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Effects of helminth infections on HIV-1 vaccines performance; a classical Review

Woodvine Otieno Odhiambo*[1,2], Rebecca Waihenya[1], Simeon Mogaka[1]

1 Department of Zoology, Faculty of Science, Jomo Kenyatta University of Agriculture and Technology, P.O. Box 62,000, 00200, Nairobi, Kenya.
2 Department of Tropical and Infectious Diseases, Institute of Primate Research, P.O Box 22481-00502, Nairobi, Kenya.

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***Corresponding author:**

Email : woodvinotieno@gmail.com
Tel.: +0 .....

ABSTRACT

The effect of chronic schistosomiasis on the efficacy of vaccines currently in clinical use and future HIV vaccines is the subject of critical research enquiry. Several candidate HIV vaccines have been tested or are in ongoing clinical trials, but it is not clear how they might perform in the presence of ongoing helminthic infections. S. mansoni infection has been suggested to be a risk factor for HIV transmission and progression in Africa. There is an extensive geographic overlap between the prevalence of helminth infections and HIV/AIDS in sub-Saharan Africa (SSA), suggesting that future HIV vaccinations in SSA will be administered to a large proportion of people with ongoing helminthic infections. A lot of speculations are based on a hypothesis that Helminth infections have been shown to skew the immune system of the host to T-helper type2 and to subsequently suppress immunity. It is on this hypothesis therefore, that helminth infected populations may not generate the desired sufficient immune responses to vaccines designed to drive Th1-type and cytotoxic T-cell responses, HIV vaccines included. This review looks at the various HIV candidate vaccines which have been developed over time and links their performance to the presence of helminthic infection, specifically *s mansoni.*

INTRODUCTION

HIV infection remains worldwide public health concern with almost 31 million people living positively and 2.7 million infections encountered daily1. The development of antiretroviral therapy, ART still remains the most memorable breakthrough in HIV control. Although the therapy slows the progression to AIDS, it cannot cure the disease completely. For most cases, untreated HIV-infected individuals rarely survive; hence ART intervention remains crucial in a patient's lifetime. This lifelong dependence on anti retroviral drug therapy raises important concerns on their sustainability and affordability and presents daunting global economic and health problems2.

A safe and most efficacious vaccine would be the most cost effective means to stop the spread of AIDs pandemic3. HIV-I vaccines designs have focused on three different paths, those that induce neutralizing antibodies to viral peptides4 , those inducing cellular immunity to kill virally infected cells5 and those that induce both neutralizing antibodies and cellular immunity6.

Developing countries have the highest burdens of HIV cases and this is where HIV vaccine trials have always been carried out7. Most people in Sub Saharan Africa are suffering from one or multiple helminthic coinfections. Over 200 million people are infected with Schistosoma species while up to 100 million are infected with *Strongyloides stercoralis* infections8. Studies have shown a relatively high seroprevalence of schistosomiasis, Strongyloides and HIV coinfections. There is scanty information to show a clear HIV vaccine performance in an ongoing helminths infection. A lot of speculations are based on a hypothesis that Helminth infections have been shown to skew the host immune system of human and animals to T-helper type 2 and to suppress immunity8. It is on this hypothesis therefore, that helminth infected populations may not generate the desired sufficient immune responses to vaccines designed to drive Th1-type and cytotoxic T-cell responses, HIV vaccines included.

This review explores the various vaccines that have been developed over a long period of vaccine pandemic, their mode of operation and a possible operation of HIV vaccines in the presence of helminth infections.

Table 1 : Showing various HIV vaccine candidates

Vector	Pros	Cons	Vaccine status/trials	Reff
ALVAC (canarypox)	Confers Antibody and CMI. Highly Immunogenic In prime boost. No preexisting population vector Immunity Evidence for clinical efficacy on HIV acquisition	immunogenicity weak by standard Laboratory assays. Unclear immune Protection correlate(s) that lead to observed efficacy in RV144	several previous clinical trials, and most advanced evaluation Phase III: RV144 Thailand Prime: subtype B and A/E ALVAC-HIV-gag-pro-gp41-gp120Boost: subtypes B and E AIDSVAX B/E (gp120 subunit proteins) Modest prevention efficacy: 31.2% in general population 3.7% in high risk	[13]
Canarypox (ALVAC)	Induce Ab and CMI. Long lasting immunity (over two years. Well tolerable express protein Env (gp160) Express Env(gp120) and synthetic peptide comprising a T-helper epitope (p24) and a B-cell epitope (V3) express Env (gp120), Gag, Pro, and CTL domains of Pol and Nef.	Low immunogenicity	Numerous clinical trials: -Nef, Gag Env lipopeptides (LIPO-6). In France. lipopeptides (Env, Gag, Nef) ANRS VAC01:ALVAC (vCP125 c) − rgp160 ANRS VAC02: rgp 160 + peptide V3. ANRS VAC03ALVAC (vCP205) + peptide CTLB-36 ANRS VAC07: ALVAC (vCP300)	[14] [15]
NYVAC (vaccinia)	Immunogenic in preclinical studies Vector able to accommodate larger inserts	Theoretical safety issues with vaccinia, but well tolerated with attenuation	Phase I completed: EV01 – NYVAC alone Phase I completed: EV02 – DNA prime + NYVAC boost – DNA prime + NYVAC boost Phase I: HVTN 096 – NYVAC, DNA and protein (AIDSVAX B/E) combinations	[16] [17] [18] [19]
MVA (vaccinia)	Induces CMI. Immunogenic in prime–boost Combinations Minimal preexisting population vector seropositivity Can accommodate larger inserts	Humble immunogenicity following Attenuation. Safety issues, even on Attenuation.	Phase IIa: HVTN 205– DNA prime + MVA62 Phase I: HVTN 055– MVA + fowlpox. Phase I: HVTN 065– DNA prime − MVA62 boost Phase I: HVTN 094 – DNA prime (with GM-CSF) + MVA62 Early studies of multigenic MVA Phase I: Ad26+ MVA	[18] [20] [21] [18] [22]
Fowlpox	Give CMI. Tolerable in breast and prostate cancer treatment	Limited clinical data	Phase I: HVTN 055 – MVA+ fowlpox	[20]
Ad5 (adenovirus)	Both Ab − CMI. Immunogenic in prime–boost system	High preexisting population vector seropositivity No efficacy in two phase IIb trials	several early clinical studies, and most advanced evaluations Subtype B, MRKAd5-gag/pol/Nef. Phambili/HVTN 503 : same outcome, no efficacy Phase IIb: HVTN 505 done in North America stopped for lack of efficacy, follow-up and data analysis on course	[23] [24] [25] [28]
Ad26, Ad35 (adeno viruses)	Low population seroprevalence. Immunogenic both alone and in prime–boost.	Can only accommodate smaller inserts	Phase I: IPCAVD 001– Ad26 dose Escalation. Phase I: Ad35 dose escalation studies Phase I: IAVI 003 – Ad26/Ad35 prime–boost Phase I: Ad26/MVA prime–boost	[26] [27] [28] [29]

METHODOLOGY

Relevant information used for this review was retrieved by searches in NCBI, Pub Med, Global Health and from the references of published manuscripts and articles. For computerized databases, the search system included only permutations of principle terms, which were found to be relevant to the study. Initially, all searches began with the text string "HIV-1 VACCINES*" and specified keywords in permutations related to co-infection, including "HIV", "HIV/AIDS", "Helminths" "multi CTL epitopes", " schistosomiasis" "Broad Neutralizing antibodies",

HIV-I vaccines updates

The HIV vaccine research has been widely categorised into induction of broad neutralizing antibodies, Cell mediated

immune response and both the two combined.

Induction of neutralizing antibodies

This was the initial HIV vaccine target research that was done from 1986 to 2003. It was thought to be the most effective way to confer protection 9. It was based on the concept that neutralizing antibodies is sufficient in protection against HIV infection. It however came clear later that HIV-an enveloped retrovirus-presents challenges for conventional neutralizing Antibody-based strategies of vaccines. It quickly mutates to alter its surface structure, uses host-derived non-immunogenic glycans to block its exposed surface, and hides its conserved and potentially susceptible regions, like the CD4 binding site in the oligomeric proteins interfaces10. Neutralizing Antibodies operates by either blocking the interaction between viral envelopes with their receptors or inhibiting viruses for their further transport to cytoplasm3. Numerous HIV vaccines constructs were developed based on the envelope glycoproteins of the Human immunodeficiency virus principally gp120 and gp160, which are critical for the viral binding to the target cells. The said envelope glycoproteins are the principal targets for the neutralizing antibodies.

The first HIV vaccine candidate trial was conducted in the USA in 1988. It evaluated a recombinant gp160 produced in a baculovirus-insect cell system. It however showed no significant antibody protection against HIV. Several lines of research have been explored targeting HIV antibodies by use of poxvirus vectors to prime the antibody responses, identification of different genetic subtypes of the virus, R5 and X4 virus phenotypes classification11. Several other vectors have also been used to prime both the antibody and cell mediated immune response as detailed in table 1.

Induction of CTL responses

These types of vaccines were developed following the failure of neutralizing antibodies. It started with the recognition of the importance of CD8+ T-cell responses in the control of HIV infection 12. This new prototype led to the development and refinement of live recombinant viral vectors, which are, poxvirus, adenovirus, canarypox, fowl pox as well as of DNA vaccines. Most recent publications of tested candidate vaccines targeting Cell mediated immunity were based on adenovirus.

Combinations of CTL and Neutralizing Antibody Immune Responses

This is an approach that was taken after the failure of the STEP trial. A successful vaccine to prevent HIV infection will likely require both the elicitation of antibody and cell-mediated responses6. This approach has also used various non replicating viral vectors as canarypox virus, adenovirus, fowl pox virus, vaccinia vectors and DNA plasmid vectors. Some of the viral-vectored vaccine approaches have reached advanced testing with two vaccine strategies reaching clinical efficacy trials canarypox virus (ALVAC) and adenovirus serotype 5 (Ad5) modified vaccinia Ankara (MVA) and highly attenuated vaccinia virus (NYVAC) 6.

Possible performance of HIV vaccines in the presence of schistosomiasis infection

Helminthic infections affect over a third of the population of the world. Geographically, it is also similarly distributed like HIV. In countries which are developing, children who are born in intestinal nematodes endemic areas harbor worms for most of their lives. Helminth infected people are chronically immune-activated and have a very pronounced TH2 immune profile.

There is not yet a valid vaccine against HIV which can be implemented. There is strong evidence that helminth infection can change cellular and antibody responses to other, existing vaccines; suppression of responses and switching to a Th2 profile has both been observed30.

An effective HIV protective vaccine should generate a potent cellular immune response, which is dependent on a dominant T-helper type 1 cellular response, rather than a T-helper type 2 humoral responses. TH1 and TH2 cells cross-regulate one another and therefore cytokines produced by one subset of T-helper is able to down regulate the production and/or functioning of the other31.

Since helminth infections revert the host immune system of human and animals to T-helper type2 (Th2) and induce immune suppression, there is a possibility that populations infected with helminths may not produce the desired immune responses to HIV vaccines which are coined to drive Th1-type and cytotoxic T-cell responses31. These populations also have expanded numbers of T regulatory cells hence leading to immune anergy32. Increased T regs populations have not only been shown to impact on self-antigen specific immune responses, but they also dampen the protective effect induced by vaccines 33. This may be a contributing factor to the pathogenesis of HIV in Sub Saharan Africa and may also make intestinal helminths compromise the ability of an HIV vaccine candidate to confer protection in vaccinees.

Associational Studies between helminths; especially *S mansoni* and HIV have been done. Many of these studies have shown that schistosomiasis mostly enhances the progression of HIV. Concomitant *S mansoni* infection has been shown to heighten gag specific CD+ 8 T cell responses to IL-10; an insignificant level of IFN-y was also heightened 34. Because of this, a question that has been left unanswered in the HIV research field is whether schistosomiasis should first be treated before looking at the HIV intervention measures in schistosomiasis and HIV endemic areas. This is because treatment of helminthic infections is possible, relatively inexpensive and simple, and has already become a priority for public health in developing countries.

In terms of HIV vaccine immunogenicity, most studies have also supported the hypothesis that helminths infections considerably impair the Th1-type vaccine specific immune responses to bacterial, viral and infections with other pathogens 32. Effects may vary for vaccines administered orally (where effects of intestinal helminths on the mucosa can subdue the development of the response), in comparison with parenteral vaccines; and for live vectors (viral vectors, *Salmonella* or Bacille Calmette Guérin), where there could be effects on the replication of the vector and hence the dose of vaccine antigen experienced. In a study investigating multi- T-cell - epitope DNA- based HIV-1 vaccine performance in the presence and absence of helminth infection in mice, it was reported that vaccination of naïve mice with this vaccine elicited a strong HIV-1 C- T-cell specific immune response showing that the vaccine was indeed potent. In the infection of mice with cercariae, then immunization with the HIV-1 C vaccine candidate, the rate of IFN-y stimulated was significantly reduced in comparison to the schistosomiasis-free but vaccinated mice. According to this study, Schistosome infection almost abrogated the ability of the vaccine to elicit specific CD8+ T cells 32.

In another study to look at the effect of antihelminthic treatment to the performance of an HIV-1 C DNA vaccine in mice, it was reported that the treatment of the disease prior to vaccination significantly restores the CD+ T-cells specific response to HIV specifically IFN-y32. It was however surprising that the levels of IL-10 and IL-4 produced after the same antihelminthic treatment also remained the same or even went higher. This is scenario is confusing because as TH2 responses, IL-10 and IL-4 are expected to be diminished after the treatment of helminths.

Some studies have also found no association of helminthic infections and HIV progression or HIV vaccine performance in that case. Some studies have reported that Helminth infection is not associated with higher viral load, lower CD4+ cell count, or faster decrease in CD4+ cell count before antihelminthic treatment. The study also reported that the effect of coinfection on progression of HIV varied with species. It showed highest CD4+ cell counts in people with hookworm and *Mansonella perstans* infection.

CONCLUSION

From all the past HIV vaccine studies, it remains to be elucidated if the failure of these HIV vaccine candidates is because the same vaccinees suffer from helminthic infections. Since several investigations have talked for and against this association, we report a strong need for further research to prove if helminths reduce the potency of HIV vaccines and if treatment of helminths will enhance the response of the said vaccines.

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