HIV Vaccine development: Challenges and Progress

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Currently 33.3 million people are estimated to be infected with HIV, with 2.6 million new infections occurring in 2009 alone (1). As we enter the fourth decade of the HIV epidemic, UNAIDS vision calls for zero discrimination, zero new HIV infections and zero AIDS related deaths through universal access to effective HIV prevention, treatment, care and support. Access to antiretroviral therapy (ART) provides the potential to curb AIDS related deaths, but there is still a very long way to go. Of the estimated 15 million HIV infected people in low and middle-income countries requiring treatment, only 5.2 million have access to ART. Increased effort and innovative ideas to upscale access to treatment and to improve coverage are evident globally, such as the broadened ART delivery platform to include nurse-initiated therapy in South Africa. This global expansion of access to treatment has resulted in an 13-fold increase in the number of people on ART since 2004, as well as 19% decline in HIV related deaths between 2004 and 2009 (1).

Whilst ART is steadily and significantly turning the tide on the HIV epidemic, the number of new infections is still unacceptably high. This is notwithstanding that the 2.6 million infections in 2009 are a 19% drop from the 3.1 million seen in 1999. Prevention efforts therefore need to continue being the major priority in the fight to halt the epidemic. Until fairly recently, most HIV prevention strategies focused on socio-behavioural interventions with condoms, 'faithful' relationships and abstinence together being hailed as the main prevention messages. We all have witnessed, especially in South Africa, the limitations of these interventions as the epidemic spiralled in the midst of those messages. Gender power imbalances, which make women most vulnerable, propelled research to develop discreet female-controlled prevention methods in the form of topical microbicides. The great enthusiasm that ensued in the microbicide research field, as seen by a surge of multiple phase III clinical trials from 2004, was unfortunately soon followed by a series of disappointing results (2-4). However, for the first time in the history of HIV research a vaginal microbicide, 1% tenofovir gel, showed a reduction of HIV acquisition in high risk women by 39% as published by a South African group in 2010 (5). Three randomised control trials in sub-Saharan Africa also showed that male medical circumcision reduces HIV acquisition in young men by up to 60% (6-8).

Although a lot of progress has been made in the prevention research arena, it is irrefutable that the development of a safe and effective vaccine becomes the best hope for ultimately ending the HIV pandemic. Vaccines in general are one of the most effective public health interventions especially for viral diseases. Yet, for the past two decades, an HIV vaccine has been elusive. The field of HIV vaccine development research, whilst arguably the most funded in the prevention arena, is fraught with many extraordinary challenges.

Challenges in HIV vaccine development

1. The ability of the virus to integrate its genome into human cells as well as its propensity to replicate and mutate rapidly has challenged the field enormously. The rapid mutation rate enables the virus to **evade the immune system** while rapid integration results in **establishment of latent viral reservoirs** very early during acute infection (within days) and this constitutes a major barrier to virus eradication. Early establishment of this latency narrows the window of opportunity wherein the virus could be eradicated by immune responses.
2. Most viral infections typically induce immune responses that involve both **neutralising antibodies** - preventing further infection of host cells and virus replication as well as **cell mediated immunity** – identifying infected cells and destroying them. This results in controlling and clearing of the viral infection and subsequent establishment of protective immunity. In HIV infection, these immune responses are inadequate and ineffective. As a result, natural clearance of infection has never been documented. This confronts researchers with a major immunological challenge because vaccine development is based on mimicking this natural clearing and establishment of long term immunity. Therefore, the immune correlates of protection for HIV are still unknown.
3. **Viral diversity** of HIV is another major challenge and has resulted in different subtypes circulating in different countries with recombinant forms in other areas. The jury is still out on whether we are likely to need a subtype specific vaccine. There is clinical evidence showing that certain subtypes (for example subtype D) are associated with rapid disease progression (9). Candidate vaccines have been tested with the hope that they would induce cross-reactive immune responses strong enough to cover most circulating subtypes. Recently, polyvalent vaccine antigens comprising of 'mosaic' proteins have been designed and shown improved coverage of viral diversity.
4. Another great challenge has been the **lack of an ideal animal model** which can mimic natural infection and pathogenesis of HIV disease in order to test candidate vaccines. HIV exclusively infects and causes disease in humans. Non-human primate (NHP) studies commonly use rhesus macaques infected with simian immunodeficiency virus (SIV) which is the closest related retrovirus to HIV-1. The obvious limitation of the interpretation of data generated from these NHP studies to humans underscores the need for human clinical trials.
5. The debates about what the characteristics of the vaccine(s) should be, which type of immune responses these vaccines must induce, and when and how to proceed to phase III trials to evaluate vaccine protective efficacy in humans are also unresolved.

Which immune responses should be targeted?

There has been a controversy about whether an HIV vaccine must induce either humoral or cell-mediated immune responses or both. The role of mucosal immunity at virus entry point has also recently become a research priority. A neutralising antibody inducing vaccine would ideally prevent HIV infection whereas one designed to elicit cell mediated immunity controls viral replication and so reduce the viral load in individuals who become infected, thus reducing infectiousness.

The first two phase III efficacy vaccine trials using AIDSVAX subtype B/E and subtype B/B (both produced by VaxGen) were done in Thailand and the USA respectively. These vaccines

targetted humoral immune responses and showed no effect on HIV acquisition (10, 11). These trials were followed by the phase IIb 'proof-of-concept' STEP and subsequently Phambili efficacy trials which evaluated a vaccine that primarily stimulated cell-mediated immune responses using a vaccine developed by Merck (12, 13). The STEP study was done in uninfected individuals in North America, the Caribbean, South America, and Australia – where subtype B virus circulates, whilst the Phambili study was done in uninfected high risk adults in South Africa – a subtype C infected population. The STEP study was stopped early because it unexpectedly met the pre-specified futility threshold at the first interim analysis by the data and safety monitoring board (DSMB). This resulted in a similar premature termination of participant enrolment in the Phambili study. The vaccine failed to prevent HIV acquisition and did not lower the viral load in those who became infected. Further, analysis of the STEP trial showed that e.g. male participants who were uncircumcised appeared to have an increased risk of HIV infection. Failure of this trial raised the question of whether a vaccine that primarily induces cell-mediated immunity can protect against HIV infection.

The results of the fourth efficacy trial done in Thailand inspired new hope and enthusiasm in 2009, showing for the first time that HIV acquisition can be reduced by a vaccine (14). It showed vaccine efficacy of 31.2% in a modified intention-to-treat analysis, with no effect on viral load of the infected participants. This vaccine stimulated both cell-mediated and antibody immune responses. Notwithstanding that this was a modest efficacy, these results have provided an opportunity to investigate immune correlates of protection in the individuals that did not become infected. It is now clear that a successful vaccine will need to both induce broadly neutralising antibodies and stimulate cell-mediated immunity.

Innovative trial designs to fast-track vaccine development

The three efficacy trials that used AIDSVAX took about seven years each from trial initiation to result publication. The urgent need for an effective vaccine does not allow us such protracted processes. Non-human primate studies in the field have unfortunately not been very helpful in assisting to identify candidates that should proceed to human trials. There is therefore a need to come up with innovative clinical trial designs that can accelerate vaccine development.

The phase 2b 'proof-of-concept' studies are one such example. These studies are carried out to determine whether there is early evidence of clinical efficacy using a small, targeted number of subjects, to warrant taking a drug further into development. This efficiency was seen with the STEP trial as it only took 3 years to reach a result of no efficacy. It therefore makes sense to use such trial designs when testing new vaccine candidates once the safety and immunogenicity studies (phase 1 and 2A) have been completed.

Adaptive designs are another attraction as these use accumulating data of an ongoing trial to decide how to modify the design without undermining the validity and integrity of the trial. Using this approach, we can rapidly screen out poor vaccine candidates whilst the evaluation of efficacious ones gets extended (15). This approach allows for further characterisation of potential candidates and correlates of immune protection and not waste time on candidates unlikely to move forward.

This means that as more novel vaccine candidates come through phase 1 trials, the promising candidates must be expediently moved to phase 2b. Multiple phase 2b studies should be run

in parallel so that generated data from these feed onto the design and modification of the adaptive trials.

Other recent highlights in HIV vaccine development

- The recent discovery of exceptionally broad neutralising antibodies in the last 2 years by different groups of researchers has suddenly expanded the antibody field and opens a potential pipeline of new immunogens. Some of these antibodies were isolated in HIV infected individuals from developing countries and appear to attach to more accessible sites on the HIV molecule, which will hopefully make immunogen design less complicated.
- The vaccine developed by the South African AIDS Vaccine Initiative (SAAVI) recently made headlines as the first HIV vaccine candidate developed in a developing country and being tested not only in South Africa but in USA trial sites as well. Results of the phase 1 studies presented earlier this year at the Retrovirus Conference showed the vaccine to be safe, well tolerated and immunogenic, eliciting high CD4+ T-cell and modest CD8+ T-cell responses. This candidate will soon be going to the next clinical trial phase in combination with an envelope protein boost.

In conclusion, despite the enormous challenges in the HIV vaccine development field, there have been significant advances in AIDS vaccine research including the identification of anti-HIV antibodies with broadly neutralising potential. The results from the RV144 trial conducted in Thailand have injected new enthusiasm into this field and an AIDS vaccine remains an important hope for the control of HIV/AIDS.

References:

1. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Geneva: UNAIDS; 2010. Link to report http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en.pdf
2. Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med. 2008;359(5):463-472. Link to article http://www.nejm.org/doi/full/10.1056/NEJMoa0707957
3. Ramjee G, Govinden R, Morar NS, Mbewu A. South Africa's experience of the closure of the cellulose sulphate microbicide trial. PLoS Med. 2007;4(7):e235. Link to article http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040235
4. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet. 2002;360(9338): 971-977. Link to article http://www.sciencedirect.com/science/article/pii/S0140673602110798
5. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996): 1168-1174.Link to abstract http://www.sciencemag.org/content/329/5996/1168.short
6. Auvert B, Taljaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2(11):e298.Link to article http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0020298
7. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369(9562):657-666. Link to article http://www.sciencedirect.com/science/article/pii/S0140673607603134
8. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369(9562):643-656. Link to article http://www.sciencedirect.com/science/article/pii/S0140673607603122
9. Kaleebu P, French N, Mahe C, et al. Effect of human immunodeficiency virus (HIV) type 1 envelope subtypes A and D on disease progression in a large cohort of HIV-1-positive persons in Uganda. J

Infect Dis. 2002;185(9):1244-1250. Link to article http://jid.oxfordjournals.org/content/185/9/1244.long
10. Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis. 2006;194(12):1661-1671. Link to article http://jid.oxfordjournals.org/content/194/12/1661.long
11. Gilbert PB, Peterson ML, Follmann D, et al. Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. J Infect Dis. 2005;191(5):666-677. Link to article http://jid.oxfordjournals.org/content/191/5/666.long
12. Buchbinder SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008;372(9653):1881-1893. Link to article http://www.sciencedirect.com/science/article/pii/S0140673608615913
13. Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili Study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis. 2011;11(7):507-515. Link to article http://linkinghub.elsevier.com/retrieve/pii/S1473-3099(11)70098-6
14. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209-2220. Link to article http://www.nejm.org/doi/full/10.1056/NEJMoa0908492
15. Corey L, Nabel GJ, Dieffenbach C, et al. HIV-1 vaccines and adaptive trial designs. Sci Transl Med. 2011;3(79):79ps13. Link to abstract http://stm.sciencemag.org/content/3/79/79ps13.short