



Heterologous Insert Prime-Boost Vaccination Has the Potential to Overcome HIV-1 Antigen Diversity

- Selective Boosting Immunogen Design

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Outline

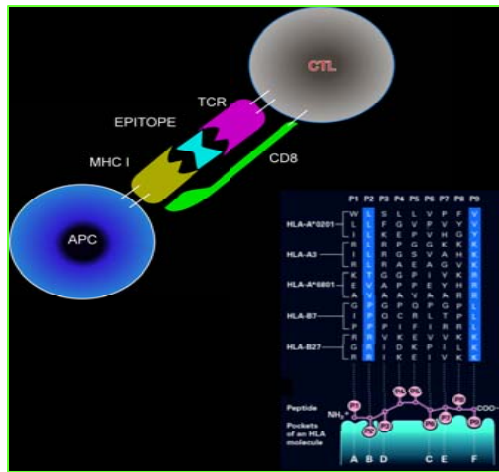
- PTE concept for capturing HIV antigenic variation and better vaccine insert design.
- HIV-1 epidemic patterns in China.
- Expected epitope coverage by natural immunogen (in homologous insert prime-boost vaccination).
- Expected epitope coverage by intra-subtype heterologous insert prime-boost vaccination.
- Expected epitope coverage by inter-subtype heterologous insert prime-boost vaccination.
- Selective boosting immunogen design.



HIV-1 Genetic and Antigenic Diversity

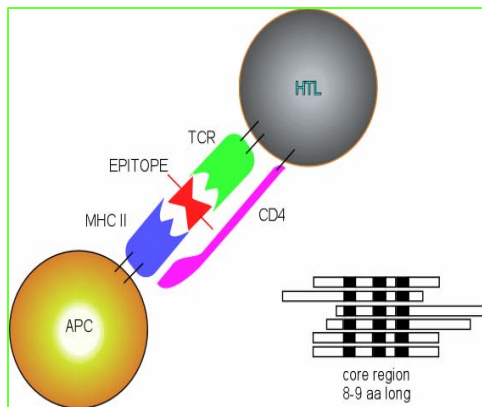
- HIV-1 has evolved into over ten distinct subtypes and circulating-recombinant forms (CRFs) since its fairly recent emergence in the human population.
- The **antigenic variations** within and between these subtypes are huge.
- Vaccine-elicited immune responses usually lack reactivity to the circulating strains, resulting in the failure of the first two phase III trials.

PTE Concept for Capturing HIV Antigenic Variation



- We define Potential T-cell Epitopes (PTE) for a given protein as the set of all unique embedded 9-mers to capture CTL and HTL epitope determinants in an unbiased manner.

- PTEs (and true epitopes) have different frequencies in circulating strains. We define PTEs with relative high frequencies in circulating strains as Vaccine Important PTEs (VIPs), to which vaccine evaluation should be targeted.

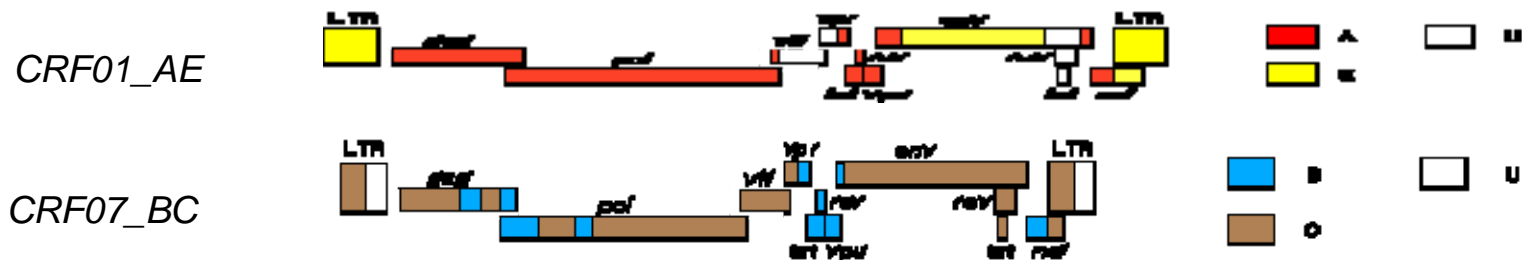


- A VIP-10 peptide set covers all the PTEs represented by at least 10% of the circulating strains.
- This concept is well-suited to evaluate the expected epitope coverage provided by vaccine immunogen.



HIV-1 Epidemic Pattern in China

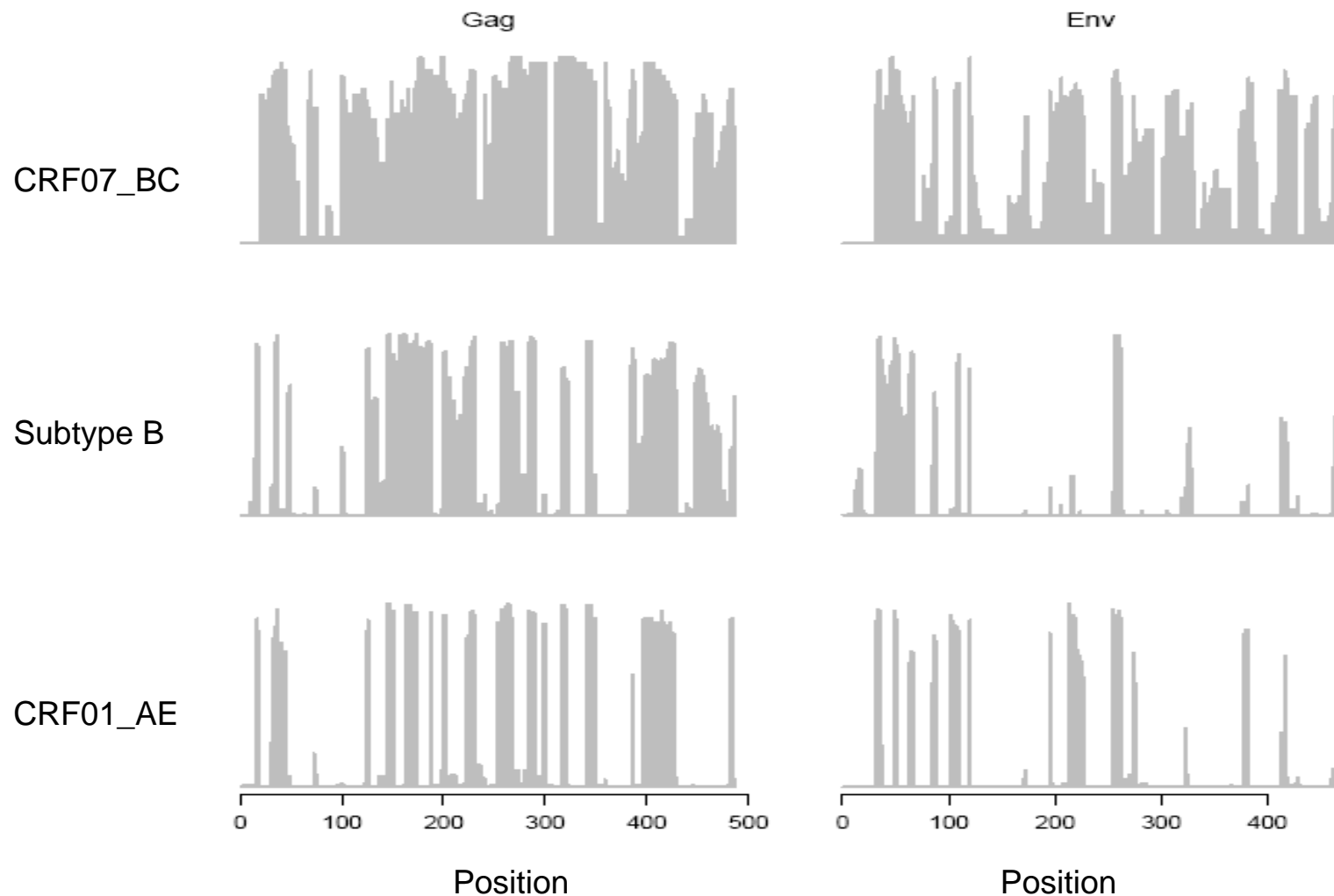
- Three major viral forms co-circulating in China:
 - CRF07_BC.
 - CRF01_AE.
 - Subtype B.
- Different regions have distinct epidemic patterns:
 - Xinjiang Autonomous Region is dominated by CRF07_BC.
 - Yunnan province are co-circulated by all the three viral forms.
- A CRF07_BC strain, **CN54**, was selected as vaccine immunogen.
- We intended to use this epidemic pattern for demonstration of selective boosting strategy.



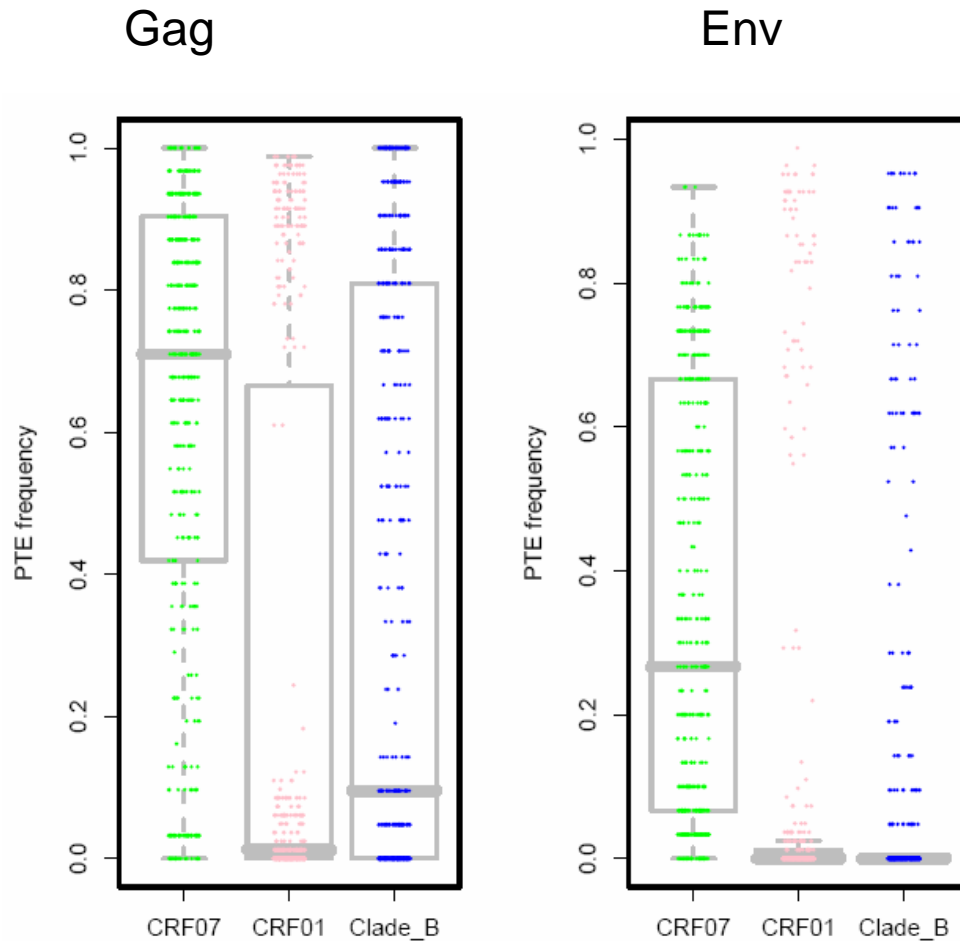
* From LANL



CN54 *Gag* and *Env* PTE Frequency Distribution in Three Subtypes (by Position)



CN54 *Gag* and *Env* PTE Frequencies in Three Subtypes



- We define the expected epitope coverage (E_c) of an immunogen as the average (mean or median) frequency of PTEs from the immunogen in consideration of immunodominance.
- E_c can be interpreted as, when one dominant epitope is recognized from vaccine immunogen, the expected probability of this epitope occurring in circulating strains.
- Only reasonable epitope coverage can be expected by CN54 *Gag* for protection of the same subtype.



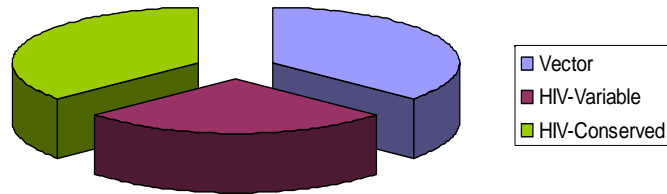
The Need to Direct Vaccine-elicited Responses on Relative Conserved Epitope Determinants

- In essence, a vaccine immunogen provides a collection of epitope determinants with different frequencies in targeted circulating strains, among which the dominant epitopes are recognized.
- Variable (low-frequency) epitopes **compete** with conserved ones for dominance, Resulting in low epitope coverage.
- A better vaccine regimen should seek to avoid the competition by variable epitopes and **direct the responses on the relative conserved epitopes**.
- **But how?**

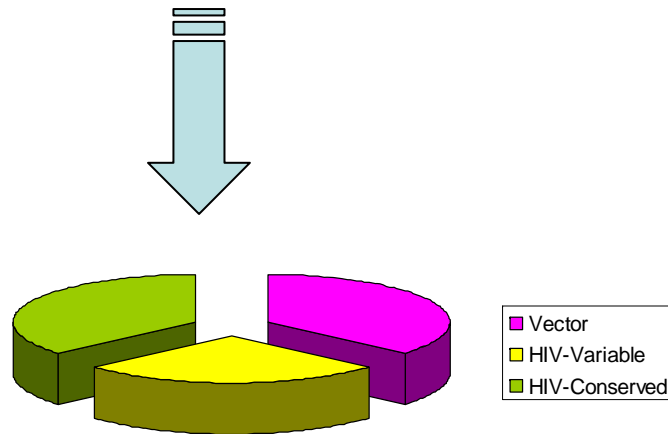


Heterologous Insert and Vector Prime-Boost Vaccination

Prime



Boost

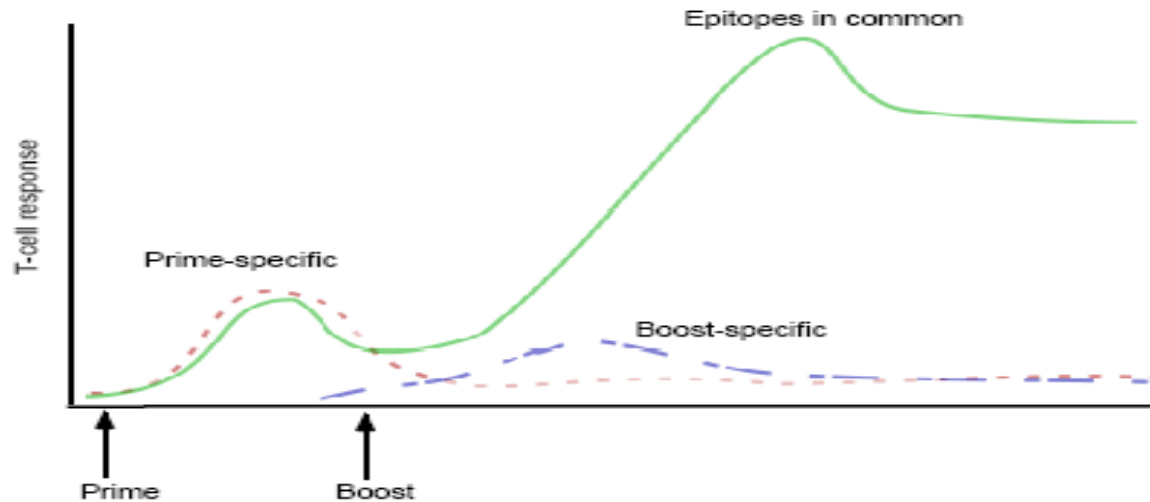


Only the conserved HIV epitopes are shared (green)

- Heterologous vector prime-boost (HetVPB) vaccination direct the responses on the HIV insert.
- Similarly, Heterologous insert prime-boost (HetIPB) vaccination could direct the responses on the conserved HIV epitopes, if the inserts are designed so that the shared epitopes are conserved.



Selective Boosting By HetIPB Vaccination



- When heterologous inserts are immunized sequentially, very likely only the **shared** epitopes are preferentially recognized due to the continuous stimulation.
- **Prime-specific** responses are “canceled” at boosting stage.
- **Boost-specific** responses are actively suppressed in the existence of cross-reactive responses (“original antigenic sin”).



Selective Boosting Immunogen Selection

- The key rationale of heterologous insert prime-boost vaccination is to **selectively boost the desired (conserved) epitope responses**.
- Selective boosting of conserved epitopes through HetIPB vaccination can be achieved by:
 - Heterologous immunogens from distinct field isolates.
 - Artificial selective boosting immunogen .

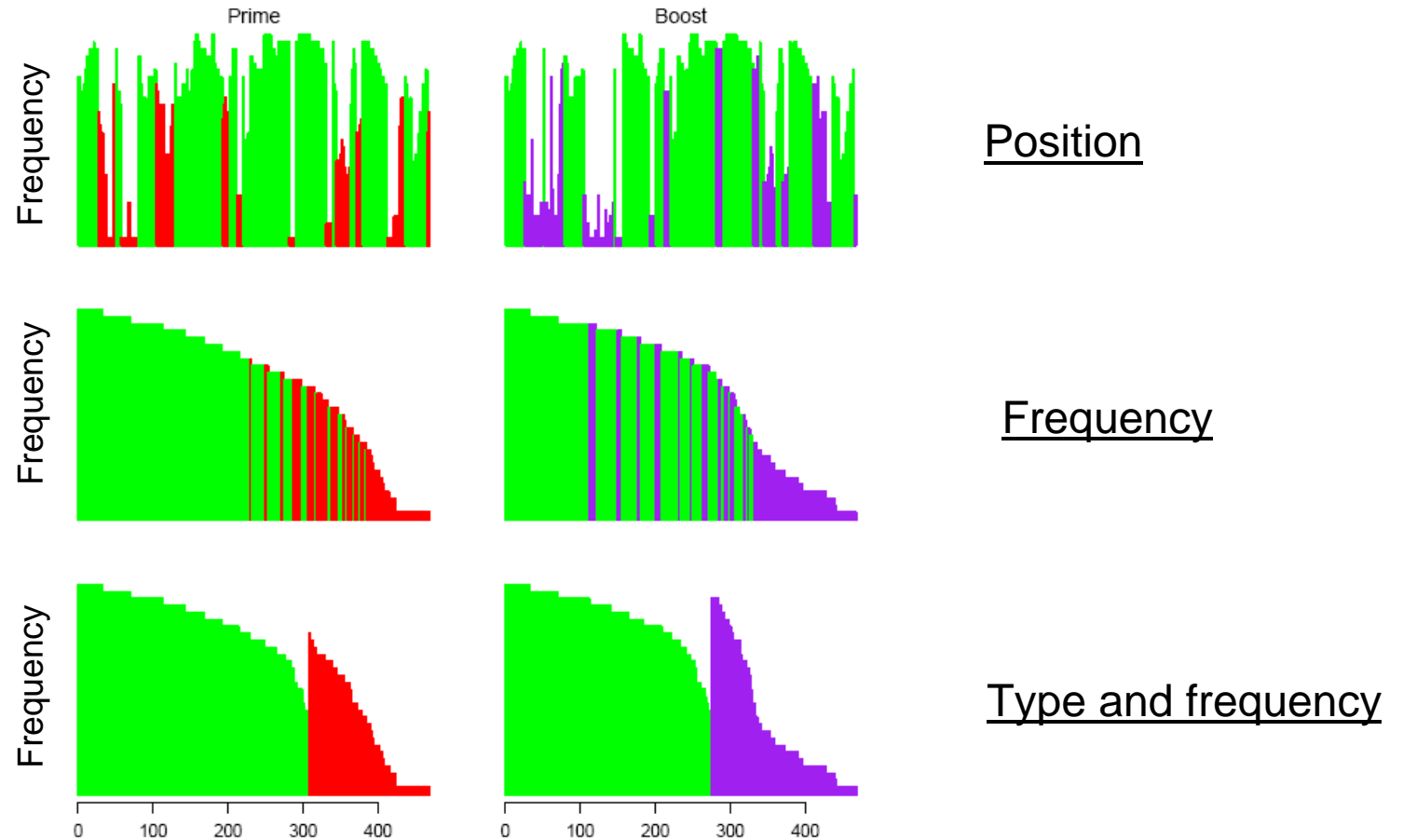


Shared Epitopes Between Two Distinct Isolates Are Usually Conserved Among Other Strains

- We have long observed that shared T-cell epitopes between two distinct isolates are also conserved among other circulating strains.
- Conserved epitope responses are preferentially detected from HIV-infected patients when non-autologous peptide reagents are used (founder effect).
- This fundamental property of HIV-1 immunology gives many researchers the wrong conclusion that conserved epitopes are preferentially recognized by immune system.
- This property can be exploited to direct the responses on the conserved epitope regions through a HetIPB strategy!



Intra-subtype Combination: *CN54 Gag* + Another CRF07_BC Strain

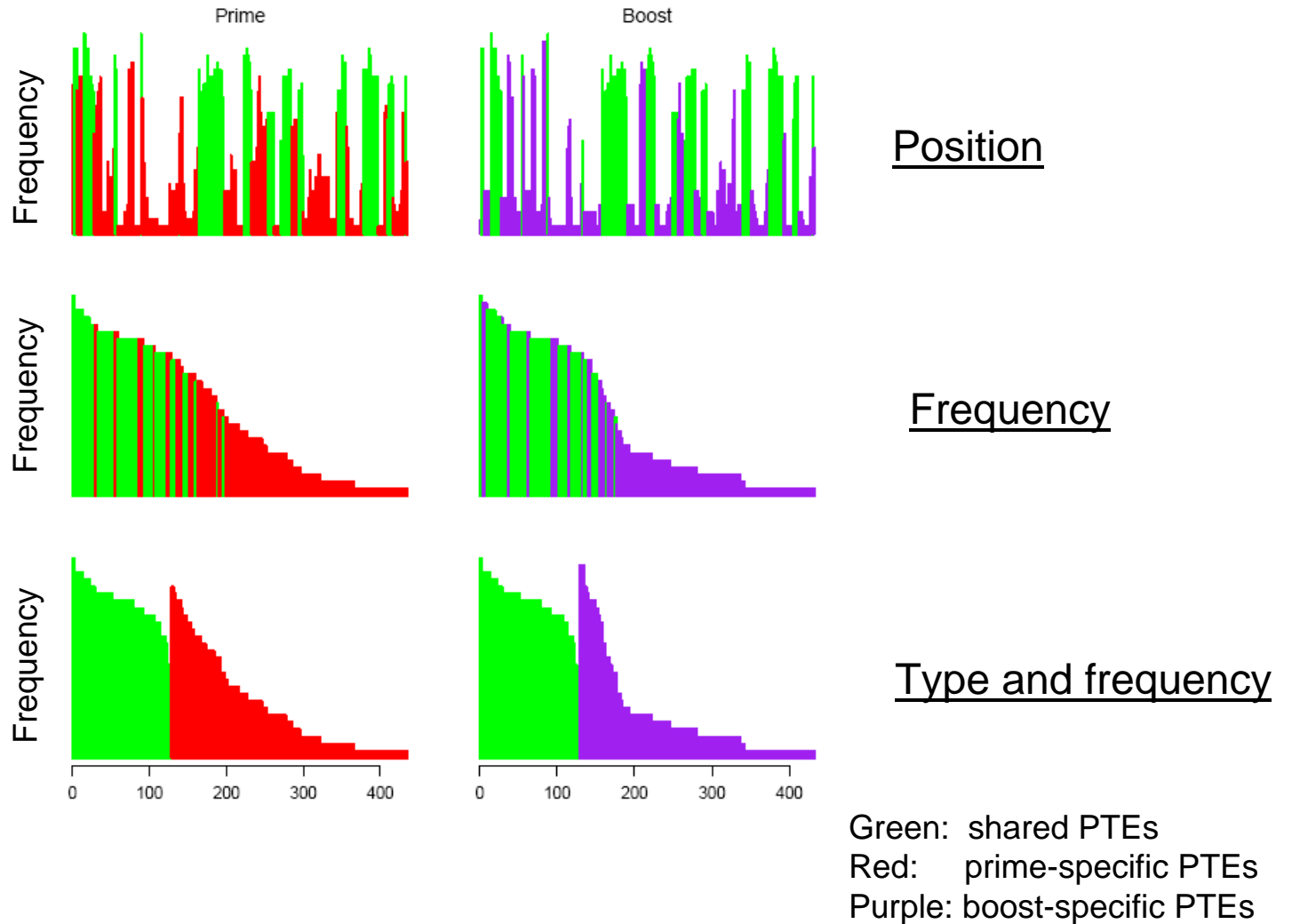


Shared PTEs are more conserved than PTEs from the full-length immunogens

Green: shared PTEs
Red: prime-specific PTEs
Purple: boost-specific PTEs

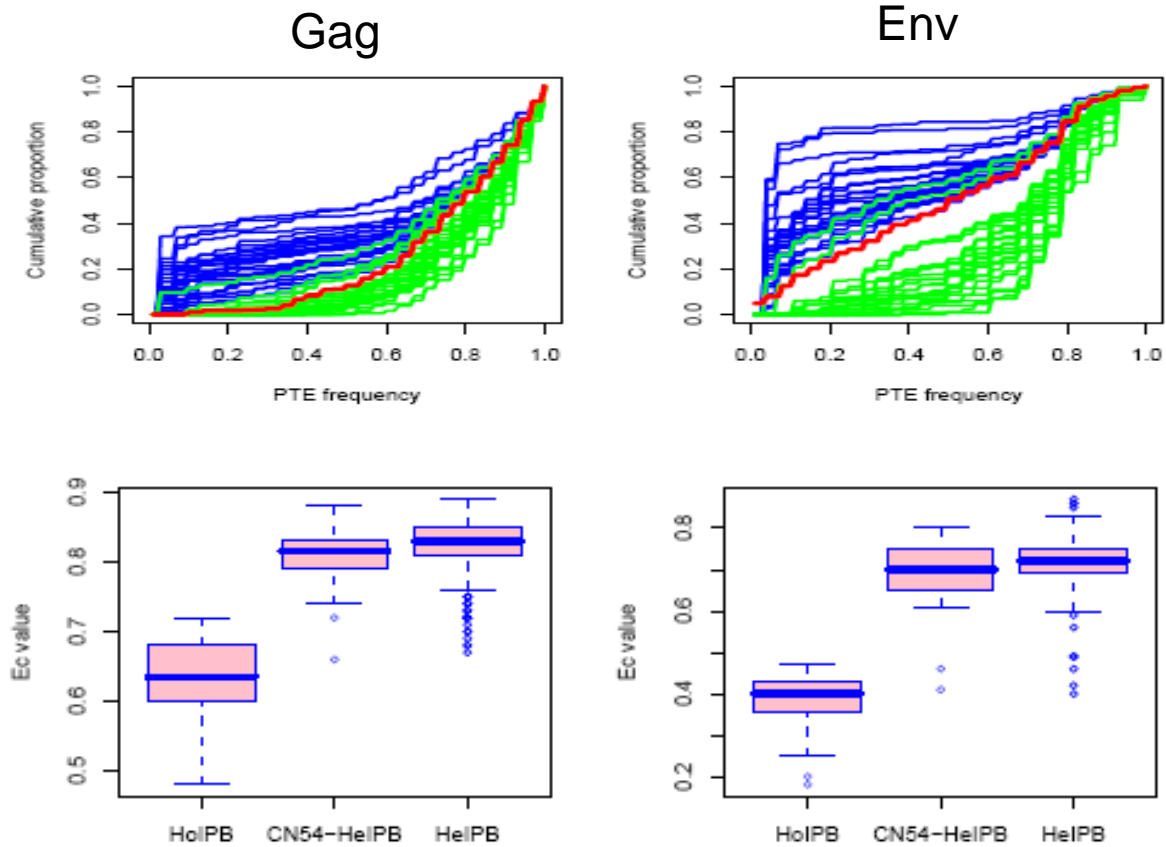


Intra-subtype Combination: *CN54 Env* + Another CRF07_BC Strain





Comparison of HetIPB and HomIPB



Ec for HetIPB are the average frequency of shared PTEs between isolate pairs

Red line = Consensus
Blue: All PTEs from HomIPB immunogen
Green: Shared PTEs between isolates

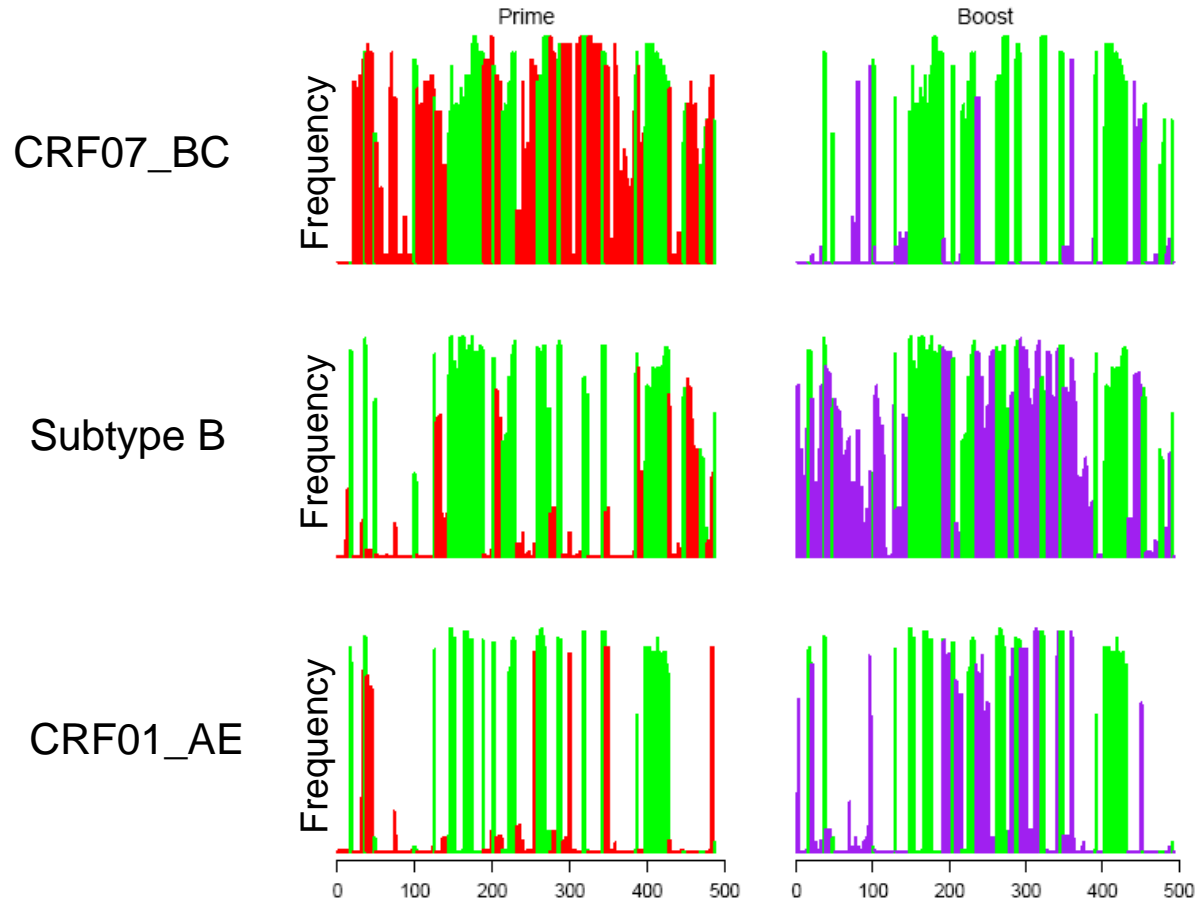


Conclusion – Intra-subtype HetIPB Vaccination

- Intra-subtype HetIPB can significantly enhance the E_c for the same subtype, due to the enrichment of conserved epitope determinants in the shared subset.
- The enhancement for the variable immunogen is even more striking. HetIPB vaccination has the ability to bring variable and relative conserved immunogens to the same high E_c level, at which level HIV antigen diversity seems no longer a problem.
- Intra-subtype HetIPB vaccination is only optimized for the same subtype.
 - PTEs from any field isolate immunogen can be roughly classified as strain-specific, subtype-specific and cross-subtype. **Subtype-specific PTEs become the problem when intra-subtype HetIPB vaccination is used for other subtypes.**



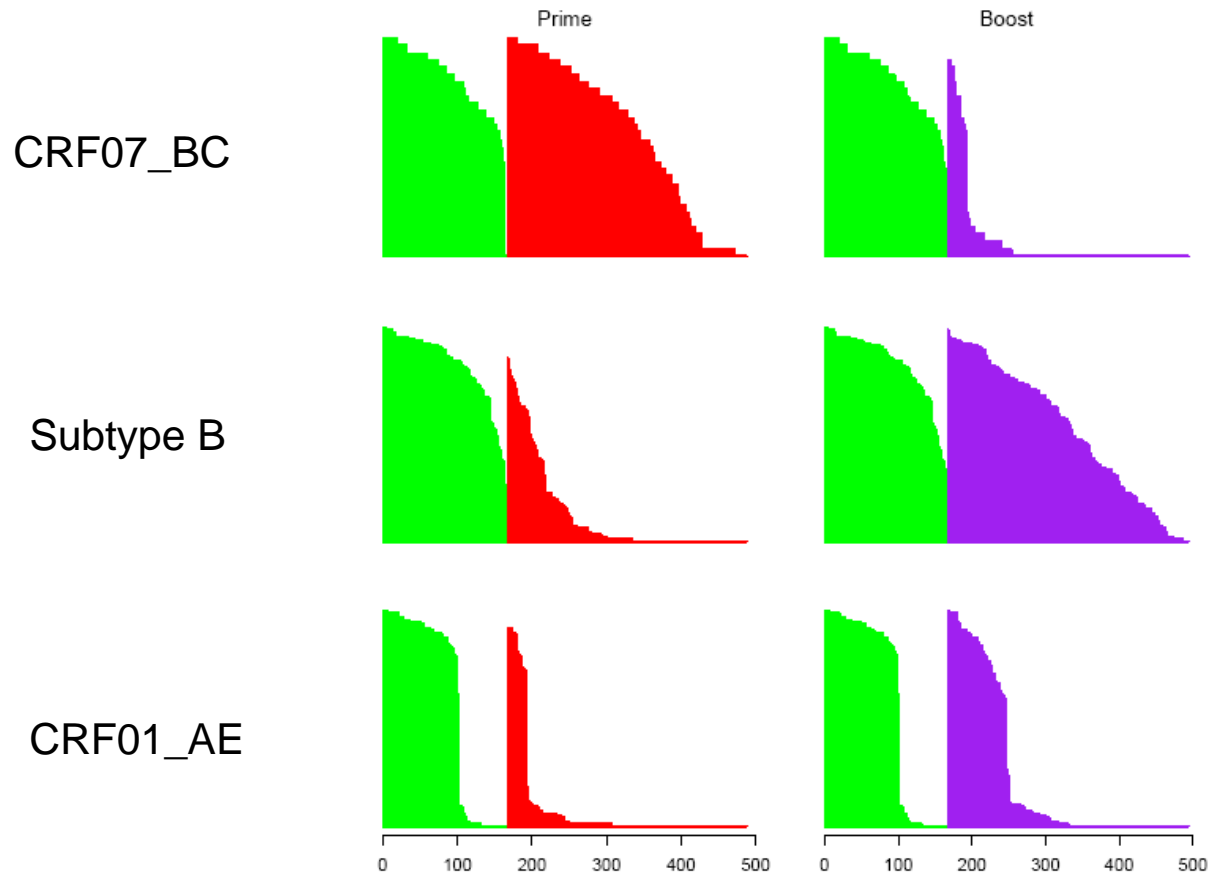
Inter-subtype HetIPB: *CN54 Gag* + *HXB2 Gag*



Green: shared PTEs
Red: prime-specific PTEs
Purple: boost-specific PTEs



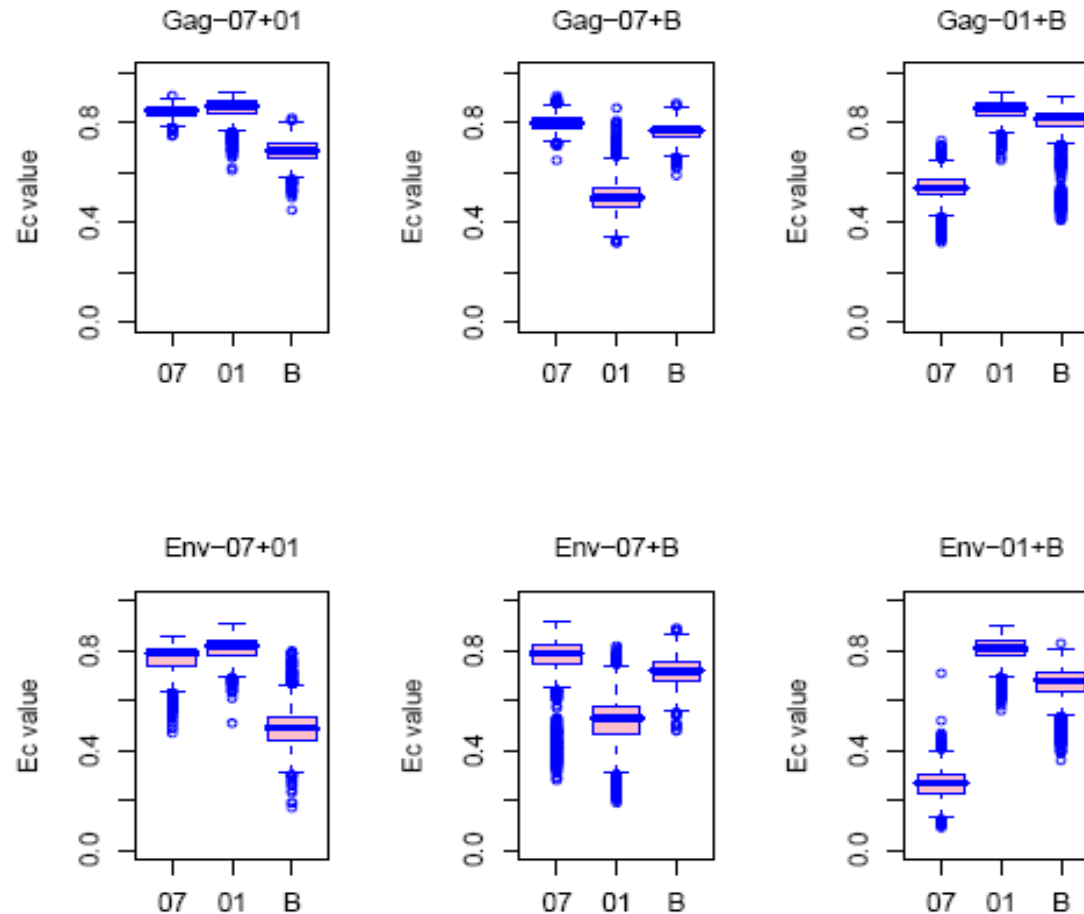
Inter-subtype HetIPB: *CN54 Gag* + *HXB2 Gag*



Green: shared PTEs
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Expected Epitope Coverage of Inter-subtype HeIPB vaccination



All possible combinations are evaluated



Conclusion – HetIPB Vaccination Using Natural Immunogens

- Overall, HetIPB vaccination using natural immunogens can significantly enhance the theoretical epitope coverage.
- HetIPB using natural immunogens for selective boosting has some limitations.
 - Selective boosting of desired T-cell epitope determinants can not be fully controlled. The efficiency of selective boosting is limited by the availability of viral sequences.
- Design of better artificial selective boosting immunogen.

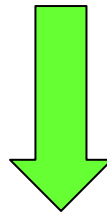


Selective Boosting Immunogen Design

Define the set of selective boosting PTEs conserved in circulating strains



Select natural/artificial immunogen with good coverage of this defined PTE set as prime insert



Design a selective boosting immunogen as boost insert. This immunogen selectively boosts the set of PTEs defined in the first step



CN54 Gag Selective Boosting Immunogen Design

PTEs from CN54 Gag with frequency $> 50\%$ in ALL of three subtype/CRFs circulating in China will be considered as the vaccination targets.



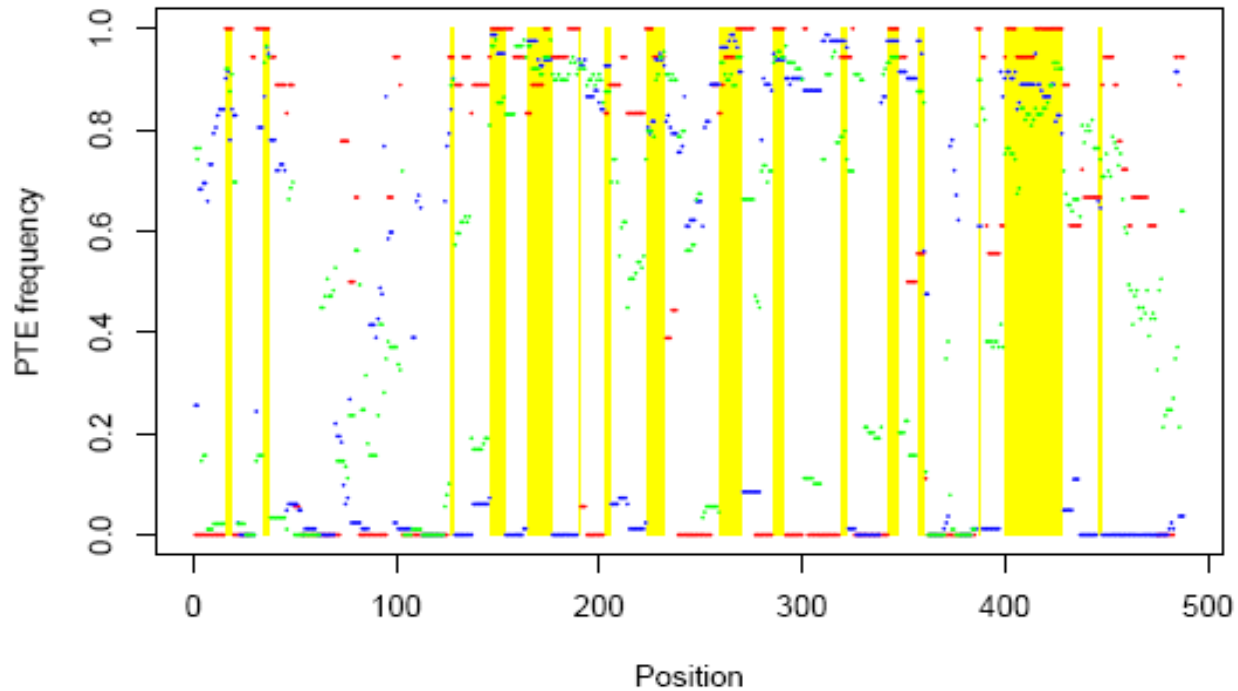
CN54 Gag covers 95% of the above defined PTEs as prime insert



Design a selective boosting immunogen as boost insert. This immunogen selectively boost the defined set of PTEs in CN54 Gag



Gag Selective Boosting Immunogen Design



Yellow bar: selective boosting PTE positions in CN54 Gag with frequency > 50% in all the three subtypes. A Gag selective boosting immunogen was designed to only boost these PTEs.



Selective Boosting Immunogen Design Approaches

- Many details and complications in designing the optimal selective boosting immunogens.
- Potential approaches:
 - Natural immunogen + artificial selective boosting immunogen.
 - Central immunogen + artificial selective boosting immunogen.
 - Artificial selective boosting immunogen + artificial selective boosting immunogen.



Conclusion

- Heterologous insert prime-boost vaccination have the great potential to overcome HIV-1 antigen diversity by **selectively boosting** the conserved T-cell epitope determinants.
- Selective boosting immunogens retain the high immunogenicity and simplicity of natural proteins.
- We have developed an analytical approach to select and design the optimal selective boosting immunogen.
 - **ANY vaccine candidates could be transformed into super vaccine products** (on a good prime-boost vector system).
- Some researchers have begun testing the selective boosting effect of heterologous insert prime-boost vaccination.



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Thank You!

