A PHASE 1 CLINICAL TRIAL WITH A CONSENSUS SEQUENCE-BASED NATIVE-LIKE HIV-1 ENV TRIMER

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BACKGROUND

In spite of effective antiretroviral treatment, HIV-1 continues to infect 1.5 million people annually, stressing the need for a protective HIV-1 vaccine. The only target of antigen design for antibody-based vaccines is the HIV-1 envelope glycoprotein (Env). Inducing broadly neutralising antibodies against the Env protein would be a major step towards having a prophylactic vaccine capable of curbing the HIV pandemic.

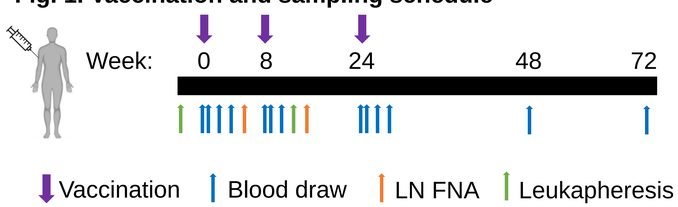
ConM SOSIP.v7 (ConM) is a native-like Env trimer with SOSIP stabilising mutations, based on an artificial consensus sequence of all HIV-1 isolates in group M, responsible for the pandemic. When used to immunise non-human primates, ConM induces strong autologous neutralising antibody responses.

We here aim to evaluate the safety of ConM in humans, as well as explore its immunogenic properties and provide proof-of-concept of the utility of native-like Env trimers as components of an HIV-1 vaccine regimen.

METHODS

The ACTHIVE-001 study is an ongoing single center, phase 1 clinical trial at the Amsterdam UMC, the Netherlands (NCT03961438). 24 healthy adults are vaccinated with ConM at zero, two and six months (**Fig. 1**). Participants are randomised to receive either a consistent dose of vaccine (group A), or a reduced booster dose at six months (group B), aimed to increase antibody responses and levels of somatic hypermutation. Safety information is solicited throughout a period of 18 months. Peripheral blood draws are performed, as well as leukaphereses and ultrasound guided lymph node fine needle aspirates (LN FNA) in order to investigate Env-specific germinal center (GC) responses.

Fig. 1. Vaccination and sampling schedule



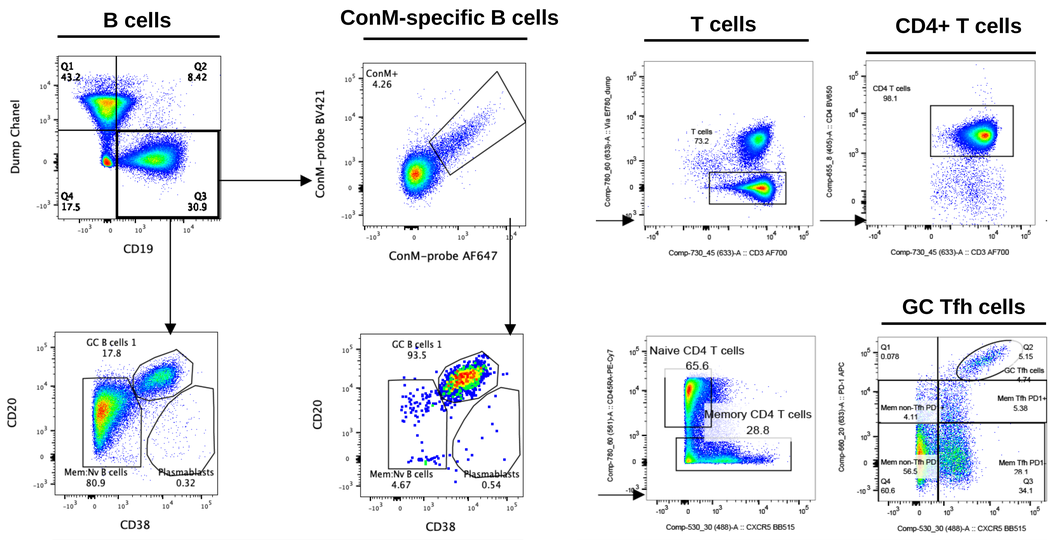


Fig. 3. Fluorescently labeled cell sorting (FACS) of ConM-specific germinal center B and Tfh cells

RESULTS

At present, 24 participants received an accumulated total of 63 vaccine administrations (current median follow-up 10 months), while seven participants are not yet fully vaccinated. No Serious Adverse Events (SAE) or Suspected Unexpected Serious Adverse Reactions (SUSAR) were observed. The majority of Adverse Events (AE) were mild to moderate and self-limiting in nature.

An interim study of the first thirteen participants revealed a strong serum neutralising antibody response against the autologous Tier 1A ConM virus in all individuals, two weeks after the third vaccination. In the majority of participants (77 %), some level of autologous neutralisation was already present two weeks after the first boost (**Fig. 2**). No neutralisation was detected in these samples against the related Tier 1B ConS virus.

Fig. 2. ConM serum neutralisation (TZM-bl assay)

Group A			Group B		
ConM serum neutralisation (TZM-bl)					
ID	**Week 10**	**Week 26**	**ID**	**Week 10**	**Week 26**
005	183	1057	**006**	102	997
010	40	172	**018**	<20	1147
013	<20	224	**020**	490	1539
017	80	1579	**022**	4104	2008
019	<20	43	**024**	707	1290
021	155	372	**027**	1997	2634
023	603	856			

IC_{50}
<20
20-40
41-100
101-1000
>1001

A current total of 37 LN FNA's were performed three weeks after the first and second vaccination, with 25 (68 %) yielding sufficient lymph node mononuclear cells (LNMC) for nine colour flow-cytometry analysis.

In 13 (52 %) out of these 25 procedures, ConM-specific GC B cells could be detected following one and/or two vaccinations. These cells, as well as GC T follicular helper (Tfh) cells, were fluorescently labeled and sorted for further downstream analysis (**Fig. 3**).

Strikingly, in some cases, > 90 % of ConM-specific B cells were GC B cells. Enrichment of ConM-specific B cells towards immunoglobulin gamma (IgG), compared to total B cells confirmed an isotype switch.

CONCLUSIONS

The ConM vaccine is safe when administered to humans and is capable of inducing strong neutralisation titers against the autologous Tier 1A ConM virus in all recipients.

We were able to successfully sample draining lymph nodes in roughly half of the participants and could demonstrate that the vaccine elicits vaccine-specific germinal center reactions. Downstream (sequence) analysis of collected LN FNA samples, paired with data gathered from peripheral blood samples, will help elucidate which properties of GC B and Tfh cells drive the durability and quality of the antibody response.

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