Development of VLP Vaccine Harboring the DC-targeting domain of Ebola glycoprotein and HIV Envelope Conserved Elements

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Introduction

The development of an effective vaccine against HIV infection remains a global priority. HIV-1 envelope glycoprotein (Env) plays a key role in viral infectivity and is the only viral antigen that is present on the surface of virion and infected cells as a main target of host protective immune responses.

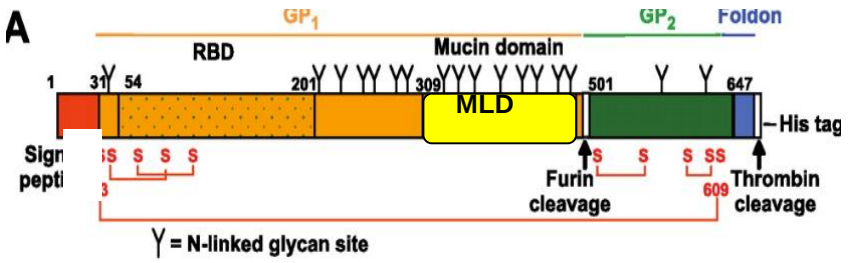
In this study, we have developed a new HIV vaccine approach by fusing HIV Env conserved regions (EnvCEs), including the membrane proximal external region (MPER), with a DC-targeting/activation domain (EbΔM) derived from the Ebola virus envelope glycoprotein (EbGP) and incorporated in the virus like particles (VLPs). The goal of this study is to provide proof-of-principle for this unique vaccine strategy that can enhances the immunogenicity of HIV EnvCEs and be able to induce specific immune response targeting these HIV Env conserved regions presented in various HIV subtypes.

Our results showed that the EboGPΔM-9CE or EboGPΔM-MPER was expressed in the cells and incorporated into VLPs that can efficiently target a human monocyte cell line (THP-1) and human monocyte-derived macrophages (MDMs). Animal studies revealed that immunization with VLPs containing the above chimeric proteins, especially EboGPΔM-MPER, induced significantly higher anti-HIV Env antibodies than a native Env-VLPs in a mouse model.

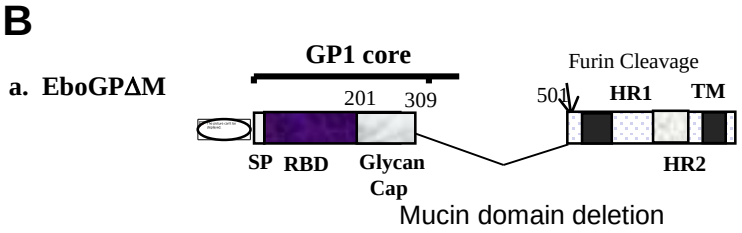
Overall, EboGPΔM-MPER pseudotyped HIV VLPs significantly enhanced HIV-specific immune responses and represented as a potential universal vaccine candidate. Further analyses of whether the EboGPΔM-MPER- and the EboGPΔM-CEs-induced neutralizing activity and/or ADCC activities is still under the way.

EbΔM-based vaccine technology

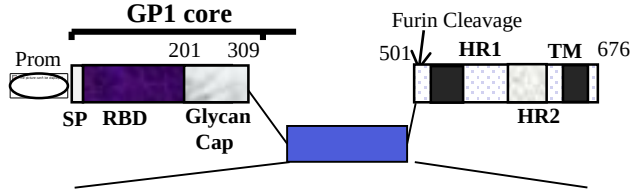
Ebola virus glycoprotein (EbGP)



EboGPΔM



C EboGPΔM-polypeptides fusion protein



Antigenic polypeptide of viral pathogens (up to 243 aa), such as V3 of HIV Env

Ao et al., J. Virol. 2021. 95(15):e0236820

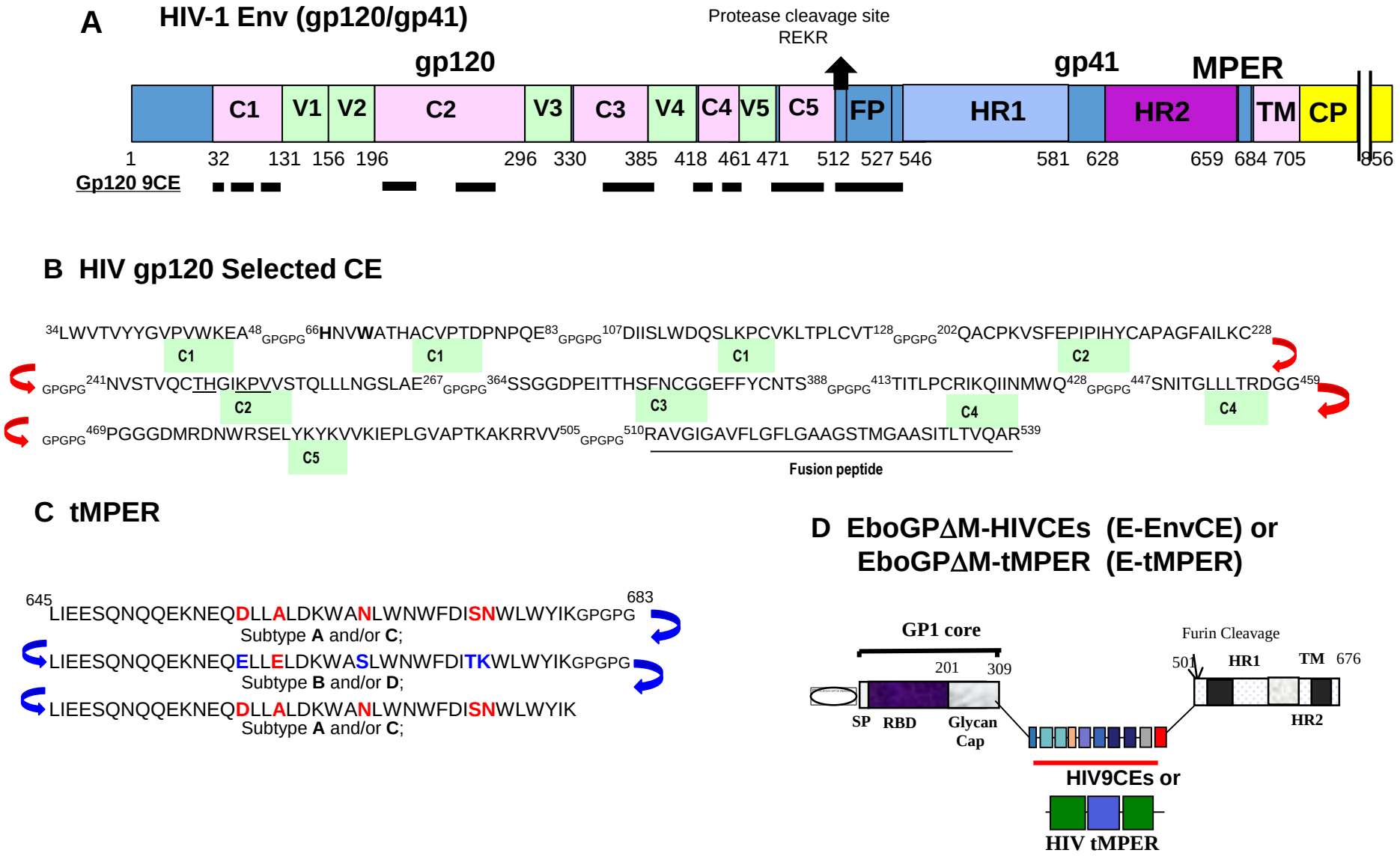


Fig. 1. The designation for EboGP-EnvCE and EboGP-tMPER immunogens. A) Schematic representation of the HIV Env gp120/gp41 glycoprotein and selected conserved elements (CEs). **B)** Sequences of conserved elements (CEs) from HIVgp120 that were linked by a spacer (GPGPG). **C**)Three conserved MPER (tMPER) from different HIV subtype that were linked by a spacer (GPGPG). D) HIV EnvCEs or tMPER was inserted into the EboGPΔM at the location of Mucin-like domain and named as E-EnvCE or E-tMPER.

E-EnvCE or E-tMPER was incorporated into HIV-based VLPs that efficiently target THP1 and THP-1 derived macrophages

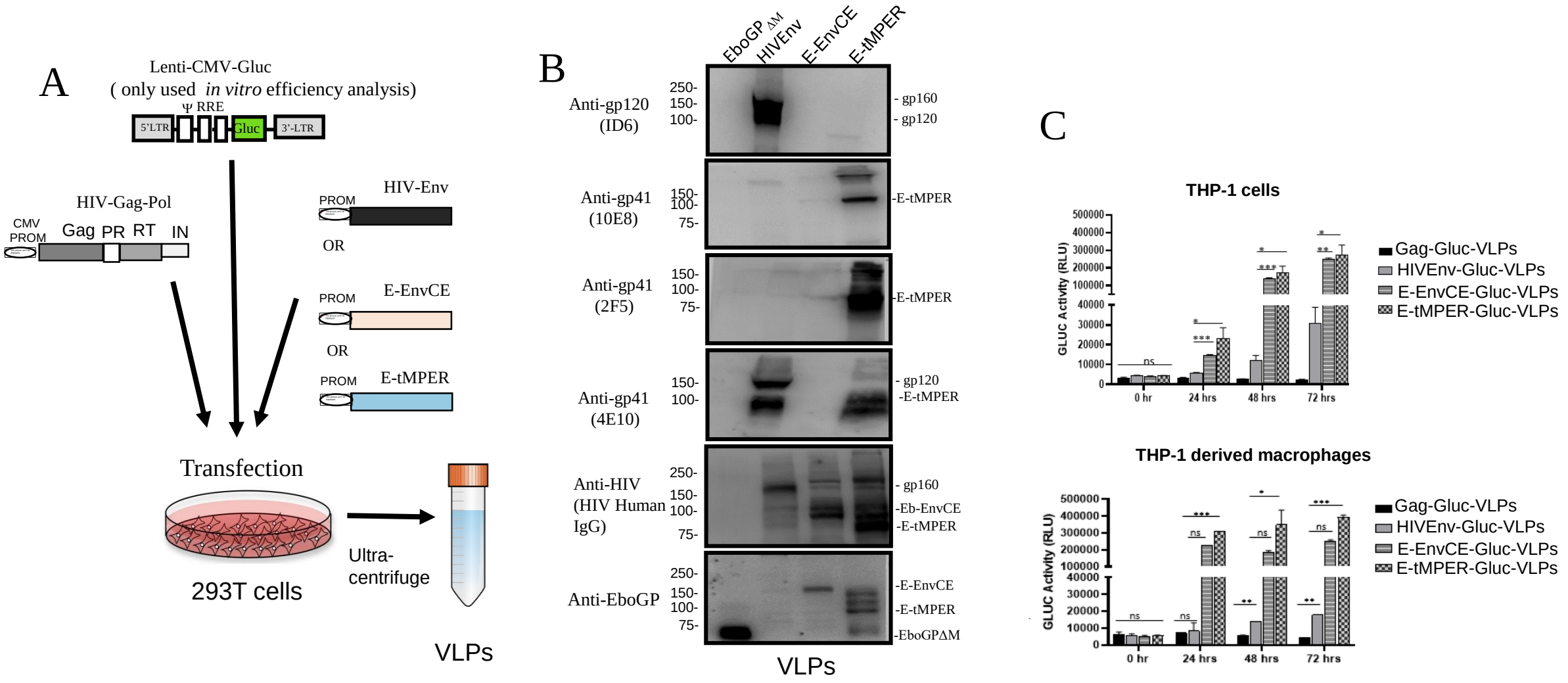


Fig. 2. A) Generation of psedotyped HIV based VLPs. **B**) Detection of HIVEnv, E-EnvCE or E-tMPER in VLPs by WB using different specific antibodies. **C)** THP1 or THP1 derived macrophages were infected by E-EnvCE, E-tMPER, HIV Env pseudotyped Gluc^{+}-VLPs or control VLPs. At different time points post-infection, the supernatants were collected and subjected to detection of Gluc activity.

EboGPΔM-MPER pseudotyped HIV VLPs significantly induced HIV-specific immune responses

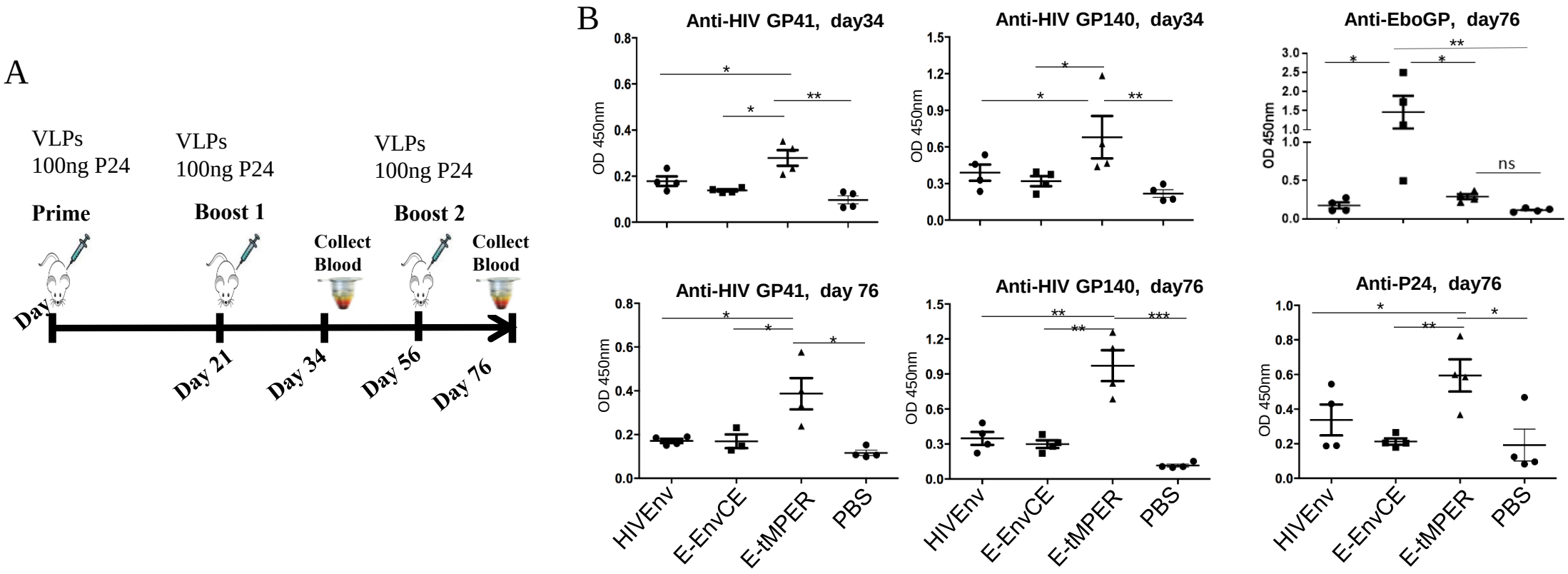


Fig. 3. A) Mouse immunization protocol. **B)** The levels of anti-HIV GP41, anti-HIV GP140, anti-HIVp24, anti-EboGP antibodies in the sera of immunized BALB/c mice were detected by corresponding ELISA. Data represent Mean ±SD. Statistical significance was determined using unpaired T-test. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.