MOSAICO

HVTN 706/HPX3002

Global Stakeholder Update Webinar – Wednesday, January 25, 2023
Questions and Answers

As of 10 February 2023 at 5:00pm EST

Thank you for joining this important webinar to share some information about the discontinuation of the Mosaico study. While we are preparing for the CROI presentation, we are limited in what data can be shared at this time; however, the study team is committed to remaining in conversation with global stakeholders and the HIV community about this study and its results. In the meantime, we have prepared answers to the questions shared in the Q/A function of the webinar below. If you have any additional questions about the Mosaico study, please feel free to reach out to the HIV Vaccine Trials Network at info@hvtn.org.

General Study Questions:

1. Can you provide more information about the vaccine used in the study? How was it meant to work? How is it similar/different to other types of vaccines that have been tested?
    a. The vaccine regimen evaluated in Mosaico consists of two components: One component is a tetravalent vaccine of a recombinant, replication-incompetent adenovirus (Ad) type 26 encoding Mosaic 1 human immunodeficiency virus (HIV) type 1 group-specific antigen (Gag), Polymerase (Pol) and Mosaic 1 and 2 envelope (Env) proteins. The second component is a Clade C gp140 and Mosaic gp140 bivalent proteins.
    b. The vaccine regimen was evaluated to determine if it would elicit an immune response against HIV-1 viral proteins. In an earlier study, the vaccine regimen was evaluated in individuals at low risk of HIV acquisition and showed to develop functional humoral and cellular immune responses.
    c. This regimen was not designed to induce broadly neutralizing antibodies. The Mosaico vaccine regimen is similar to the one used in the Imbokodo study conducted in women and Southern Africa, although in Imbokodo only a single-valent soluble protein was given (Clade C gp140), whereas in Mosaico, a mosaic-based mixture of soluble proteins was given (Clade C/Mosaic gp140), which was shown to induce greater and broader immune responses in human studies.

2. Was thrombosis without concurrent thrombocytopenia observed?
    a. Thrombotic adverse events with and without thrombocytopenia were required to be promptly reported to the Sponsor regardless of the causal relationship to study product and seriousness. These adverse events were considered as adverse events of special interest (AESI).
    b. Two adverse events of thrombosis were reported in the Mosaico study. One case occurred in a participant in the placebo arm, and one case occurred in a participant in

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the vaccine arm. Neither case also had associated thrombocytopenia, and no safety issues with the vaccine regimen were identified.

3. What was the "intended use" language regarding PrEP interest that was not recommended, and how was this changed?
    a. Following close community consultation during the planning phases of the study, the study team ensured that anyone interested in PrEP was able to access it, and that potential participants had an authentic choice between an effective HIV prevention option (PrEP) and enrollment in the study. As we wanted this to be an authentic choice, each site developed and implemented a PrEP plan, in which they could link potential participants (and participants enrolled in the trial) into low- or no-cost PrEP services. Once enrolled in the study, HIV prevention counselling occurred on a regular basis, and in the event a participant decided they wanted to start PrEP, they were provided a link to PrEP and allowed to continue in the study.

4. Were there any suspected unexpected serious adverse events (SUSARs) reported apart from the mentioned unsolicited events?
    a. Beside the unsolicited events which are to be reported until 28 days after vaccination, serious adverse events, regardless of causality, have to be promptly reported for the entire study duration. SUSARs are serious adverse events requiring reporting to the regulatory authorities. In Mosaico only one SUSAR was reported, which was assessed as not related to the study vaccinations, and no safety issues with the vaccine regimen were identified.

5. How did participants react to the results? How do you see the results of this study affecting future HIV vaccine trials?
    a. Many participants have been disappointed that the vaccine did not provide protection, but deeply committed to the study and are often volunteering for other studies at those sites.

6. Did the trial screen or track any participants that were on hormone therapy?
    a. Yes, some participants were on hormone therapy. We do not yet have any data analyzed on this group, but it is likely to be too small a number to look specifically at efficacy in this subgroup.

7. Why follow-up seroconverters for 6 months, and non-seroconverters for 24?
    a. The purpose of following seroconverters for 6 months after acquiring HIV was to ensure they were linked immediately to care, and to see if there was any initial impact of the

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vaccine on early post-infection outcomes. The purpose of following the participants in the trial who remained HIV negative was to determine whether the vaccine provided protection against HIV infection.

8. Regarding results dissemination, how do you plan to inform participants and local communities about the trial results? What does community engagement look like with the closure of this study?
    a. Each site has developed their own dissemination strategies, which was a part of their overall Community Engagement Work Plan. All participants were immediately contacted to be informed of the study results and to unblind them about whether they got the vaccines or the placebo. Sites are also doing other things to share information with their local communities including community forums, town halls, and other strategies to present the data.

9. For individuals not attending CROI or part of the broad research/academic community, how will the information presented at CROI be share with the broader public?
    a. The CROI presentation is now public on the CROI website (https://www.croiwebcasts.org/s/2023croi/SPECIAL%20SESSION-1). We will also be doing follow-up webinars to provide the data presented at CROI to the community.

Efficacy Questions:

1. How many events were on the placebo and active arms?
    a. The pre-defined non-efficacy monitoring rules were met and the number of events were similar across both treatment arms, placebo and vaccine.

2. Do you have a point estimate for efficacy? Is this just not effective or reminiscent of the Step Study?
    a. The results are not reminiscent of the Step Study, in that there was no increased risk of HIV acquisition in the vaccine recipients, and no safety issues with the vaccine regimen were identified. We are still in the process of analyzing the data on outcomes, so numbers may change, but there was no efficacy (4.1/100 person-year infection rates in both the vaccine and placebo recipients in the modified intent to treat analysis through month 23.7).

3. What was the estimated efficacy and CI?
    a. No efficacy was observed as the non-efficacy criteria was met. The lower 95% confidence bound was below 0%, and the upper 95% confidence bound was below 50%.

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4. Can you rule out that a different regime with the same vaccine may have produced a different outcome?
    a. The Mosaico regimen, as designed, was what the study team believed would give this vaccine regimen the best chance of providing protection based on earlier research and clinical and pre-clinical studies. Unfortunately, no protection was observed.

PrEP Questions:

1. Were participants allowed to take PrEP at the enrollment date in the Peruvian sites?
    a. Participants were linked to PrEP services if interested instead of trial participation at all sites, including the Peruvian sites. If participants decided after enrollment that they wanted to initiate PrEP, they were also linked to PrEP services at all sites.

2. What access will participants have now to PrEP that the study is discontinued?
    a. Each Mosaico site has a PrEP plan and individuals requiring PrEP will continue to access PrEP as described in these plans.

3. For how long did people who started PrEP in the study stay on PrEP on average?
    a. PrEP data will be available once the study final analysis has been conducted.

4. Did study participants indicate reasons behind not wanting PrEP? What factors seemed to change that position, among those who became interested in PrEP as the trial proceeded?
    a. We conducted a substudy at some of the sites to delve into reasons why people chose to take or not to take PrEP. Those data have not yet been analyzed.

5. Can you comment on if/how the PrEP communication and plans changed after HPTN 083 results became available?
    a. Participants were informed about the HPTN 083 results. However, long acting cabotegravir was not available at many sites outside of the United States, as it has not received regulatory approval.

6. Is there a means to monitor/observe if there is a secondary uptake by the participants in PrEP s/p the trial's end-point closure? The hypotheses being a) previous belief the vaccine would work and protect, b) knowledge and intra-peer communication by study participants increased community PrEP acceptability, i.e., lowering the threshold to PrEP uptake.
    a. Once the study ended, we don't have a way to track PrEP uptake in the participants. However, all participants were counseled about PrEP and linked to PrEP services at exit from the study.

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7. Did PrEP use increase after results of the Imbokodo study? As a caution? Hinted at by investigators?
    a. PrEP data will be available once the study final analysis has been conducted. We also conducted a substudy at some of the sites to delve into reasons why people chose to take or not to take PrEP. Those data have not yet been analyzed.

8. What is going to happen to the stock of Prep? Will it be returned or can it be given to the participants?

Before starting in the study, all sites were required to have PrEP plans that included how they would link potential participants (prior to enrollment) to low- or no-cost PrEP services, and how they would link enrolled participants to PrEP after enrollment, and upon study exit. Sites first attempted to link participants to PrEP – those who took PrEP were not enrolled in the trial.

After enrollment, any participant who changed their mind and wanted to take PrEP was linked to PrEP services. This was true for all Mosaico sites. We don't yet have data on the duration of PrEP use for participants in the trial. We have a substudy to investigate why people did or did not take PrEP – those data have not yet been analyzed. We do not have a mechanism to monitor secondary uptake of PrEP after trial closure. We haven't yet analyzed PrEP uptake by temporal trend (e.g., after the Imbokodo results were available.)

Demographic Questions:

1. Sorry if I missed it but did you have enrollment targets specifically for trans and gender diverse people? How many TGD ppl actually enrolled?
    a. An enrollment target of 10% globally was defined for transgender individuals.

2. Will disaggregated transgender enrollment data be released, showing enrollment of transgender men, transgender women, and gender nonbinary people, respectively?
    a. Gender identity data will be available once the study final analysis will be conducted.

3. Will behavioral and sociodemographic data of participants be presented here, or elsewhere?
    a. We had hoped to enroll 10% persons who were trans or gender diverse. We enrolled 328 participants who self-identified as something other than male gender, 8.5% of the total number.

VISP Questions:

1. Did you have any issues with VISP and if so, how did you manage referral to local providers of PrEP as they usually conduct HIV testing as part of their service?

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   a. Participants were asked to get all of their HIV testing done through the study site, so as not to unblind them as to whether they got vaccine or placebo. Sites worked with PrEP providers to do the HIV testing and share the results (i.e., HIV negative vs. HIV positive).

2. The participants will need to have access to VISP SERVICE centers all over the world. How is going the process in Europe? Can we expect to view reduced the 2 weeks of waiting for the PCR results?
   a. A post-study HIV testing service is available in all European countries (including the United Kingdom and Switzerland) for Mosaico participants residing in Europe.

Future Directions Questions:

1. Do we have any other vaccine trial currently in progress? At what stages are they?

2. Where do these results leave us for the present and future of HIV vaccine research?

3. How long will it take to advance another candidate to phase 3?

4. Some of the messaging has talked about how the Mosaico trial will contribute to HIV vaccine research moving forward. Could you talk a little more about what more we might learn and how — e.g., subanalyses, correlates analyses?

5. Is there a feeling by the health care professionals that some positive steps have been achieved and if so what steps?

6. Do you get a sense of how the flat results in MOSAICO may impact community interest in MAb trials? Do you know to what extent participants differentiate between active immunization and passive transfer of mAbs?

7. Would RNA vaccines be more successful than Mosaico? If so why?

8. Winnie Byanyima said "Global research efforts into vaccines and a cure must carry on. At the same time, the world cannot wait for, or depend on, a vaccine or cure." final thoughts on that?

9. Can we end the epidemic without an HIV vaccine?

The future of HIV research is an extremely complex topic and will likely be discussed in a wide array of forums by representatives from across the HIV community. Our responses represent only a specific slice of this discussion, and should not be taken as definitive statements on the direction of the field.

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The results of this trial, in combination with other trials that came before, suggest that the approach of using vaccines to generate non-neutralizing antibodies is not successful at producing efficacious vaccines. There is a robust pipeline of studies (within the HIV Vaccine Trials Network, International AIDS Vaccine Initiative, and other groups) to develop and test both broadly neutralizing antibodies themselves, or vaccines that will generate neutralizing antibodies.

We explain to study volunteers and the community the difference between the trials testing broadly neutralizing antibodies (that are made in the lab, and then infused, like an antibody version of PrEP) vs. vaccines that teach the body to make its own neutralizing antibodies. It will take at least several years to mount another Phase 3 trial, and that likely will be of broadly neutralizing antibodies themselves, not of a vaccine per se.

The vaccines that are being developed to help your body generate its own neutralizing antibodies are still in very early stages of development and testing. mRNA is a vaccine platform that allows for rapid manufacture of vaccines, and is being used as part of the effort to develop a vaccine to generate neutralizing antibodies.

It is still early to know what types of analyses will be done with the Mosaico study results, but could instead be combined with studies being done in Imbokodo to look for potential immune correlates of protection.

We agree that global research on vaccines and cure must continue, and as noted above, there are some promising approaches to developing a different type of vaccine, one that generates neutralizing antibodies. It is also true that we must ensure immediate access to and desirability of other approaches to HIV prevention, including PrEP and PEP, to those in need of prevention.

The world should try to end the epidemic even as the quest to develop a vaccine continues through scale-up of proven prevention strategies, including antiretroviral treatment for people living with HIV, and prevention modalities for people at risk of HIV (e.g., PrEP, PEP, vaginal ring, voluntary medical male circumcision). We also need more research into new PrEP and PEP modalities. We believe vaccines can play a vital role in combination with other modalities in ending the HIV epidemic.