The RV144 vaccine primed IgG4 and V1V2-ADCP responses in HIV breakthrough infections

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ABSTRACT

Background. The RV144 vaccine efficacy trial showed a reduction in HIV infections that associated with stronger binding antibody (Ab) responses against Env variable loops V1V2. High levels of Ab-dependent cellular cytotoxicity (ADCC) together with low plasma levels of Env-specific IgA also correlated with decreased infection risk. Exact mechanisms of prevention remain unclear.

Methods. To better understand the effect of vaccine priming, we performed a systems serology analysis in breakthrough infections in 42 vaccine and 63 placebo recipients, using plasma samples collected 6, 12 and 36 months after HIV diagnosis. We analyzed Ab binding features corresponding to immunoglobulin (Ig) subclasses and nine variant Fc gamma receptors (FcgR) (tested against 51 HIV antigens (Ag) for a total of 896 immune variables) together with functional Ab responses: ADCC, Ab-dependent cellular phagocytosis (ADCP), trogocytosis, NK cell activation measured by ICS and neutralization. Machine-learning analyses included clustering, CART trees, LASSO multinomial logistic model, and Partial Least Squares (sPLS). We filtered redundant immune features to reduce the number of variables to 221, 286 and 284 at 6, 12 and 36 months, respectively.

Results. RV144 vaccination primed B cells responses post HIV-1 diagnosis. Vaccinees were classified by a specific Fc binding profile with IgG4 responses as the strongest distinguishing feature dominating until 3 years. When effector functions were included, vaccinees were characterized by strong V1V2-specific Ab responses synergized with V1V2-specific ADCP responses, whereas placebo recipients had stronger IgG3 and gp120-specific responses. None of the vaccine recipients developed more than 70% neutralization breadth while 8 out of 49 placebo recipients showed such breadth after 3 years of infection. The development of neutralization breadth, which was linked to gp120/gp140 binding features, did not cluster with the vaccine group.

Conclusions. Our results showed that the RV144 vaccine primed a specific IgG4- and V1V2-ADCP-dominated profile post-breakthrough infection while it did not prime broad neutralizing responses. By contrasting the immediate (post-vaccination, pre-infection) and long-term (post-infection) impact of vaccine priming, we can obtain a novel understanding of vaccine-elicited immunity, with characteristic features that can be harnessed to design more efficacious vaccine strategies.

BACKGROUND

RV144 HIV-1 vaccine trial (Rerks-Ngarm et al., 2009)

- >16,000 Thai participants
- 121 infections (MITT): 110 CRF01_AE infections
  - 44 vaccine and 66 placebo participants
- Here: 27 vaccine and 49 placebo

METHODS

Systems serology approach

- Plasma samples collected at 6 months, 1 and 3 years post HIV diagnosis
- Ab binding profile using Luminex-based assay
- Four Fc effector functions
  - gp120 for trogocytosis and ADCC
  - gp120 and V1V2 for ADCP and NK ICS
- Neutralization breadth assayed against 35 strains
- Analysis: Random forest, PLSDA classifiers and correlation approaches

- RV144 vaccine priming of B cells had long-term effects, up to 3 years post infection
- V1V2 antibody responses were recalled after infection and linked with Fc effector functions
- Vaccinees showed high IgG4 responses compared to placebo recipients
- Broadly neutralizing antibody responses were restricted in vaccinees compared to placebo recipients

RESULTS

RV144 vaccination primed IgG2, IgG4 and V1V2 binding responses after HIV-1 breakthrough infections

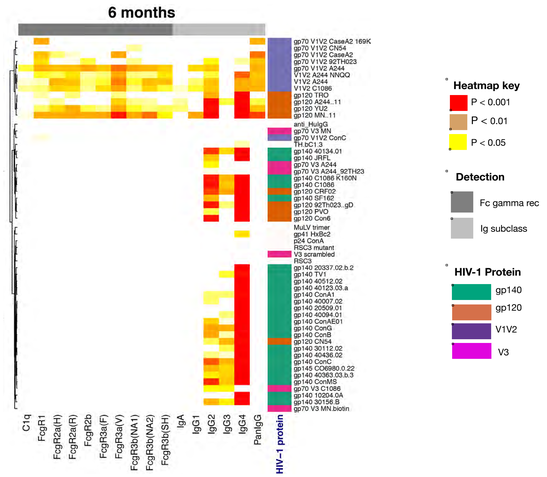

Figure 1: Significant differences between vaccine and placebo groups measured at **6 months** after diagnosis are represented with colored cells. Each cell represents FDR-adjusted p-values where the color indicates the statistical significance. Columns represent detection reagents and rows represent each HIV-1 antigen.

IgG4 differences persistence three years after diagnosis

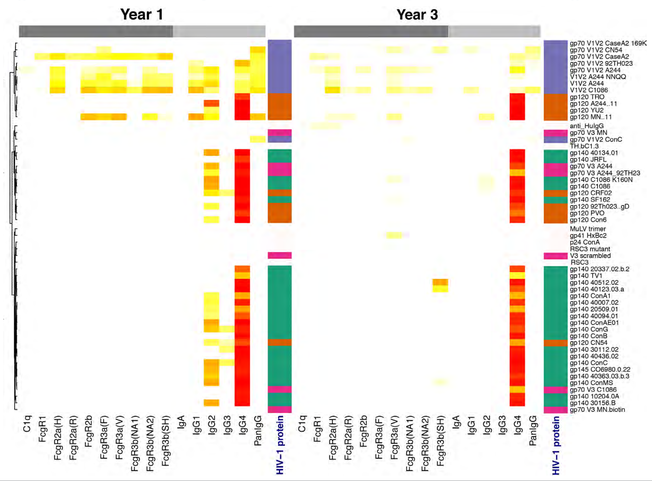

Figure 2: Significant differences between vaccine and placebo groups persisted at **1- and 3-years** after diagnosis. Each cell represents FDR-adjusted p-values where the color indicates the statistical significance. Columns represent detection reagents and rows represent each HIV-1 antigen.

Higher V1V2-mediated Fc effector functions in vaccinees

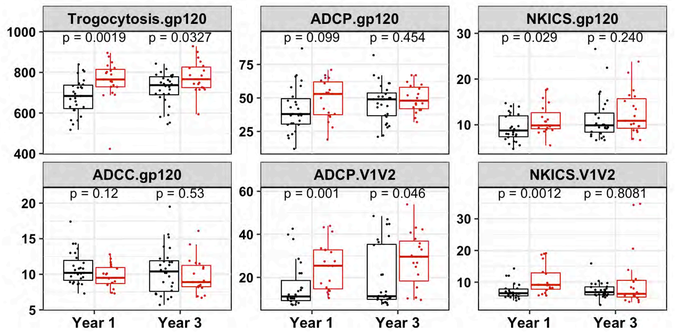

Figure 3: Fc effector functions were measured 1 and 3 years post diagnosis.

- Except for ADCC, Fc effector functions were higher in vaccinees than in placebo recipients
- V1V2-specific ADCP and trogocytosis were still significantly higher in vaccinees 3 years after diagnosis

RV144 vaccine profile linked V1V2 responses with V1V2-specific ADCP

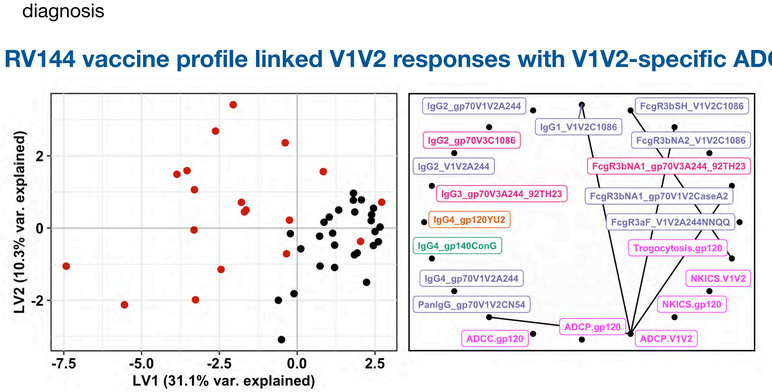

Figure 4: PLSDA model separated vaccine from placebo recipients. Correlation network showing significant correlations (black edges) and non correlated features (no edges).

- V1V2 responses associated with V1V2-specific ADCP
- IgG4 responses were not associated with FcgR binding responses or Fc effector functions

Restricted neutralization breadth in vaccinees

- Development of 70% neutralization breadth 3 years after infection:
- 0 (of 27) vaccinees, 8 (of 49) placebo
- Neutralization breadth was not associated with V1V2-specific features
- No correlation between Fc effector functions and neutralization breadth or potency

CONCLUSION

- Breakthrough infections can inform our understanding of the mechanisms behind vaccines
- Priming in vaccinees led to high IgG4 and V1V2-specific antibody responses post-infection
  - V1V2 responses were linked to ADCP responses
  - IgG4 responses were not associated with Fc effector functions
- Vaccine priming was associated with strong Fc effector functionality and poor neutralization breadth

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