**Supplementary Experimental procedures:**

**Vaccine Samples**

RV144 (Rerks-Ngarm et al., 2009): Plasma samples from 30 vaccinated subjects at week 26 (2 weeks post final vaccination) were provided by the MHRP. Vaccinated subjects were administered ALVAC vCP1521 prime, a recombinant canary pox vector genetically engineered to express CRF01_AE HIV-1 gp120 (92TH023) linked to the transmembrane anchoring portion of subtype B gp41 and HIV-1 gag and protease (weeks 0, 4, 12, 24), followed by a boost with AIDSVAX® B/E containing bivalent rgp120 MN (clade B) and A244 (clade E) protein (week 12 and 24). RV144 case:control study data were provided by the RV144 study team (Haynes et al., 2012) (Yates et al., 2014)

VAX003 (Pitisuttithum et al., 2006): Serum samples from 30 vaccinated subjects at month 30.5 (two weeks post final vaccination) were provided by GSID. Vaccinated subjects were administered AIDSVAX® B/E at month 0, 1, 6, 12, 18, 24 and 30.

HVTN204 (Churchyard et al., 2011): Serum samples from 30 vaccinated subjects taken at 2 weeks post final vaccination were provided by the HVTN. Subjects were administered a six-plasmid HIV-1 DNA prime (envA, envB, envC, gagB, polB, nefB) at month 0, 1, and 2 followed by a boost with recombinant adenovirus serotype-5 (rAd5) expressing HIV-1 at month 6.

IPCAVD 001 (Barouch et al., 2013): Serum samples from 30 vaccine subjects taken at 2 weeks post final vaccination were provided by Dan Barouch. Subjects were administered a single dose of rAd26 encoding Clade A HIV-1 Env at week 0.

All vaccine samples included in this analysis were balanced for sex and were collected from subjects 20–-50 years of age who provided signed, informed consent.

**Antibody-Dependent Cellular Phagocytosis (ADCP) Assay**

The THP-1 phagocytosis assay was performed as previously described (Ackerman et al., 2011). Briefly, THP-1 cells were purchased from ATCC and cultured as recommended. Biotinylated rgp120 (clade specific for respective vaccination as mentioned previously) (Immune Technology) was used to saturate the binding sites on 1 μm fluorescent neutravidin beads (Invitrogen) overnight at 4°C. Excess antigen was removed by washing the pelleted beads, which were then incubated with patient Ab samples for 2 hr at 37°C. Following opsonization, THP-1 cells were added, and the cells were incubated overnight to allow phagocytosis. The cells were then fixed, and the extent of phagocytosis was measured via flow cytometry on a BD LSR II flow cytometer equipped with high-throughput sampler. The data are reported as a phagocytic score, which takes into account the proportion of effector cells that phagocytosed and the degree of phagocytosis (integrated MFI: frequency x MFI) (Darrah et al., 2007). Each Ab sample was tested over a range of concentrations (0.1–100 μg/ml).

**Antibody-dependent cellular cytotoxicity (ADCC) assay**

The rapid fluorescent ADCC (RFADCC) assay was performed as previously described (Gomez-Roman et al., 2006). In brief, CEM-NKr cells were pulsed with vaccine clade-specific rgp120 proteins (6 μg/ml) and labeled with the intracellular dye CFSE and the membrane dye PKH26. NK cells were enriched directly from seronegative donor whole blood by negative selection using RosetteSep (Stem Cell Technologies). Purified IgG was added to the labeled, antigen-pulsed CEM-NKr cells after which fresh NK cells were added. The cells were incubated for 4 hr at 37°C and then fixed. The proportion of cells that maintained membrane expression of PKH26 but lost CFSE staining (i.e., lysed cells) were quantified via flow cytometry.

**Antibody-dependent complement deposition (ADCD)**

Ab-dependent complement deposition was assessed by the measurement of complement component C3b on the surface of target cells. CD4-expressing target cells were pulsed with the relevant vaccine-specific gp120 protein (60 mg/ml), and incubated with purified Abs. Freshly isolated HIV negative donor plasma diluted with veronal buffer and 0.1% gelatin (1:10 dilution) was added, the cells were incubated for 20 min at 37°C. The cells were then washed with 15 mM EDTA in PBS, and complement deposition was detected via flow cytometry following staining for C3b (Cedarlane). Replicates using heat inactivated donor plasma were used as negative controls.

**Antibody-dependent NK cell activation**

Ab-dependent NK cell degranulation and cytokine/chemokine secretion was measured using the CEM-NKr CCR5+ T lymphoblast cell line pulsed with vaccine-specific gp120 (60 mg/ml), as previously described (Chung et al., 2014b). Fresh NK cells were isolated from whole blood from seronegative donors using negative selection with RosetteSep, as recommended by the manufacturer. The antigen-pulsed CEM-NKr cells and isolated primary NK cells were mixed at a ratio of 1:5, and purified Abs, anti-CD107a, brefeldin A (10 mg/ml) (Sigma), and GolgiStop (BD) were added and the cultures incubates for 5 hours at 37°C. The cells were then washed and stained for surface markers using anti-CD16, anti-CD56, and anti-CD3. The cells were then washed, fixed and permeabilized using Fix & Perm (Invitrogen), and then stained intracellularly with anti-IFN-γ and anti-MIP-1β. The cells were then fixed in 4% paraformaldehyde and analyzed using flow cytometry. NK cells were defined as CD3-negative and CD16- and/or CD56-positive. All antibodies for flow cytometry were purchased from BD.

**FcγR Surface Plasmon Resonance (SPR)**

Antibody affinity for FCGRs was determined using surface plasmon resonance and a Biacore 3000 as previously described (Chung et al., 2014a). Briefly, research grade CM5 plasmon surface resonance chips were coated with recombinant FcGRIIa, IIb, IIIa or no protein. The subjects Abs were added at 125 ug/ml. The binding of Abs to the individual FCGRs was quantified as the relative response units of signal following each sample injection.

**Luminex Isotype Assay**

A Luminex isotype assay was used to quantify the relative concentration of each Ab isotype among the HIV-specific Abs as previously described (Brown et al., 2012). Briefly, Luminex microplex carboxlyated beads (Luminex) were coupled to the indicated proteins via covalent NHS-ester linkages by combining EDC and NHS (Thermo Scientific) in PBS, as recommending by the manufacturer. The coupled beads (50 µl of a 100 microspheres/µl solution in 0.1% BSA in PBS) were added to each well of a 96-well filter plate (Millipore). The purified IgGs (50 µl of each vaccine sample diluted to 200 µg IgG/ml) was added to five wells of the 96-well plate and incubated at 4°C overnight. The beads were washed three times with 100 µl of PBS-Tween, and individual IgG isotype detection reagents (i.e., bulk IgG, IgG1, IgG2, IgG3, and IgG4 for all vaccines plus IgA was assessed for the RV144 study from plasma samples) conjugated to PE (Southern Biotech) were added individually to each of one of the five wells. The 96-well plate was incubated with shaking for 2 hr, washed three times, and read on Bio-Plex 200.

Importantly, to maintain complete objectivity, identical reagent sets/assays were performed on all vaccine samples. Thus, Ags were tested across all immunogenicity vaccine trial specimens, regardless of their inclusion in the trial's immunizing strategy.

Importantly, even though non-specific responses to Ags not included in the vaccine regimen, such as gp41, were rarely detected (Figure 2), these responses appeared in the network (Figure 4A), simply reflecting the previously reported presence of low-level cross-reactive responses to these peculiar Ags (Trama et al., 2014). Thus, excluding particular Ags that are not included in a particular vaccine trial at the time of the analysis may alter the objective nature of the analysis, the exclusion of these responses could be considered in subsequent supervised analyses.

**Identification of vaccine-specific signatures with LASSO and PLSDA**

Key features that contribute to profile differences, in multidimensional space, were defined using a combined feature selection (LASSO method) (Tibshirani, 1997) and partial least squares discriminant analysis (PLSDA) (Arnold et al., 2015; Lau et al., 2011), implemented using Matlab software (version 2014a, Mathworks, Natick, MA). K-fold cross-validation determined the optimum value of the tuning parameter ("s"), such that the resulting model had the lowest possible MSE for prediction and associated features were chosen as the minimum set of biomarkers. PLS (Partial Least Square) analytical approaches were specifically selected for these analyses, as the method was designed for small samples sizes relative to number of latent variables defined by weighting coefficients(Haenlein and Kaplan, 2004; Janes et al., 2005). Partial least square discriminant analysis (PLSDA) (Arnold et al., 2015; Lau et al., 2011) assessed the predictive ability of LASSO-selected biomarkers for classifying vaccine groups. Prior to PLSDA analysis, the data was normalized with mean centering and variance scaling, and cross-validation was performed by iteratively excluding random subsets (in groups of 10%) during model calibration, then using excluded data samples to test model predictions. Orthogonal signal correction was used to improve model visualization and

interpretability. Quality of each PLS model was confirmed by posteriori cross-validation calculation, which was reported for each of our models in the associated figure legends.

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