Sex-based differences in antibody responses induced by a native-like HIV-1 envelope trimer vaccine

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BACKGROUND

A protective vaccine would be the most powerful tool towards reducing HIV-1 infections worldwide and sustainably ending the AIDS epidemic as a public health threat. We here assessed the safety and immunogenicity of ConM SOSIP.v7, a native-like envelope trimer vaccine based on an HIV-1 group M consensus sequence, in HIV-negative adults.

METHODS

24 individuals were enrolled in a phase 1 clinical trial (ClinicalTrials.gov Identifier NCT0396143) to receive three intramuscular dosages of adjuvanted ConM SOSIP.v7 (baseline, eight and 24 weeks) and followed-up for one year thereafter (**Fig. 1**). Out of 23 per-protocol vaccine recipients, 10 received a one-fifth fractional third dose, aimed to increase B cell somatic hypermutation. Outcomes included ConM-specific total immunoglobulin G (IgG), IgG subclasses, pseudovirus neutralisation and single B cell sequencing. Plasma levels of sex hormones were measured over time.

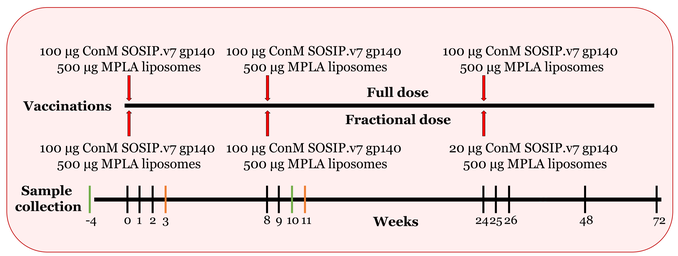
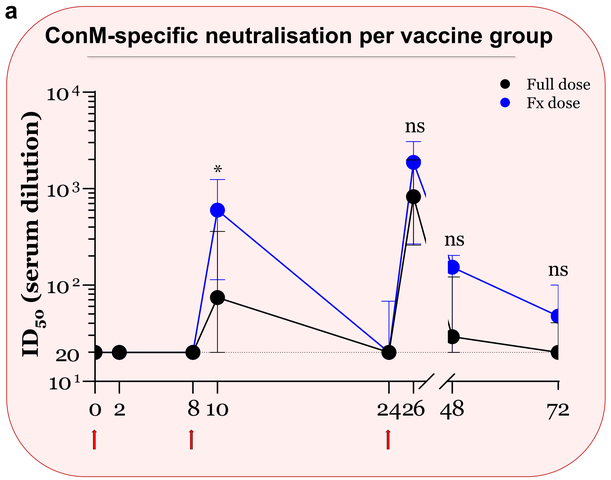
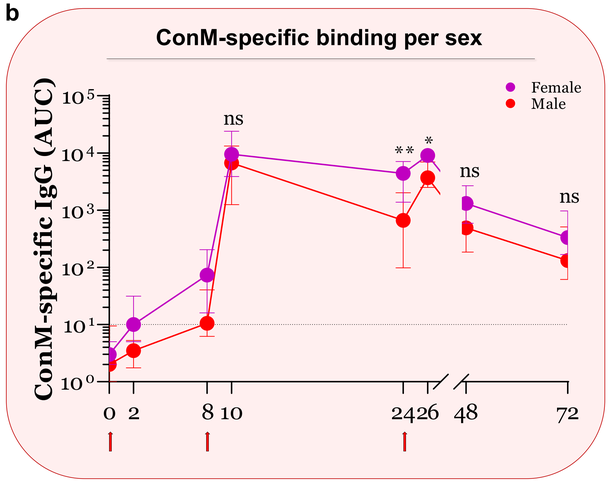
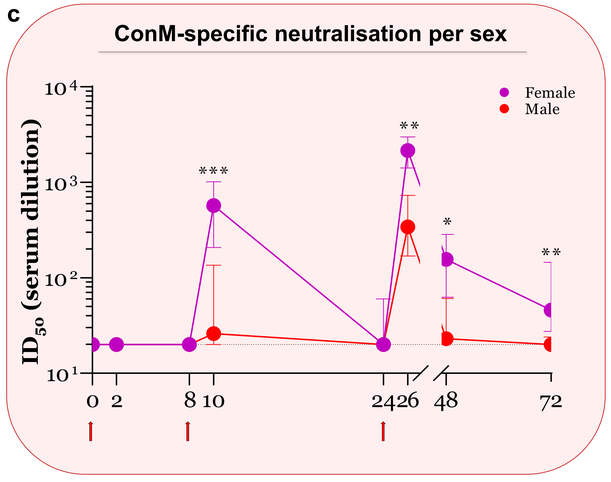


Figure 1. Vaccination and sampling schedule. Participants received vaccinations at baseline, eight weeks and 24 weeks. Dosing between vaccine groups differs at 24 weeks, as indicated. Vaccines were administered i.m. Blood samples were collected as indicated in **black**. **Green** bars represent leukapheresis procedures. **Orange** bars indicate lymph node fine needle aspirations in addition to blood sampling.







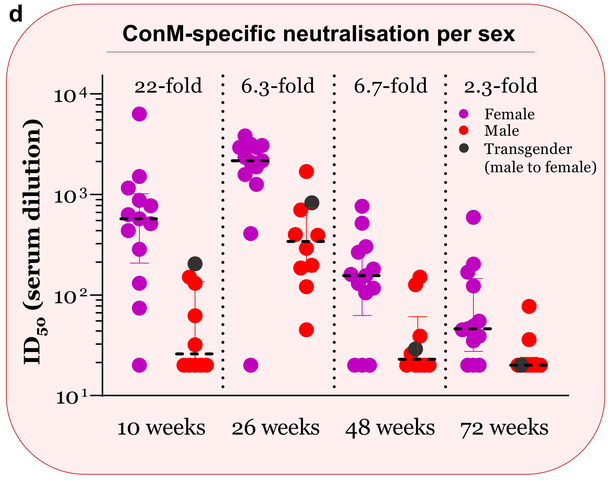


Figure 2. ConM-specific antibody binding and neutralisation. **a**. ConM-pseudovirus serum neutralisation per vaccine group. 50% inhibitor dilution (ID_{50}) values are depicted at each vaccination baseline, two weeks post-vaccination and at 48 and 72 weeks. Full dose n = 13. Fractional (Fx) dose n = 10. **b**. ConM-specific IgG levels measured by binding antibody multiplex assay (BAMA). Values indicate the median area under the median fluorescence intensity (MFI) titration curve (AUC) and are shown at each vaccination baseline, two weeks post-vaccination and at 48 and 72 weeks. **c-d**. ConM-pseudovirus serum neutralisation (ID_{50}) per sex at birth. Female n = 13. Male n = 10. Only per-protocol vaccine recipients (n=23) were included in the analyses above.

RESULTS

The majority of adverse events were mild (84.4%) to moderate (12.9%), self-limiting and similar between dosage groups and sexes. No serious adverse events were reported. Similar to non-human primates, adjuvanted ConM SOSIP.v7 was consistently capable of inducing an autologous neutralising antibody response in humans, which remained detectable in half of the participants six months after the final vaccination. Antibody binding to several heterologous envelope proteins could be detected in the majority of participants, but no neutralisation breath (*not shown*). No differences in serological outcomes could be attributed to the fractional third dose (**Fig. 2a**).

RESULTS (CONTINUED)

Female born participants developed higher levels of ConM-specific IgG over time, albeit only significant during and after the third vaccination (**Fig 2b**). Interestingly, female participants had an earlier increase in neutralising antibodies than males, resulting in a 6.3-fold higher peak neutralisation titer post third vaccination (**Fig. 2c-d**). Sex-based differences in IgG1 and IgG4 subtype responses were also observed. Subtle correlations, both positive and negative, were seen between ConM-neutralisation, IgG2 and IgG3 levels on one hand, and oestradiol and testosterone on the other hand, but the small sample size limits drawing strong conclusions. Single B cell sequencing should reveal whether the fractional dose and/or sex influence B cell affinity maturation.

CONCLUSIONS

The adjuvanted ConM SOSIP.v7 native-like trimer vaccine is safe and elicits a robust strain-specific neutralising response in nearly all recipients, making it an interesting boosting immunogen candidate. Females responded earlier and had a striking 6.3-fold higher neutralisation titer after the final vaccination, indicating not only a difference in magnitude but mainly the functionality of the antibody response. This study highlights that sex-based differences should be taken into consideration when assessing HIV-1 vaccine candidates and adjuvants.

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