HIV: Current Research

Extended Abstract

Long-term follow-up of study participants from prophylactic HIV vaccine clinical trials in Africa

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Abstract

Long-term safety is critical for the development and later use of a vaccine to prevent HIV/AIDS. Likewise, the persistence of vaccine-induced antibodies and their impact on HIV testing must be established. IAVI has sponsored several Phase I and IIA HIV vaccine trials enrolling healthy, HIV-seronegative African volunteers. Plasmid DNA and viral vector based vaccines were tested. No vaccine-related serious adverse events were reported. After completion of vaccine trials conducted between 2001–2007, both vaccine and placebo recipients were offered enrolment into an observational long-term follow-up study (LTFU) to monitor potential late health effects and persistence of immune responses. At scheduled 6-monthly clinic visits, a health questionnaire was administered; clinical events were recorded and graded for severity. Blood was drawn for HIV testing and cellular immune assays. 287 volunteers were enrolled; total follow-up after last vaccination was 1463 person years (median: 5.2 years). Ninety-three (93)% of volunteers reported good health at their last LTFU visit. Infectious diseases and injuries accounted for almost 50% of the 175 reported clinical events, of which over 95% were mild or moderate in severity. There were 30 six pregnancies, six incident HIV infections and 14 volunteers reported cases of social harm. Persistence of immune responses was rare. No safety signal was identified. No potentially vaccine-related medical condition, no immune mediated disease, or malignancy was reported. HIV vaccines studied in these trials had a low potential of induction of persisting HIV antibodies.

Keywords: Africa, HIV vaccine trials, long term follow-up, safety, healthy adult volunteers

The long-term follow up (LTFU) study was a prospective, observational study to monitor both vaccine and placebo recipients from previous HIV vaccine trials for any late health effects and the persistence of vaccine-induced immune responses. Placebo recipients were followed up as successfully as vaccine recipients. No significant or potentially vaccine-related medical problems have been detected. No autoimmune or potentially immune mediated disease and no malignancy have been reported in enrolled volunteers.

These observations are consistent with previously published data on long-term safety of HIV candidate vaccines. To our knowledge, our paper is the only one reporting on long-term safety of HIV vaccines in healthy African adults.

The most common clinical events reported were mild or moderate infectious diseases, and the proportion of volunteers with respective symptoms or conditions did not differ between vaccine and placebo recipients. This observation is consistent with data published on background morbidity, as assessed by unsolicited adverse events in clinical trial participants.
Three of the IAVI sponsored trials testing an MVA-based HIV vaccine began prior to, and one within a few weeks after the publication that, rarely, pericarditis/myocarditis may occur a few weeks after vaccination against smallpox. No such event occurred in our HIV vaccine trials, at the peak time observed for recipients of the replication-competent DryVax®. Therefore we did not look for late occurrences following our highly attenuated MVA. Surveillance in subsequent IAVI trials and a meta-analysis have shown no such events following MVA to date.

No background data on congenital anomalies are available from the countries where the LTFU study was conducted. The types of anomalies observed are also known to occur in children born to women in industrialized countries and to women who have not participated in HIV vaccine trials. The numbers are too small to draw any conclusion on a teratogenic potential of the vaccines tested.

Six participants acquired HIV infection after the end of the respective vaccine trial. The proportions of vaccine and placebo recipients are similar. The number is too small to draw any conclusion as to whether or not receipt of an HIV candidate vaccine affects the susceptibility for HIV-acquisition. False positive HIV test results by HIV rapid test kits in volunteers with no (previously detected) vaccine-induced antibodies were spurious.

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Persistence of vaccine-induced sero-reactivity was demonstrated in a few VRC DNA prime-Ad5 boost recipients. Overall, the 4th generation HIV ELSA test kit was much more sensitive to detect vaccine-induced antibodies than HIV Rapid kits. Therefore, use of rapid tests for standard HIV testing seems appropriate for use in non-research settings and likely eliminates issues associated with VISR in uninfected vaccines who have received the previously studied HIV vaccines.
Isolated incidents of social harm were reported and handled appropriately and efficiently by the volunteers themselves and/or study team members. None of the volunteers who did have vaccine-induced sero-reactivity (VISR) reported social harm. Nevertheless, concepts of HIV vaccine clinical research, such as, the potential of VISR, lack of protection against HIV-infection despite vaccine-induced antibodies and the need for continuous safe sexual practices were re-emphasized and reviewed with study participants, their partners, staff at study sites and at non-study clinics performing HIV tests, as appropriate. Community education is provided continuously by CRC staff members and/or members of the community advisory board (CAB) to address misconceptions about participation in clinical research in general, and in HIV vaccine clinical trials in particular, to alleviate potential social harm.

With an increasing number of trials of prophylactic HIV vaccines enrolling healthy, HIV-uninfected volunteers, the number of individuals who have VISR, but are not HIV-infected, is increasing. VISR varies depending on the HIV antigens in the vaccine construct, the immunogenicity of the vaccine, and the HIV test kits used. VISR may pose problems with discrimination or stigmatization in health care institutions, during ante-natal care, in blood banks or for organ donation. It is crucial to educate volunteers prior to and during their participation in HIV vaccine trials and ensure comprehension of the concept of VISR, assist them and offer long-term post trial follow-up with accurate HIV testing that can differentiate between VISR and natural HIV infection. Health care providers need to be made aware of this problem and trained appropriately. Collection and publication of VISR data may help alleviate the problem.
The benefit of participating in the LTFU study included general HIV counseling, HIV risk reduction counseling, regular assessments of health status, medical check-ups including children born to female participants and referrals for treatment and care as needed.

Conclusions

The summary analysis of clinical events reported during long-term follow-up is unremarkable. No safety signal has been identified. These data contribute to the long-term safety profile of HIV vaccines tested in healthy, HIV-seronegative African adults. For HIV vaccines studied to date, there was only a small potential for VISR, but current and future vaccines may induce stronger antibody responses that potentially pose difficulties for the individual volunteers, as they may be falsely identified as infected with HIV.