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Major HIV vaccine candidates

Wojciech Zdziennicki[1], Patryk Zimnicki[2], Marta Lato[3], Konrad Iberszer[4], Maria Litwiniuk[5], Marcin Zaniuk[6], Kamil Hurkała[7], Dominika Antonik[8], Barbara Denys[9], Karolina Góra[10]

[1] Uniwersytecki Szpital Kliniczny w Poznaniu - ul. Przybyszewskiego 49, 60-355 Poznań, Poland

[2] Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Lublinie, ul. Grenadierów 3, 20-331 Lublin, Poland

[3] Szpital Specjalistyczny im. J.Dietla w Krakowie, ul.Skarbowa 1, 31-121 Kraków, Poland

[4] Samodzielny Publiczny Szpital Kliniczny nr 4, ul. Jaczewskiego 8, 20-954 Lublin, Poland

[5] WOJEWÓDZKI SZPITAL SPECJALISTYCZNY im. Stefana Kardynała Wyszyńskiego Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lublinie, Al. Kraśnicka 100, 20-718 Lublin, Poland

[6] Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Lublinie, ul. Grenadierów 3, 20-331 Lublin, Poland

[7] Samodzielny Publiczny Szpital Wojewódzki im. Papieża Jana Pawła II w Zamościu, ul. Aleje Jana Pawła II 10, 22-400 Zamość, Poland

[8] 5 Wojskowy Szpital Kliniczny z Poliklinika w Krakowie, ul. Wrocławska ⅓, 30-901 Kraków, Poland

[9] WOJEWÓDZKI SZPITAL SPECJALISTYCZNY im. Stefana Kardynała Wyszyńskiego Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lublinie, Al. Kraśnicka 100, 20-718 Lublin, Poland

[10] Samodzielny Publiczny Szpital Kliniczny nr 4, ul. Jaczewskiego 8, 20-954 Lublin, Poland

Wojciech Zdziennicki, ORCiD: https://orcid.org/0009-0005-1254-9740; e-mail: wojtekzdziennicki@gmail.com
Patryk Zimnicki, ORCiD: https://orcid.org/0000-0002-5808-8661; e-mail: patryk.zimnicki.97@o2.pl
Marta Lato, ORCiD: https://orcid.org/0000-0003-4121-3400; e-mail: coronarysulcus@gmail.com
Konrad Iberszer, ORCiD: https://orcid.org/0000-0002-4290-9883; e-mail: konrad.iberszer@gmail.com
Maria Litwiniuk, ORCiD: https://orcid.org/0009-0004-5396-7482; e-mail: litwiniuk.mm@gmail.com
Marcin Zaniuk, ORCiD: https://orcid.org/0000-0003-4643-0594; e-mail: marcin.zaniuk@gmail.com
Kamil Hurkała, ORCiD: https://orcid.org/0009-0007-5961-9894; e-mail: kamilhurkala@gmail.com
Dominika Antonik, ORCiD: https://orcid.org/0009-0004-7575-8016; e-mail: antonikdominika97@gmail.com
Barbara Denys, ORCiD: https://orcid.org/0009-0003-1951-1142; e-mail: barbaradenys11@gmail.com
Karolina Góra, ORCiD: https://orcid.org/0000-0002-5377-3010; e-mail: gora.karolina7@gmail.com

Keywords

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Abstract

Introduction and objective: *Human immunodeficiency virus* (HIV) is a virus, which is responsible for an *acquired immunodeficiency syndrome* (AIDS). This pathogen is widespread worldwide causing a pandemic that has been going on for decades. Researches around the world are trying to end this situation and it seems that the greatest hope lies in finding an effective vaccine. It is important due to the fact that AIDS and its consequences are responsible even nowadays for death of many people infected around the world. The aim of

this study was to provide the most important information about major HIV vaccine trials and efficacy of vaccine candidates.

Materials and methods: For the purposes of writing this article, the available literature was reviewed. The database of medical publications – Pubmed datebase and other publicaly available books, database and online sites was searched, with the use of keywords such as HIV, HIV vaccine, HIV epidemiology.

State of knowledge: According to review studies HIV vaccine trials has been going for 4 decades. Over 250 trials has been conducted since then, but unfortunately, none of them resulted in effective vaccine. The difficulties of this task are mainly connected with the nature of HIV virus. To date, one study has shown some effectiveness, but not enough to claim success. Other studies are ongoing around the world and more are planned.

Conclusions: Developing an effective HIV vaccine is the clue to solving the problem, which is new HIV infections. Further researches, further research funding and international cooperation are needed to end this pandemic.

Introduction

Human race is exposed to many forms of infectious bacteria, viruses and fungi from the very beginning of its existence. The diseases caused by these pathogens range from mild to severe, acute to chronic, curable to incurable. Different types of treatments have been tried for centuries, for example bloodletting, herbal medicine and others. However, this only cured diseases to varying degrees, but did not prevent them from occurring. That changed in 1796 [1] when world's first effective vaccine was created. Dr Edward Jenner discovered that people infected with cowpox were immune to smallpox. Through years vaccines help humanity to fight many diseases, even eradicate successfully two of them – smallpox [2] and rinderpest (which affected cattle). With every year passing new vaccines were developed, previous ones improved. In 2019 new danger appeared, the COVID-19 [3]. SARS-CoV-2 rapidly spread around the world killing millions of people. This prompted scientist to search for a solution how to stop this virus.[4]. The knowledge we gained through years helped develop COVID-19 vaccines in record time [5,6]. However this pandemic is not the only one we try to fight. Another one of the dangers of humanity worldwide is the HIV pandemic.

Epidemiology

HIV has been detected in almost every part of the world. In 2021 around 38.4 million people were living with HIV on Earth [7]. Most of the lives in Africa, the summary is in Figure 1. Data provided by UNAIDS shows that in 2021 from 1.1 million to 2.0 million people became HIV positive. This is less than it was in the past when in 1996 were almost 4.3 million new cases, but it is still a huge problem – people are still dying from the consequences of HIV infection. This virus is responsible for AIDS (*acquired immune deficiency syndrome)* and its complications, which can be fatal. Mortality in 2021 was 650 000, since the start of the epidemic approximately 40.1 million people have died. Epidemiology data are summarized in Figure 2 provided by WHO.

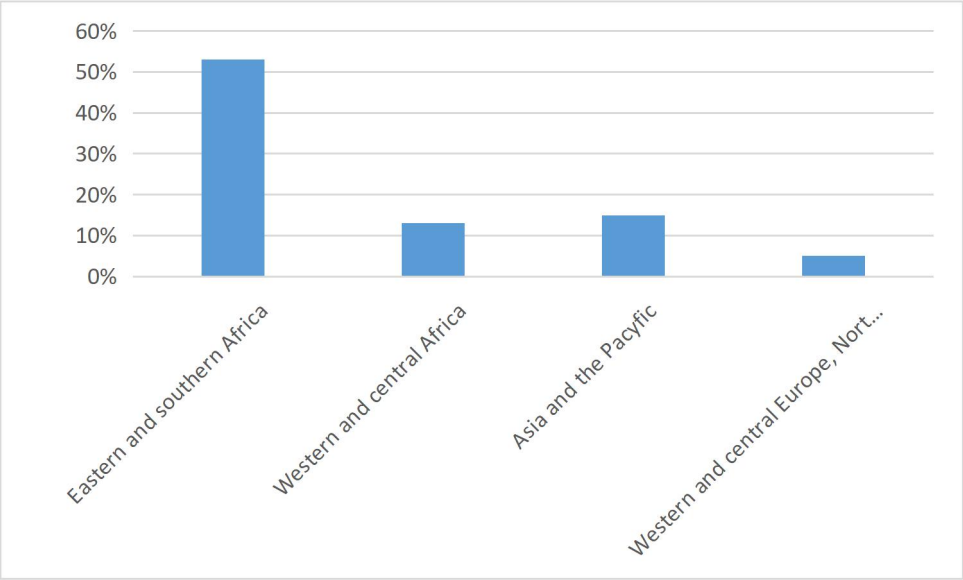

Figure 1 Percentage of people HIV positive in a given region, to all infected people https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics/

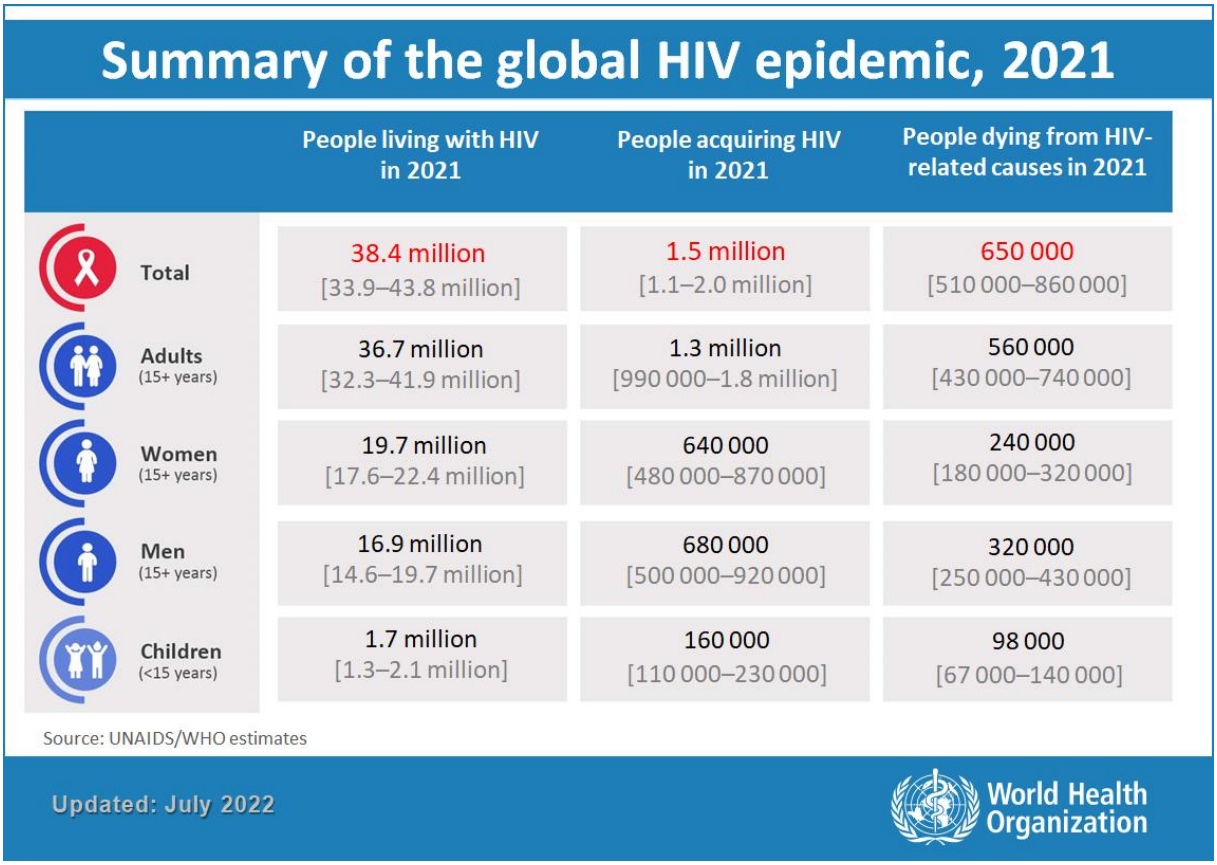

Figure 2 Summary of the global HIV epidemic, by WHO https://www.who.int/data/gho/data/themes/hiv-aids

Indeed, we have effective treatment such as antiretroviral therapy (ART) [8], which supresses virus to a level in which transmission to uninfected person is not possible. However this means that only regular use of medications and other known ways to prevent STDs such as barrier methods [5,9] stops the transmission. Unfortunately, many of the most affected countries do not have access to this type of treatment, so another solution is needed to end HIV pandemic – such as effective prophylactic vaccine.[8,10]

Difficulties

HIV poses considerable challenges for researchers due to its volatile nature [8], we know four main groups (M, N, O, P) and 9 subtype or clade (A, B, C, D, F, G, H, J, K). Error-prone viral reverse transcriptase is the main reason for a high rate of mutation - 1–10 mutations per genome per replication cycle. This error leads to changes in glycoprotein Env, which the antibodies want to neutralize. Limited information regarding the correlates of immune protection and no appropriate animal models are also important difficulties for scientists.

Most important vaccine candidates through years

Since 1986 more than 250 researches were conducted all over the world [10]. Three major of them were in Phase 3 – VAX003, VAX004, RV144. [8,10,11]. The first two were sponsored by VaxGen, and in those trials, which were held in Thailand and in the Americas respectively, the results were pessimistic. Both vaccine candidates did not show efficacy in preventing HIV infection, suggesting that these type-specific antibody responses are insufficient to induce protective reaction [10-13]. Scientists focused on another way to trigger a sustained immune response – T-cell immunity. One of the most important trials of these type vaccines is "STEP" trial, also known as HIV Vaccine Trials Network (HVTN) 502, which took place in the Americas and Australia. [10,11,14]. This ended prematurely trial, also led to pessimistic conclusion. This vaccine candidate not only fail to prevent infection, but also surprisingly, there were more infected people in the control group than in the placebo one.

After pessimistic results of VAX and STEP trials, the RV144 study yielded different outcome [8,10,11,15]. The research, which took place in Rayong and Chon Buri provinces in Thailand showed efficacy rates ranging from 60% to 31% at one year and 3.5 years after vaccination, respectively. In this trial researches evaluated four priming injections of a recombinant canarypox vector vaccine (ALVAC-HIV [Vcp1521]) and later two booster injections containing of AIDSVAX B/E glycoprotein 120 subunit vaccine, which was previously used in VaxGen trials.

One of the most recent trials, which was a Phase 3 study – The Mosaico, known as HPX3002/HVTN706 halted on January 12, 2023 after planed, interim revive by the study's independent Data and Safety Monitoring Board (DSMB) [11,16-18]. Analysis showed no evidence of effectiveness in preventing HIV compared with placebo. Unfortunately, Mosaico was the only one ongoing research in phase 3, similar to the Imbokodo trial (phase 2b), which was also stopped in 2021 for lack of prevention in HIV infections. However, overall negative results did not stop further analysis of participants. Over 3000 participants from Americas and Europe are monitored in terms of immune responses to show any evidence of protection. a summary of the efficacy of the respective vaccines is provided in Table 1.

Name	Year started	Location	Phase	Efficacy
Vax 003	1999	Thailand	3	No
Vax 004	1998	Americas	3	No
STEP	2003	Americas Australia	2b	No
RV 144	2004	Thailand	3	Yes, 31%
Mosaico	2019	Americas Europe	3	No

Table 1

Conclusion

Despite the fact that HIV infections are less common, than in the past, pandemic of HIV is still a problem around the world. Although we have treatment with satisfactory result such as antiretroviral therapy, it is not enough to stop this pandemic. Finding a vaccine that effectively prevent HIV infections would be a game changer. Despite the fact that the search has been going on for 40 years, only one trial show somewhat efficacy – the RV144 study with 31%. This shows that effective HIV vaccine is achievable, but researchers has a difficult route to overcome unsolved problems. It seems to be the biggest one of them is the extensive viral diversity within subtypes. However, through years some progress was made. The experience gathered through decades of vaccines researches helped to develop SARS-COV-2 vaccines in record time. We have to believe that HIV vaccine is within our reach in the coming years.

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