SOSIP Immunization Induces Neutralizing Antibodies to Diverse Clade B Strains in HIVACFOUND Trial

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BACKGROUND

- We previously reported that a subset of exceptional patients ("acute neutralizers") can develop broad neutralizing antibody responses early after HIV infection (Sanchez-Merino et al., J Virol 2016). These antibodies target epitopes distinct from those recognized by classical elite neutralizers.
- Transmitted/founder (T/F) viruses may preferentially expose antigenic features associated with recent infection, potentially favoring antibodies capable of recognizing early viral variants. In contrast, Env proteins from chronic viruses often show limited ability to neutralize founder strains.
- We therefore designed a stabilized SOSIP Env trimer based on a founder virus and evaluated its safety and immunogenicity in HIV-negative volunteers.

OBJECTIVES

Safety: To evaluate the safety and tolerability of intramuscular administration of 763SIP8 SOSIP immunogen adjuvanted with MPLA-5 in HIV-uninfected adults.
Immunogenicity: To assess the ability of the vaccine to induce humoral and cellular immune responses, including neutralizing antibodies.

METHODS

Trial design

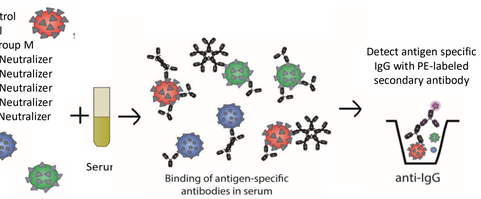
	Phase I, non-comparative, single center clinical trial to evaluate safety and immunogenicity of the 763SIP8/MPLA-5 vaccine in adult healthy volunteers. Each participant received four IM immunizations of 100µg of 763SIP8 (SOSIP v8.2 763) adjuvanted with 500 µg MPLA liposomes at 0, 8, 24 and 48 weeks.
	12 healthy adults aged 18-50
	Subjects were followed for 48 weeks after the last dose.

Immunological studies

Customized BAMA (Luminex) assay for measuring antibodies in serum

Beads coated with viral proteins

RSV Fusion (F) protein	positive control
Tetanus Toxoid (TT)	positive control
ConM Env trimer	consensus of group M
763 Env trimer	clade B–Acute Neutralizer
887 Env trimer	clade B–Acute Neutralizer
892 Env trimer	clade B–Acute Neutralizer
936 Env trimer	clade B–Acute Neutralizer
AMC011 Env trimer	clade B-Elite Neutralizer
TRO.11 Env trimer	clade B
BG505 Env trimer	clade A
ZM197M	clade C
CZA197	clade C
DU422	clade C



Virus neutralization assays

Autologous T/F recombinant virus (763)



Heterologous recombinant viruses

Name	Subtype	Tropism	Stage	Tier
VI191	A	R5	Chronic	2
NL4-3	B	X4	Chronic	1A
SF162	B	R5	Chronic	1A
JR-FL	B	R5	Chronic	2
JR-CSF	B	R5	Chronic	2
REJO4541.67	B	R5	Fiebig II	2
THRO4156.18	B	R5	Fiebig II	2

Neutralizing activity was evaluated by autologous neutralization assays using a recombinant virus expressing the 763 envelope, and by heterologous neutralization assays using Env-reporter viruses carrying Renilla luciferase in the *nef* locus. Reporter viruses were generated by cloning full-length envelopes into the pNL-lacZ/env-Ren vector.
The table summarizes the subtype, tropism, tier and infection stage of the cloned envelopes.

Cellular responses

Frozen PBMCs from individuals vaccinated with SOSIP-763 vaccine were collected prior to immunization (W0) and one week after the third vaccine dose (W25). PBMCs were stimulated with a SOSIP-763 peptide pool (1 µg/ml). Dynabeads coupled to CD3/CD28 was used as a positive control for proliferation
PBMCs were stained with fluorochrome-conjugated antibodies to surface markers listed in Table. After surface staining, cells were fixed and permeabilized followed by intracellular staining for Ki67.

Marker	Fluorochome
CCR7	BV421
CXCR5	BV750
CD3	BV510
CD25	PE/AlexaFluor700
CD28	BV650
CD127	APC/R700
CD4	CF568
CD8	BV805
CD45	PerCP
CD45RA	BUV395
CD62L	BV615
Ki67	APC

SUMMARY

We evaluated a vaccine based on a stabilized SOSIP Env trimer derived from a founder virus. The HIVACFOUND trial enrolled 12 healthy volunteers. The vaccine was safe and well tolerated. Vaccination elicited humoral immune responses, including neutralizing antibodies against multiple subtype B variants. These results support the potential use of founder virus–based SOSIP immunogens in the development of HIV-preventive vaccines.

PLAIN LANGUAGE SUMMARY

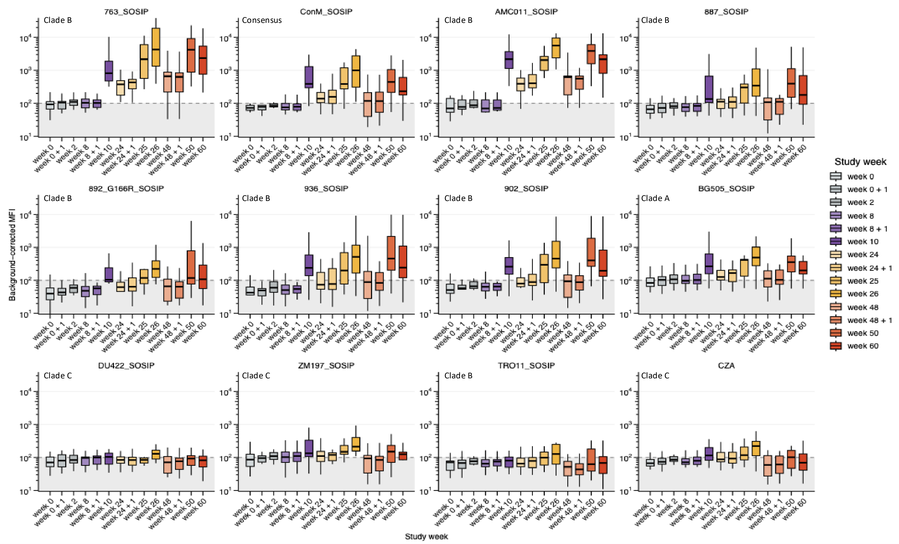
An experimental HIV vaccine using a novel design inspired by the virus that first establishes infection was tested in healthy volunteers. This strategy aims to train the immune system to recognize HIV at its earliest stages. The vaccine was safe and well tolerated. It also stimulated immune responses that produced antibodies capable of neutralizing different subtype B HIV variants.

RESULTS

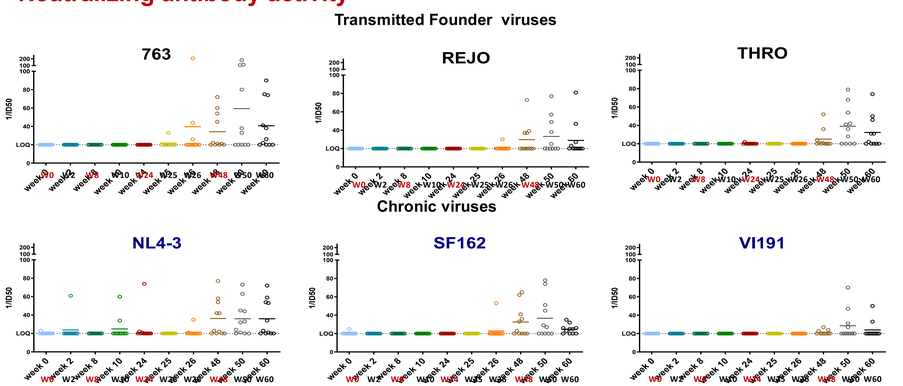
Adverse Events Related to the study medication (n=25):

Musculoskeletal, Pain injection site, Fatigue, Myalgia, Cramps at extremities (n=9)
Dermatologic (n=9) Systemic (n=3) Gastrointestinal, respiratory (n=2)
Neurological (n=1) Infection (n=1)
Severity: Mild (n=22) Moderate (n=3). ***None persisted more than 7 days***

Dynamics of anti-HIV antibodies induced by immunization

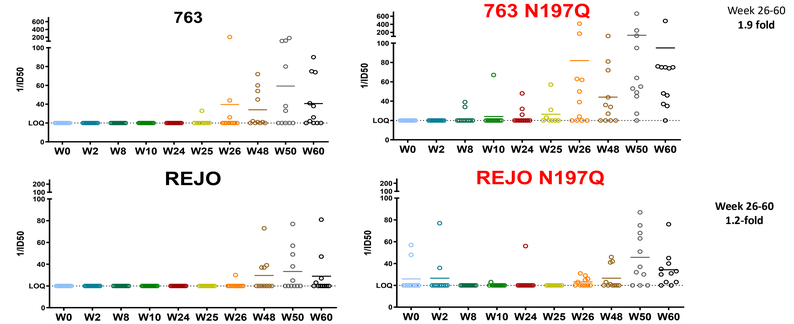


Neutralizing antibody activity



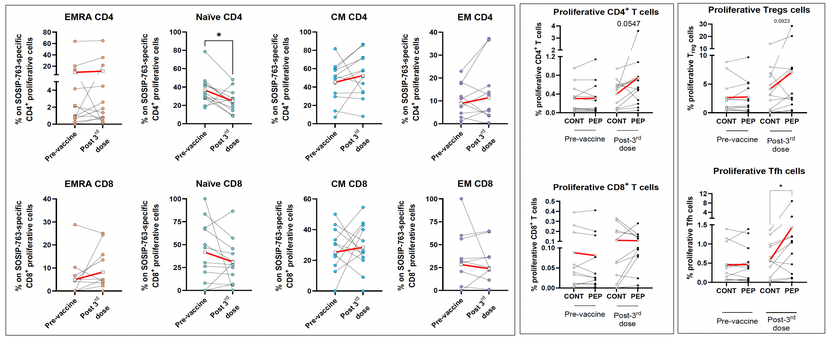
Neutralizing antibody responses are shown as ID50 values for each participant. Each dot represents the ID50 value of one volunteer at the indicated week, and the horizontal line indicates the mean ID50 for that week. Neutralizing activity emerged at week 48, prior to the fourth dose. Weeks labelled in red correspond to immunization doses.

Effect of N197 glycan removal on virus neutralization



Neutralizing antibody responses are shown as ID50 values for each participant. Lack of an asparagine at position 197 (N197Q) increased neutralization sensitivity for the autologous virus (763) but did not affect REJO neutralization.

Cellular subsets and proliferative responses after immunisation



Changes in cellular subsets after immunisation (left panels) and proliferation (Ki67, right panels) in response to 763 peptides assessed by Flow cytometry in PBMCs from volunteers participating in the HIVACFOUND trial

CONCLUSIONS

- Immunization with the SOSIP763 Env trimer was **safe and well tolerated**
- SOSIP763 vaccination induced **robust anti-HIV antibody responses**, showing strong reactivity to the autologous SOSIP and other clade B trimers, including the group M consensus ConM.
- Antibody cross-reactivity was **moderate against clade A** and **limited against clade C trimers**
- **Neutralizing activity emerged after the third dose**, with moderate autologous neutralization detected in 7/11 volunteers and moderate heterologous neutralization of transmitted/founder tier 2 clade B strains. Lower neutralization was observed against chronic tier 1 clade B viruses.
- Neutralizing antibodies targeted the **Env 197 position**, a site modulated by glycosylation.
- Vaccination was associated with increases in **CD4 central memory T cells** and **T follicular helper responses**, supporting coordinated humoral immunity.

Overall, the HIVACFOUND trial supports the potential of founder virus–based SOSIP immunogens to elicit neutralizing antibody responses with intra-subtype breadth.

ADDITIONAL KEY INFORMATION

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