

# Epitope Specific CD8 + T Cell Responses Predict Spontaneous Control of HIV Replication

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# Background

- HIV -1 elicits HLA class I restricted cytotoxic T lymphocyte (CTL) responses to multiple different epitopes
- Certain HLA class I alleles are associated with control of HIV viremia, and others with progression to AIDS
- Some persons with “protective” alleles have high viral loads, whereas others maintain control of viremia
- Attempts to correlate the magnitude and breadth of CTL responses to control of HIV -1 replication have been equivocal, but relative targeting of optimally defined epitopes has not been examined

## Question

- Is it possible that it is not just the HLA allele, but the particular optimal epitopes being targeted through the expressed HLA alleles, that is important for spontaneous control of HIV?

# Hypothesis

- Spontaneous control of HIV virus replication is associated with targeting of specific optimal epitopes by CD8 + T cells
- It is not the HLA alleles, but rather the particular optimal epitopes targeted by the HLA alleles, that account for differences in control

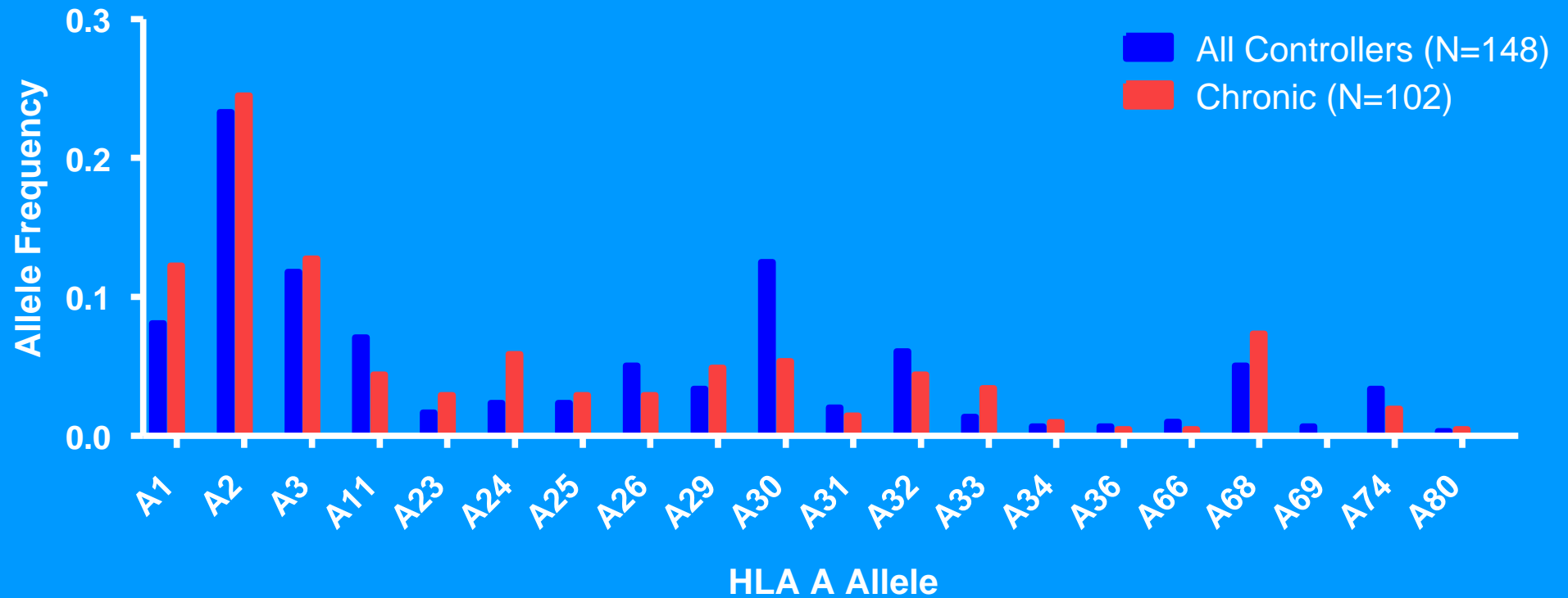
# Subjects

- Elite controllers (n=74)
  - At least 3 x VL < 50 for at least 12 months
  - Blips (usually < 500) if infrequent and non-consecutive
- Viremic controllers (n=74)
  - At least 3 x VL < 2000 for at least 12 months
  - Blips if infrequent and non-consecutive
- Chronic progressors (n=102)
  - Untreated VL > 10,000

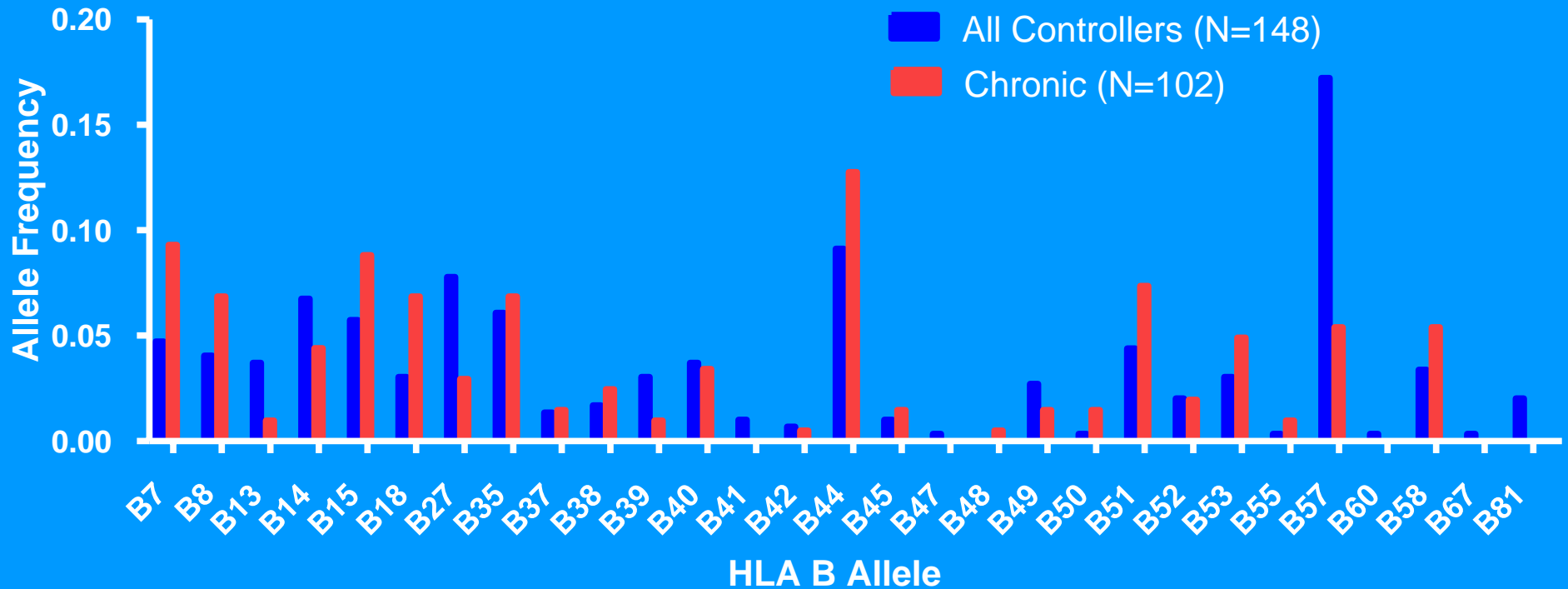
# Methods

- Define the breadth of responses to defined optimal HIV epitopes (n=222) restricted by each person's expressed HLA alleles
- Perform multivariate logistic regression model with a Bayesian L1 prior over the parameters to assess the ability of expressed class I alleles, targeted optimal CD8 T cell epitopes, or the combination of both to predict HIV control
- Use a frequentist multivariate (Mv) analysis with a q-value threshold of  $< 0.2$  to identify the epitope specific CD8 + T cell responses that correlate with HIV control

# HLA-A Allele Frequencies

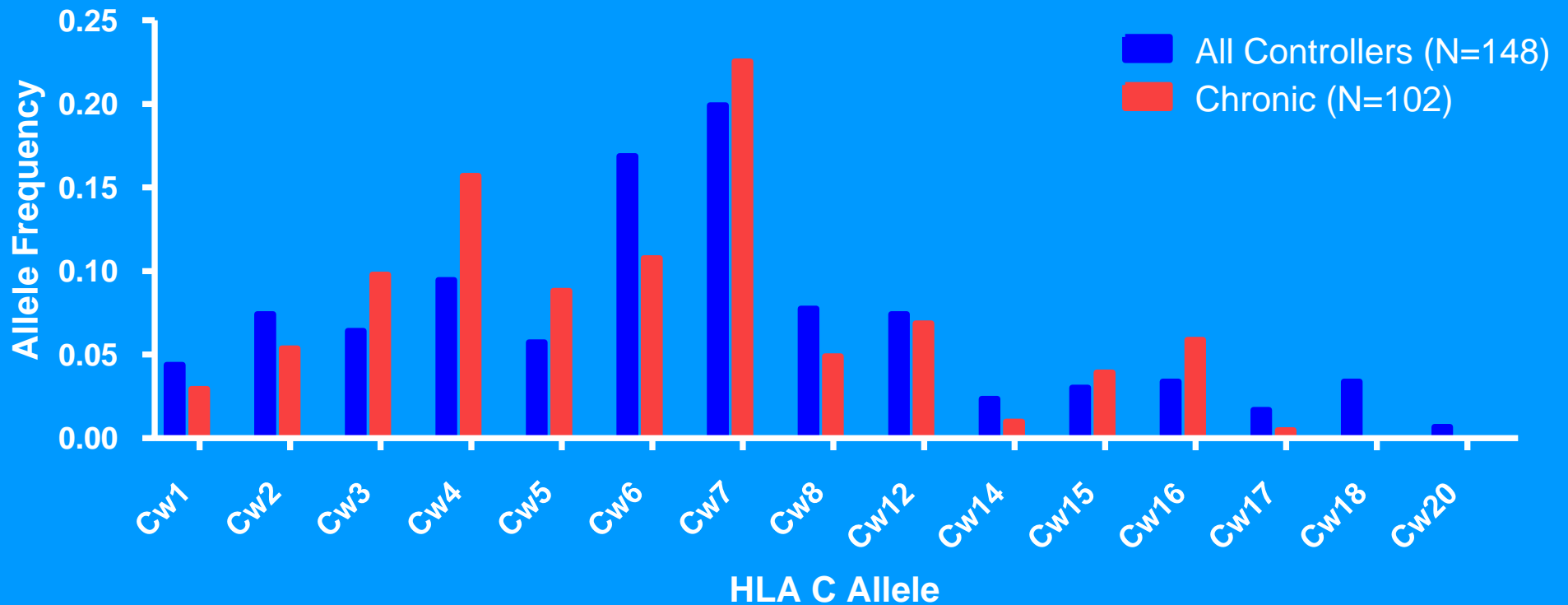


# HLA-B Allele Frequencies

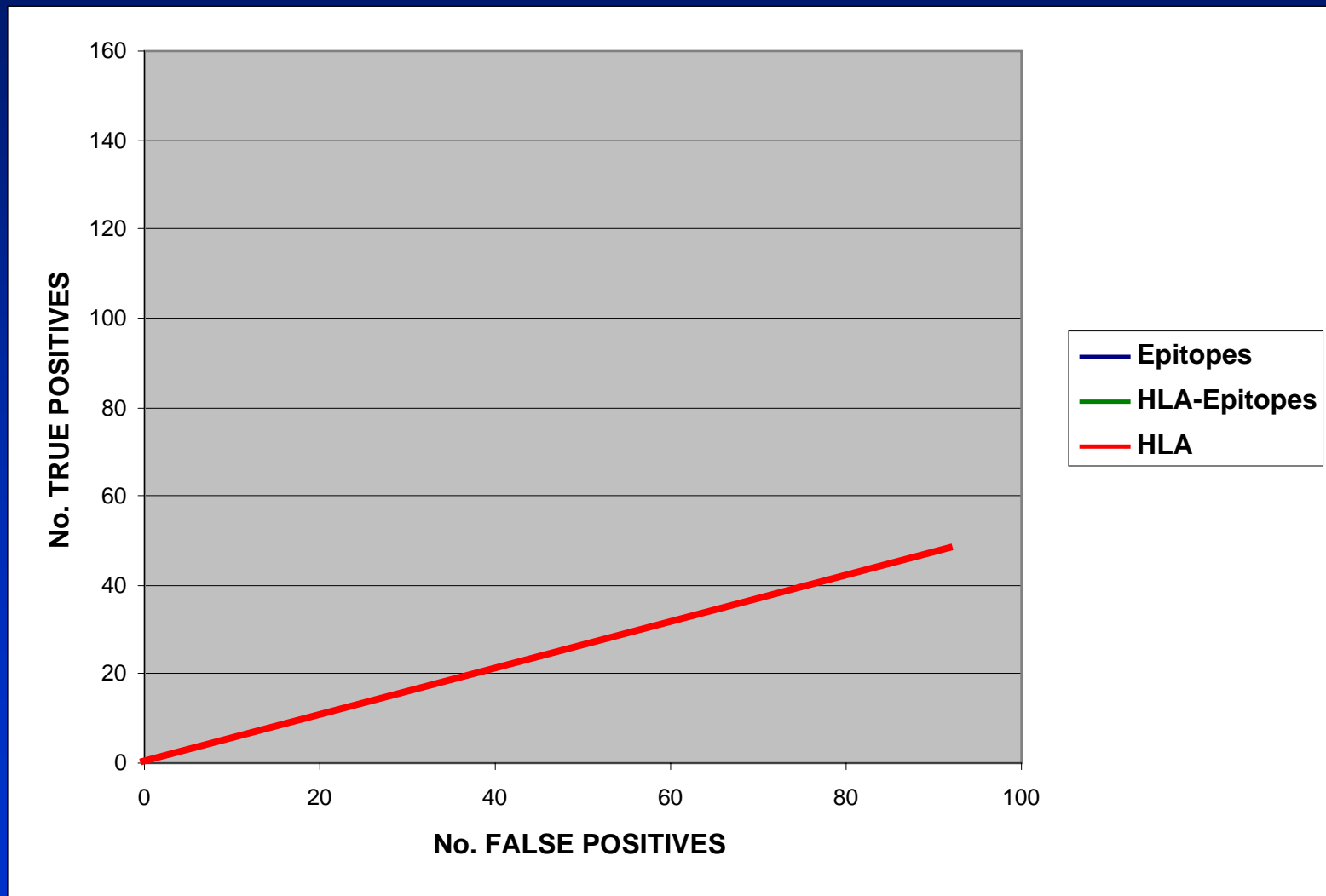




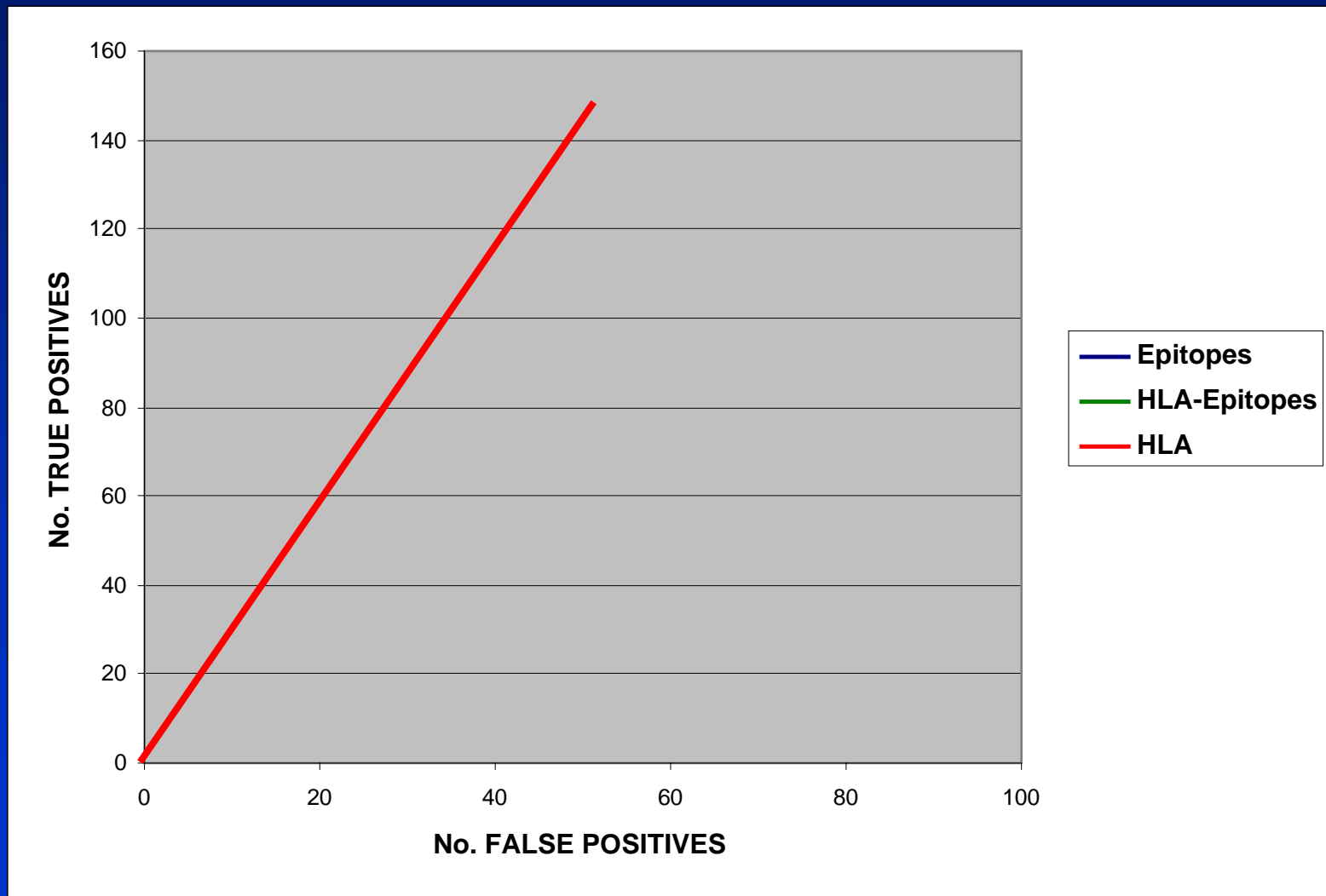
# HLA-C Allele Frequencies



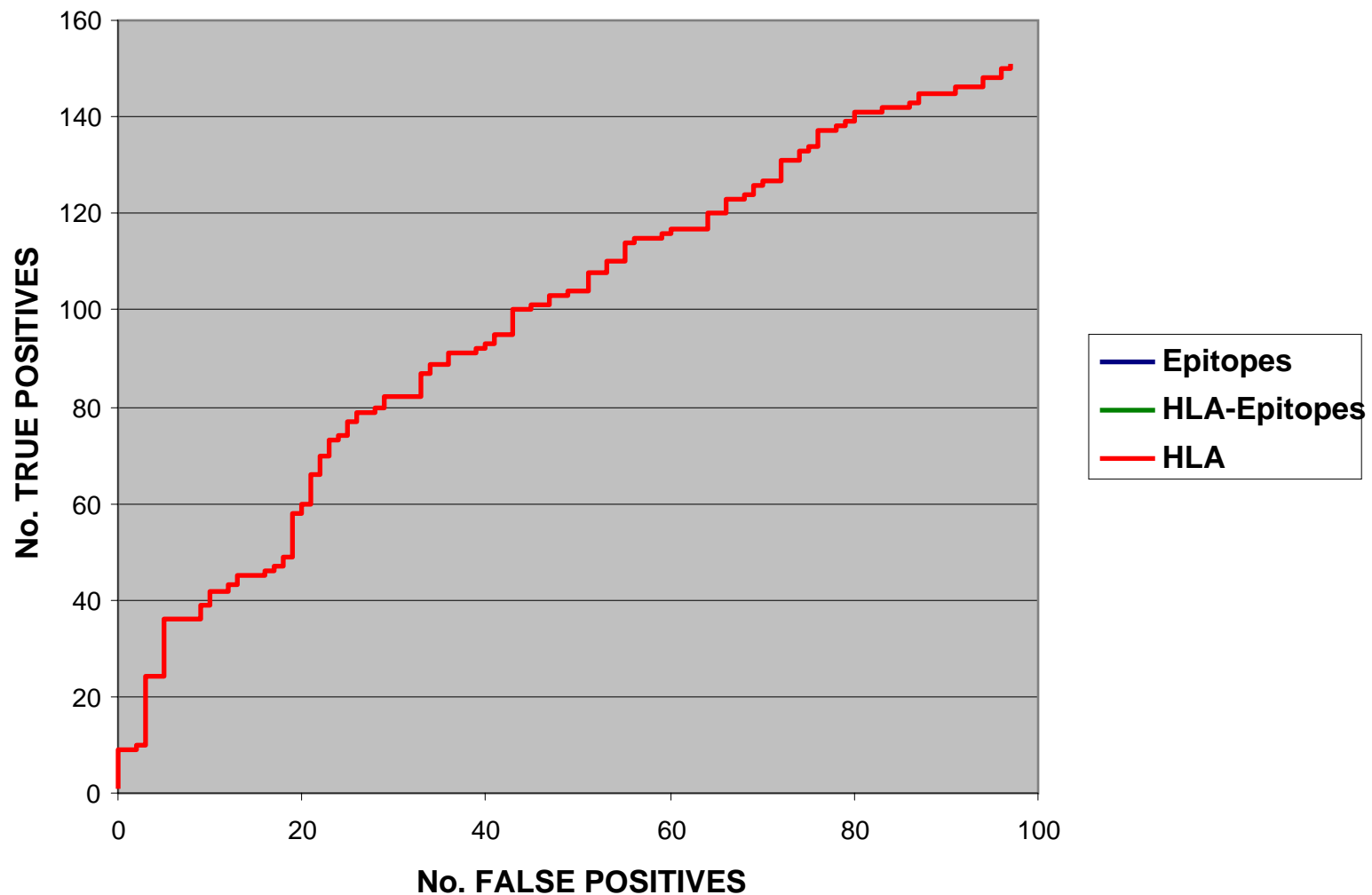
# Prediction of HIV Virus Control



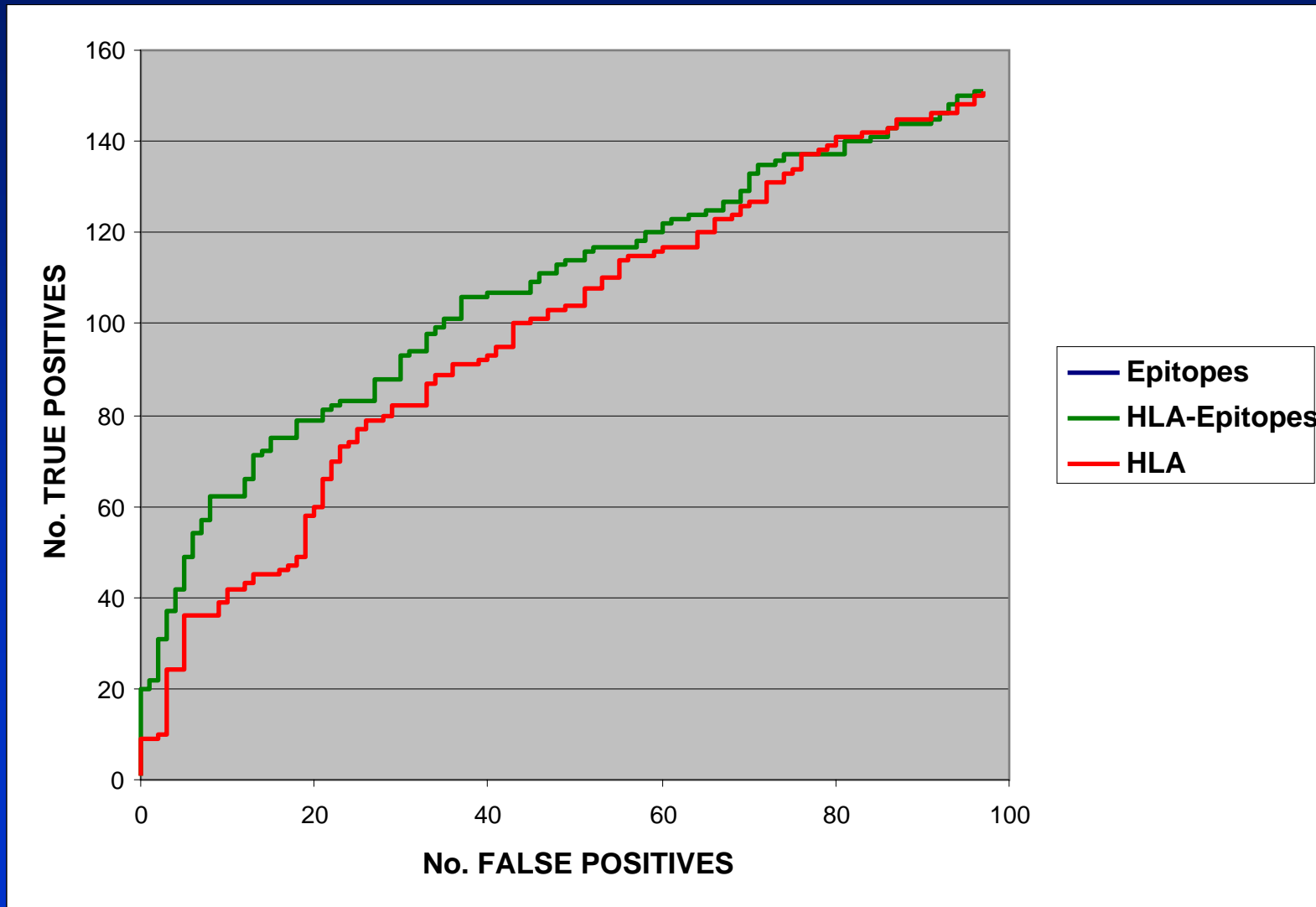
# Prediction of HIV Virus Control



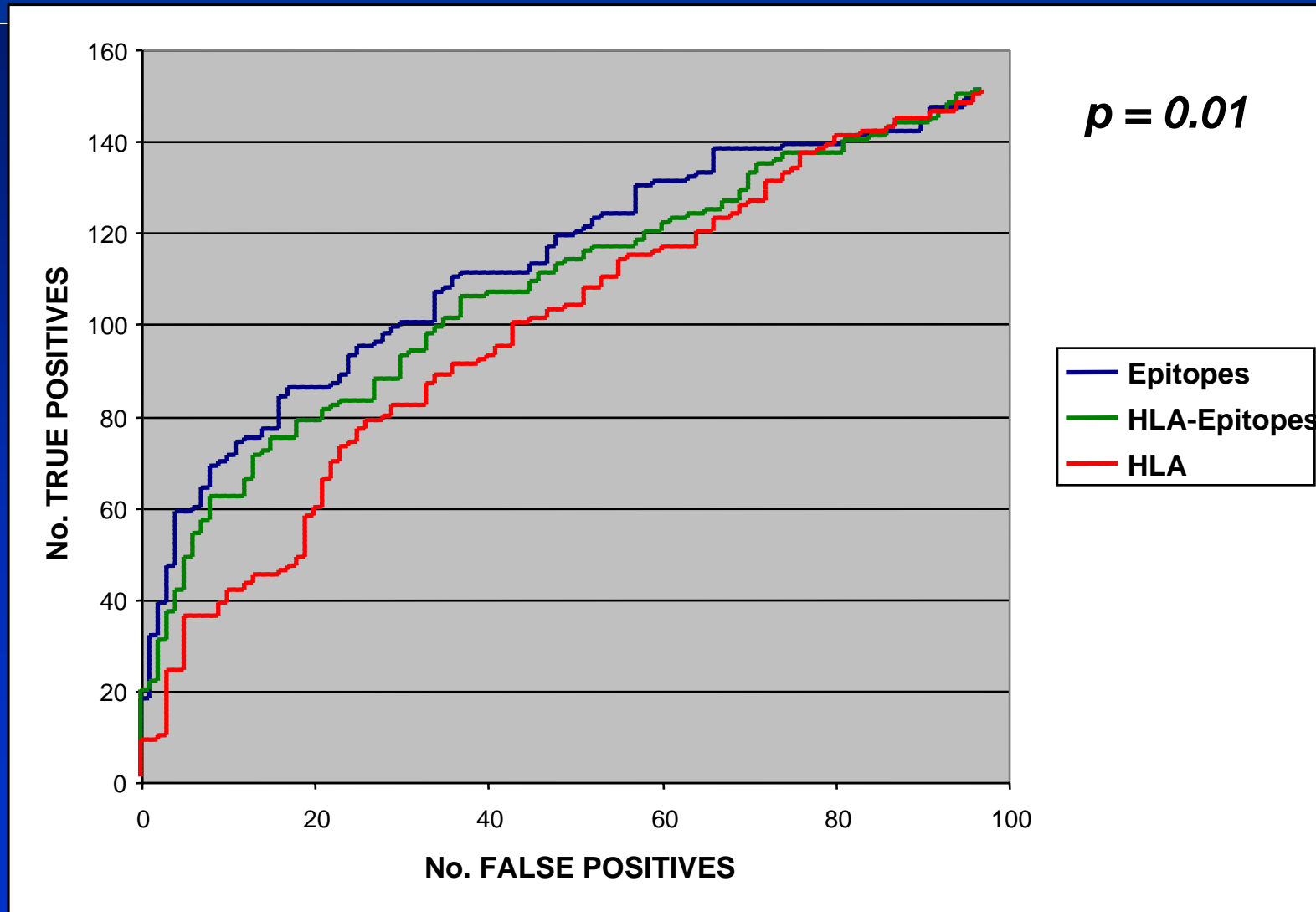
# Prediction of HIV Control: HLA Alone



# Prediction of HIV Control: HLA plus Epitopes



# Prediction of HIV Control: Epitope Alone



# Epitope specific CD8+ T cell responses associated with viral control

PEPTIDE	HLA	PROTEIN	P VALUE	Q VALUE	L1 WEIGHT
AW9	B*57	<i>Vpr</i>	$1.2 \cdot 10^{-7}$	0	3.19
KK10	B*27	<i>p24</i>	<0.001	0.02	1.78
TW10	B*57	<i>p24</i>	0.001	0.02	0.87
HW9	B*57	<i>Nef</i>	0.002	0.08	1.11
DA9	B*14	<i>p24</i>	0.003	0.12	0.88
LV10	A*02	<i>Nef</i>	0.004	0.18	0.55

## Epitope specific CD8+ T cell responses associated with chronic progression

PEPTIDE	HLA	PROTEIN	P VALUE	Q VALUE	L1 WEIGHT
FF9	B*57	<i>p24</i>	0.001	0.02	-1.92
RL11	A*24 B*44	<i>p24</i>	0.001	0.02	-1.33
GY9	A*01	<i>p17</i>	0.002	0.06	-1.59
HL9	B*15	<i>p24</i>	0.002	0.08	-0.66



# Conclusions I

- It is the optimal HIV epitopes targeted by CD8 + T cell responses and not the HLA class I alleles that are "protective"
- For a given HLA allele, there are patterns of epitope recognition that are associated with better control, and others associated with worse control
- Not all HIV specific CD8 T cell responses are created equally
- Not all Gag-specific responses are associated with control

## Conclusions II

- The following epitope responses are highly associated with HIV virus control after correction for multiple comparisons:
  - B57-AW9 (VPR), B27-KK10(P24), B57-TW10(P24), B57-HW9(NEF), B14-DA9(P24) and A2-LV10(NEF)
- The following epitope responses are associated with chronic HIV progression:
  - B57-FF9(P24), A24-B44-RL11(P24), A1-GY9(P17) and B15-HL9(P24)

# Acknowledgements



The International  
HIV Controllers Study



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[www.hivcontrollers.org](http://www.hivcontrollers.org)

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