [19].

Compared to conventional vaccines, mRNA vaccines have the potential to address current challenges in vaccine development [20].

- Rapid highly effective development
- Low-cost manufacturing
- Safe administration

During the COVID-19 pandemic, a lot of interest and confidence was gained in mRNA-based vaccines. Today, significant progress has been made in adopting the novel mRNA vaccine approach and the first mRNA-based HIV vaccines are now undergoing clinical trials to evaluate their safety and efficacy [21]. Additionally, to achieve passive immunization, dendritic cell (DC) mRNA vaccines are being tested in HIV-infected patients [21].

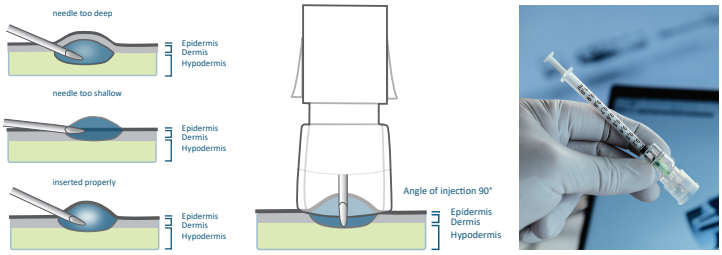
INTRADERMAL VACCINATION AS A ROUTE OF ADMINISTRATION

The route of administration, intramuscular (IM), subcutaneous (SC) or intradermal (ID) substantially affects the quality and profile of the immune response [22].

The papillary dermis, the target layer for ID immunization, is rich in antigen-presenting cells (APCs) like dermal dendritic cells (DCs) and Langerhans cells. The immunogenic properties of dermal APCs, thereby allow for only 10% or 20% of the standard amount of antigen to induce immune responses equivalent to standard doses delivered IM or SC [23].

In HIV-infected individuals, who only achieve protective anti-HBS titers in 18–71% of cases, the ID route seems to be more immunogenic than the standard IM delivery route [24]. Studies in non-responders or patients at high risk confirm higher seroconversion rates for ID injections compared to IM [25].

The currently used Mantoux technique, which uses a regular needle and syringe for ID injection, requires a high amount of training, is difficult to standardize and painful for the patient. It's very error prone as up to 70% of injections have shown to be incorrect [26]. Therefore, despite its high potential, intradermal delivery receives less attention than classical administration routes [22].



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VAX-ID® solves these challenges offering standardized, reliable, user-indepent, and painless intradermal drug delivery [27].

CONCLUSION

HIV vaccine development has been shown as notoriously challenging, but many recent advances generate renewed optimism and possibilities [5]. Further investigation will be needed to gain a better understanding on how immune responses are linked to routes of administration [22].

"Although HIV continues to prove uniquely challenging for development of a vaccine, the HIV research community remains fully committed to doing just that, and each study brings us a step closer to this realisation."

Dr. Susan Buchbinder

REFERENCES

1. Shi et al, 2022 (PMID: 35211115)
2. https://www.iavi.org/phocadownload/IR_Vol25_-No2_2021.pdf
3. https://www.unaids.org/en/resources/documents/2022/in-danger-global-aids-update
4. https://www.who.int/data/gho/data/themes/hiv-aids
5. Lee et al, 2021 (PMID: 34272086)
6. https://www.cdc.gov/hiv/basics/index.html
7. Kirchhoff, 2010 (PMID: 20638642)
8. Brenchley et al, 2008 (PMID: 19079157)
9. Franzetti et al, 2019 (PMID: 30919779)
10. Bohlius et al, 2018 (PMID: 29461329)
11. https://www.who.int/news/item/16-11-2020-who-releases-new-estimates-of-the-global-burden-of-cervical-cancer-associated-with-hiv
12. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer
13. Stelzle D et al, 2021 (PMID: 33212031)
14. Yoshimura et al, 2022 (PMID: 35491226)
15. Bonsignori et al, 2017 (PMID: 28133802)
16. Ng'uni et al, 2020 (PMID: 33193428)
17. https://www.jnj.com/janssen-and-global-partners-to-discontinue-phase-3-mosaico-hiv-vaccine-clinical-trial
18. Gebre et al, 2021 (PMID: 33740454)
19. Khalid et al, 2021 (PMID: 34367800)
20. Chakraborty et al, 2021 (PMID: 34305909)
21. Fortner et al, 2022 (PMID: 36438441)
22. Rosenbaum et al, 2021 (PMID: 33959127)
23. Schnyder et al, 2020 (PMID: 32898704)
24. Filippelli et al, 2014 (PMID: 25132754)
25. Van Mulder et al, 2018 (PMID: 30587432)
26. Micheels et al, 2018 (PMID: 29320593)
27. (2023, January 24). https://idevax.com/device/