

# CTL and the Control of HIV-1 Replication

*Or*

*Lessons learned from mixing HIV-1 and CTL*

AIDS VACCINE 2007

Seattle, Washington

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## Evidence that CTL are protective in HIV-1 infection:

- Temporal associations with reduction in acute viremia and AIDS
- SIV-macaque model: CD8<sup>+</sup> T cell depletion leads to sharply increased viremia, and recovery with decreased viremia
- HIV-1 sequence evolution in CTL epitopes *in vivo*: selective pressure (escape)

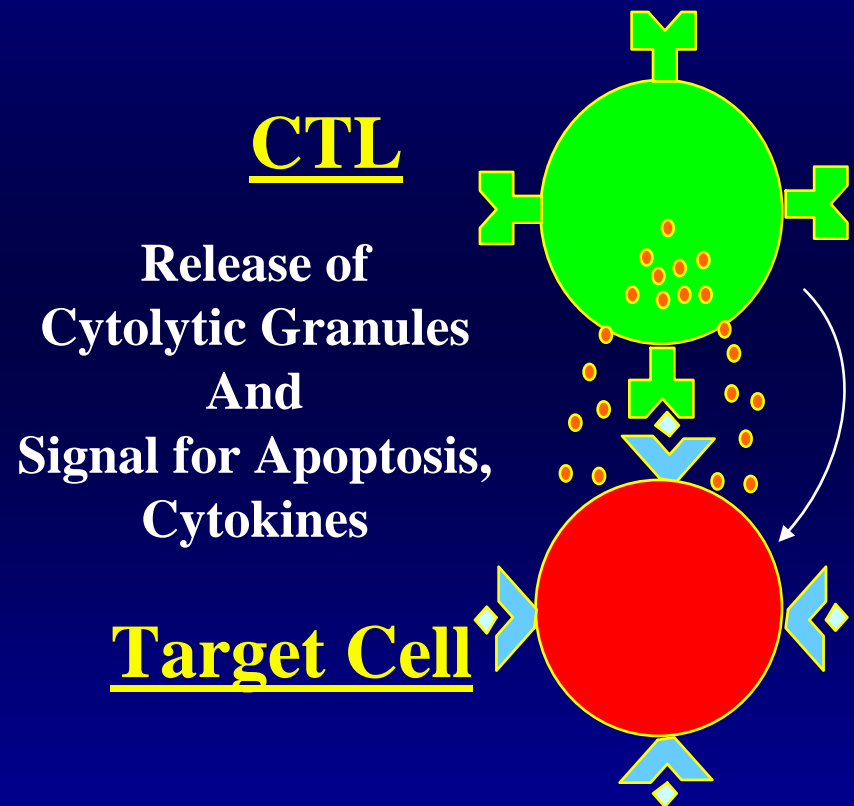
# New technologies offer amazingly precise characterizations of CTL

- **ELISpot**: rapid, robust, validated measurements using few cells
- **ICS**: ability to examine phenotypes and functional markers in remarkable detail
- Such assays tell us about CTL: how many, what specificity, and what functional potentials
- How do these correlate to antiviral activity? These assays offer a detailed picture of the effector end of the CTL interaction, but what about CTL-HIV-1 interaction and the upstream events in infected cells?

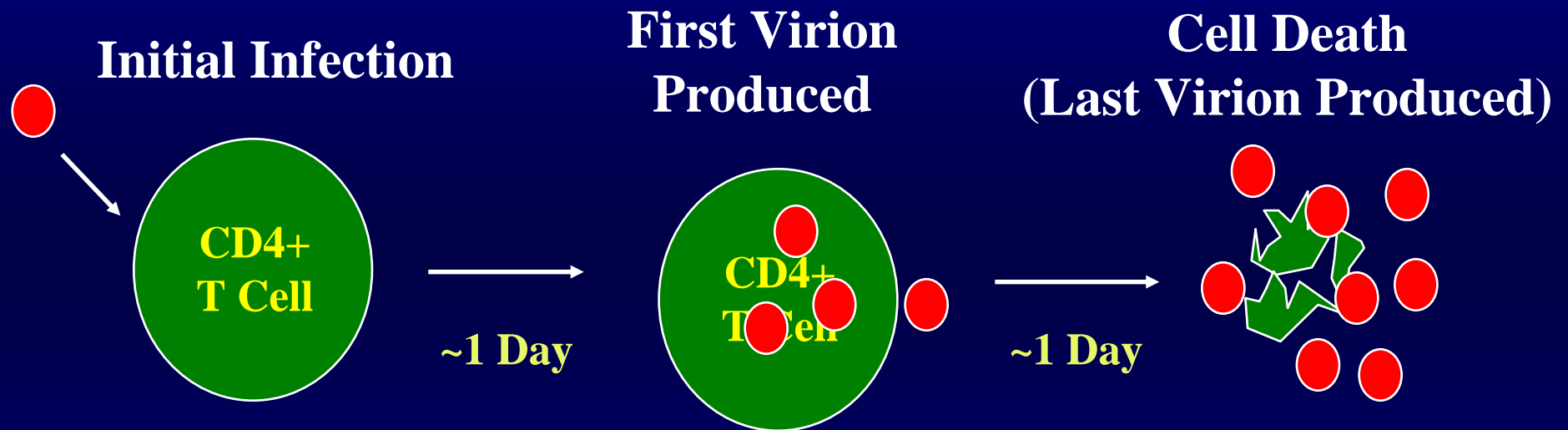
# Questions about the antiviral activity of HIV-1-specific CTL

- Do they kill HIV-1-infected cells?
- Do they suppress HIV-1 replication (via what mechanisms?), and what factors influence efficiency?
- Why do they fail *in vivo*, and how can a vaccine prevent that failure?

# CTL recognize cells displaying foreign protein epitopes



# HIV-1 replicates rapidly, posing a challenge to CTL

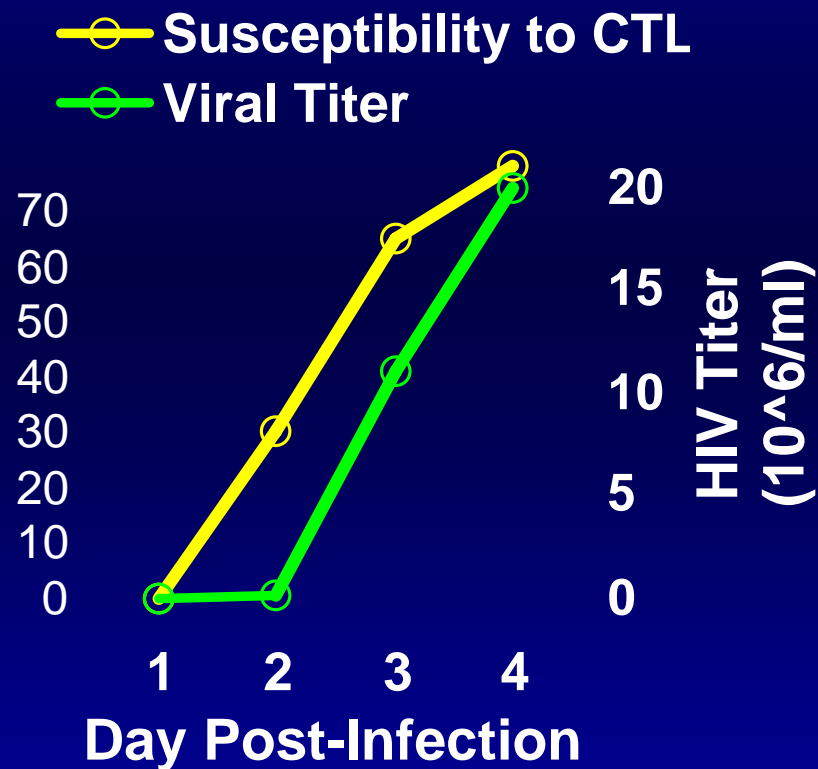


**Killing  
Would  
Result in:**

*Prevention of  
Virion  
Production*

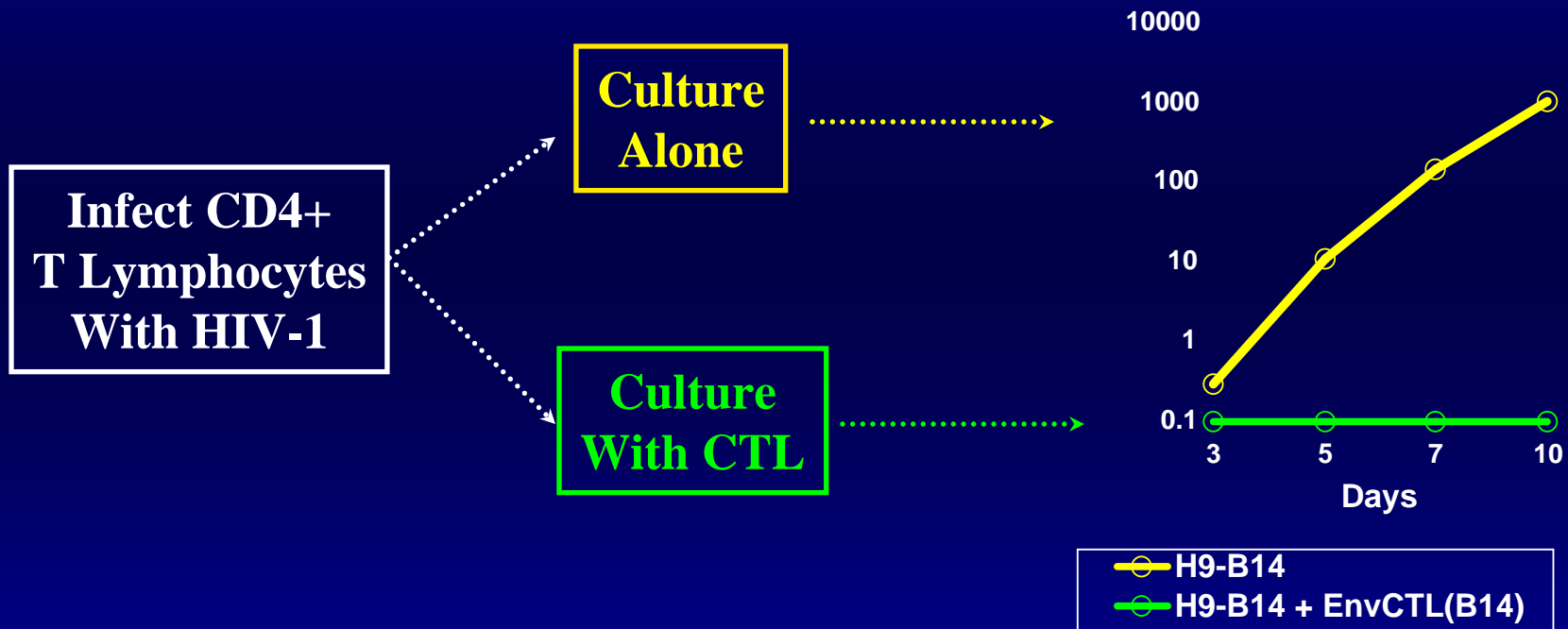
*Reduction of  
Virion  
Production*

# HIV-1-infected cells early in viral replication are susceptible to CTL



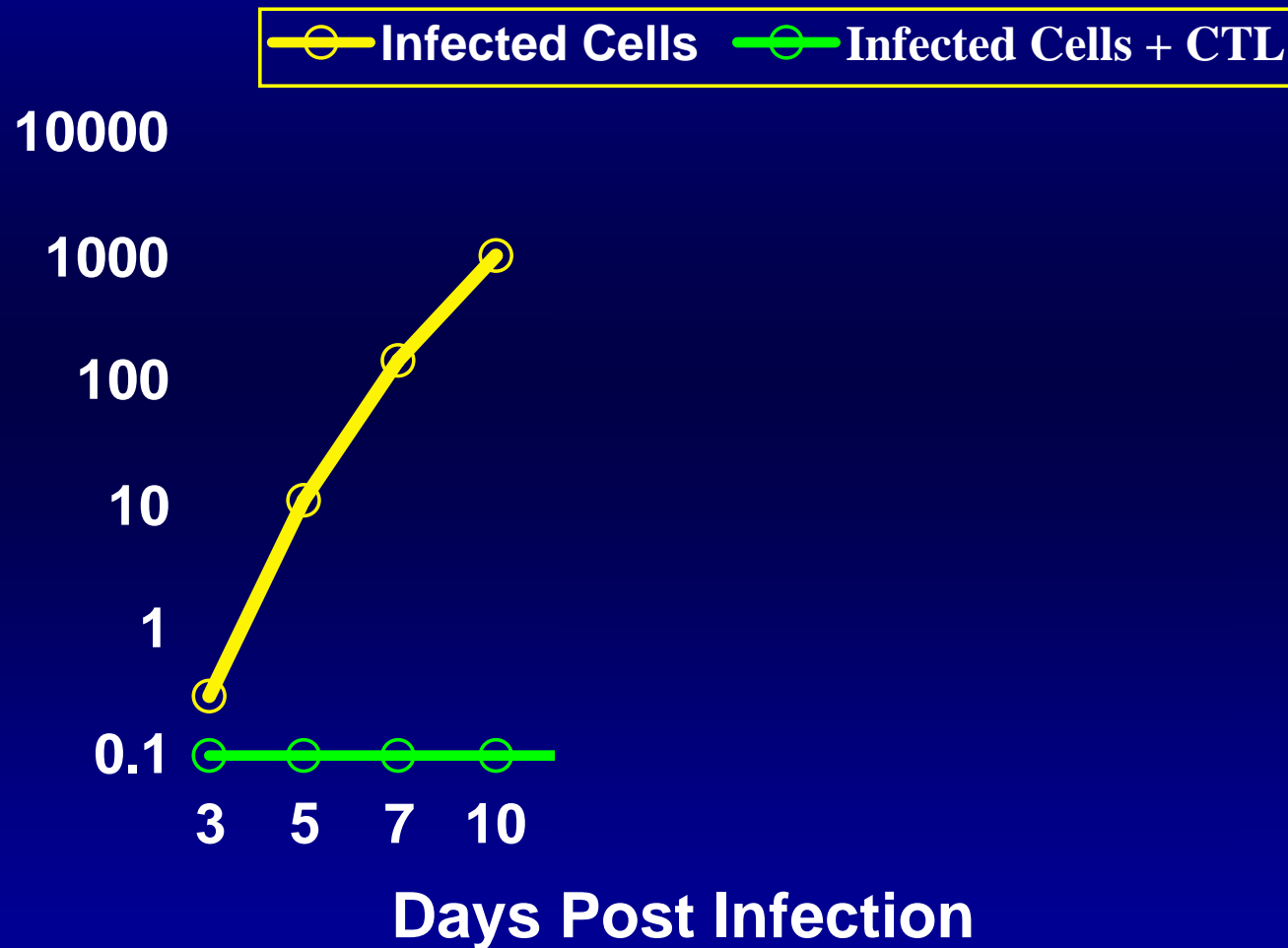
O.O. Yang and R.P. Johnson et al,  
1996, J Virol, 70:5799

# HIV-1-specific CTL can potently inhibit viral replication



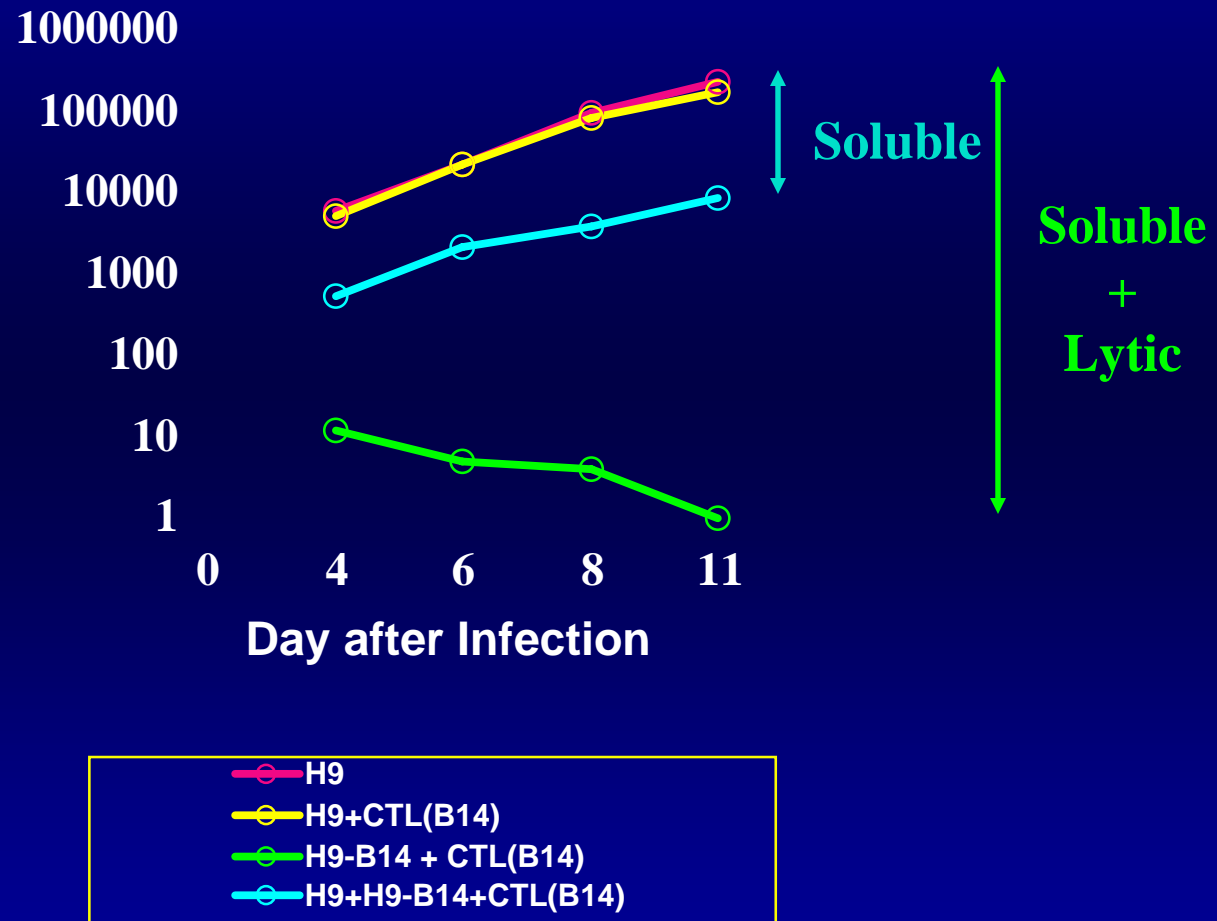
Adapted from O.O. Yang and B.D. Walker et al. J. Virol 1997, 71:3120

# Suppression of HIV-1 by CTL can be irreversible



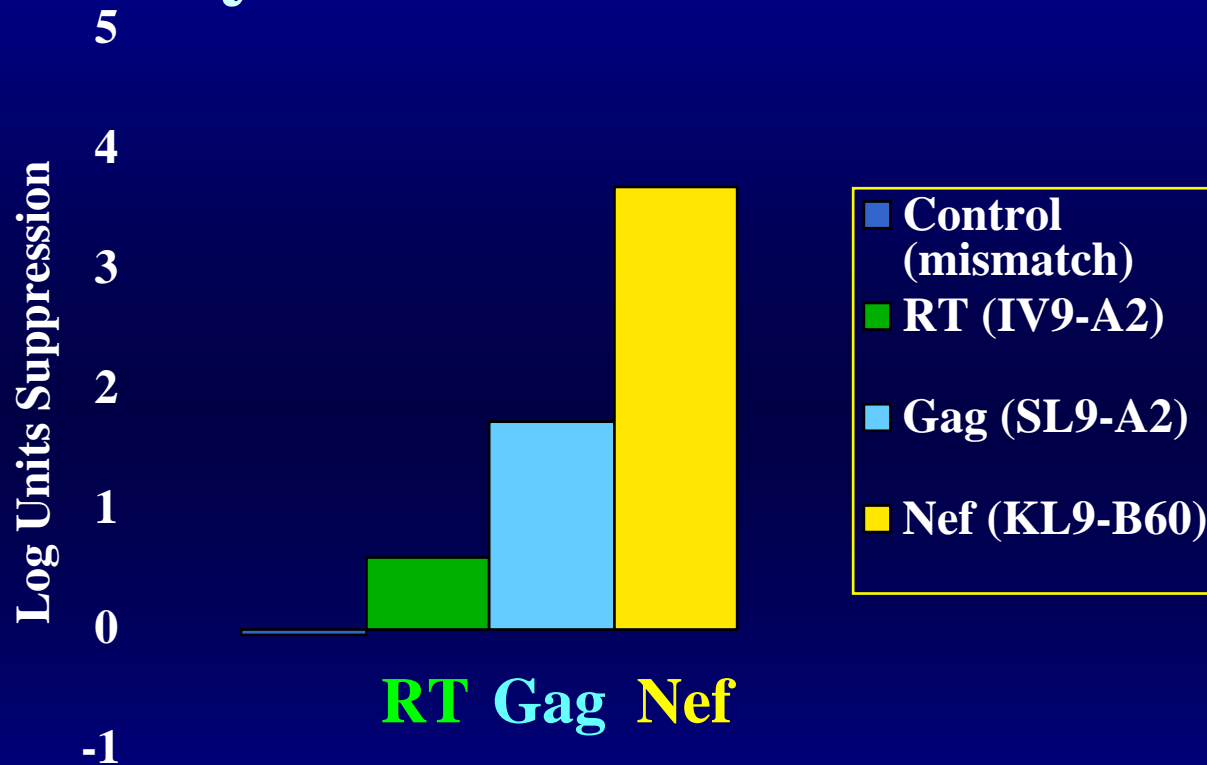
Adapted from O.O. Yang and B.D. Walker et al. J. Virol 1997, 71:3120

# CTL can suppress HIV-1 via cytokines and direct cytolysis



Adapted from O.O. Yang and B.D. Walker et al. J. Virol 1997, 71:3120

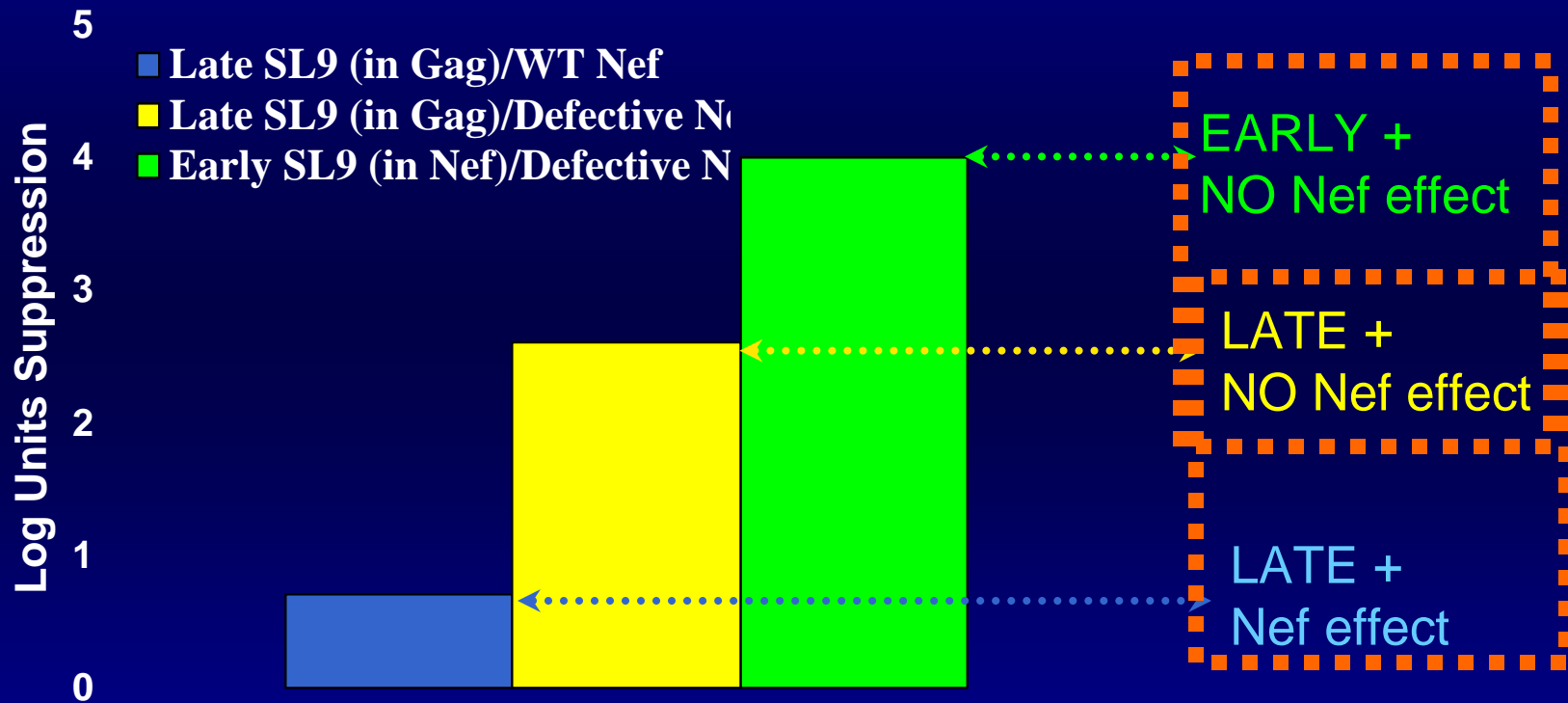
# CTL recognizing different epitopes can vary in their antiviral efficiency



Note that T.J. Tsomides and H.N. Eisen *et al* (JEM 1994, 180:1294) showed that IV9 is presented ~12/cell and SL9 is presented ~400/cell.

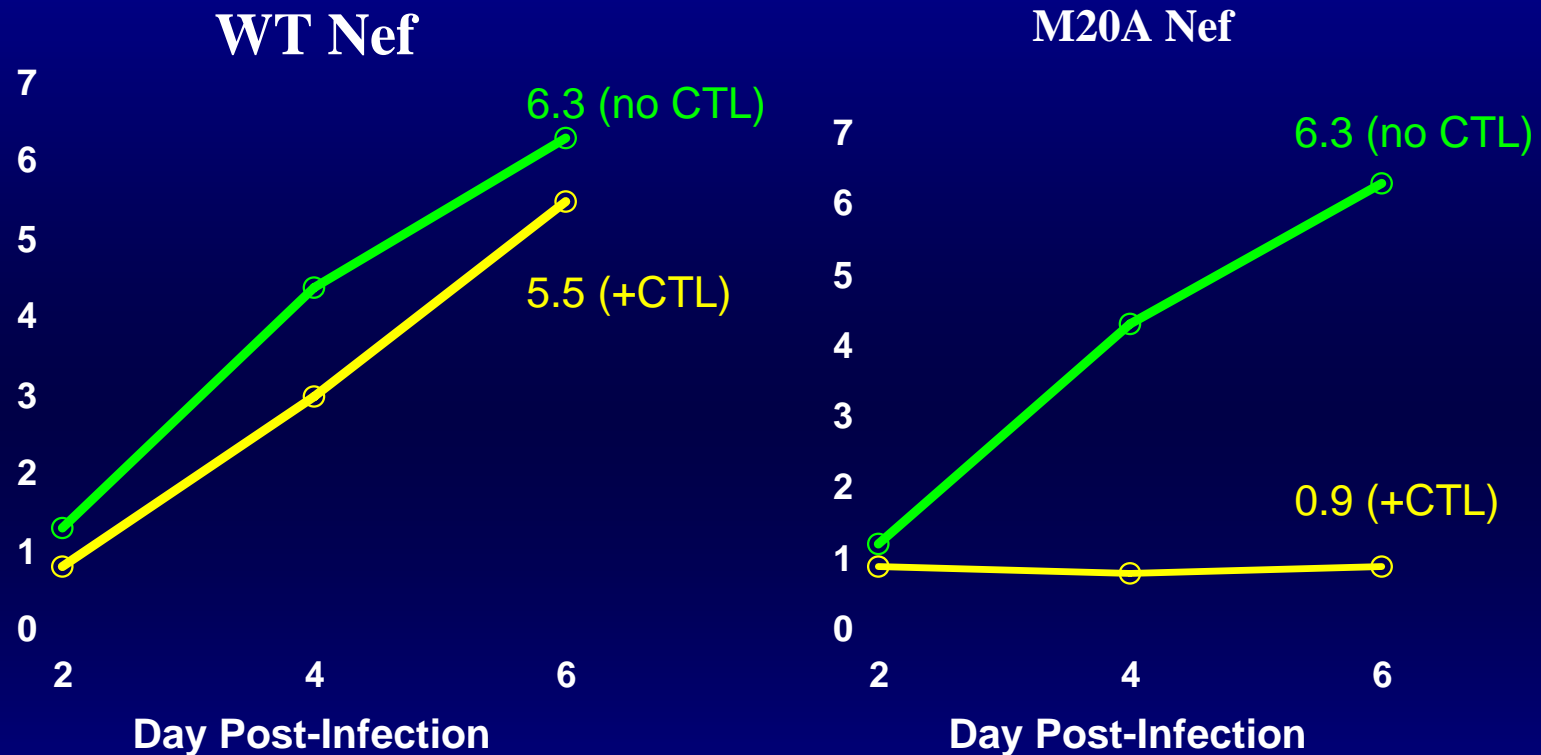
Unpublished data

# Both Nef-mediated HLA-I downregulation and epitope kinetics affect CTL antiviral activity



Adapted from A. Ali and O.O. Yang et al. J. Virol 2004, 78:561

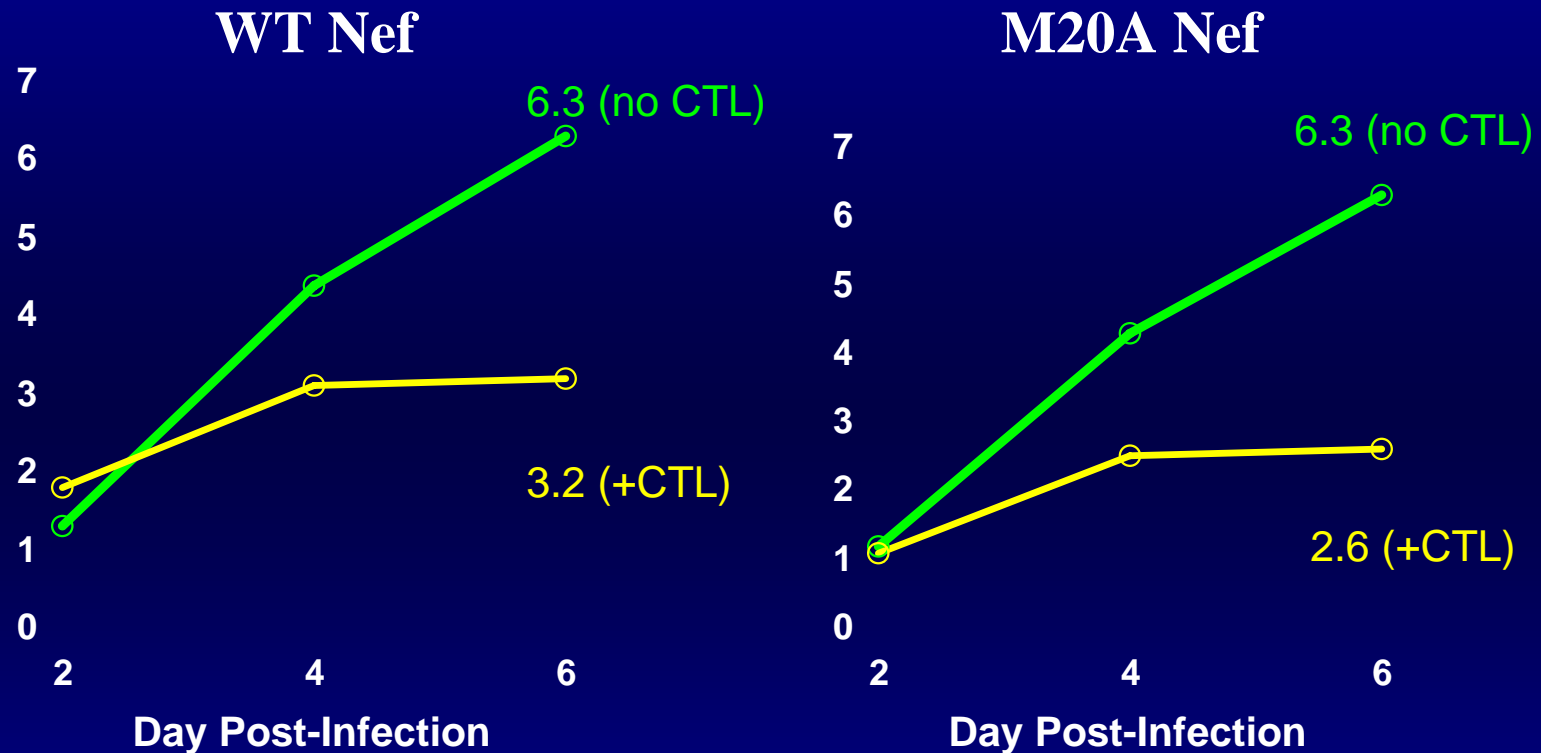
# The impact of Nef on CTL antiviral activity can be quantitated



$$\text{Nef Impact Ratio} = (6.3 - 5.5) \div (6.3 - 0.9) = 0.15$$

Adapted from S. Adnan and O.O. Yang et al. Blood 2006, 108:3414

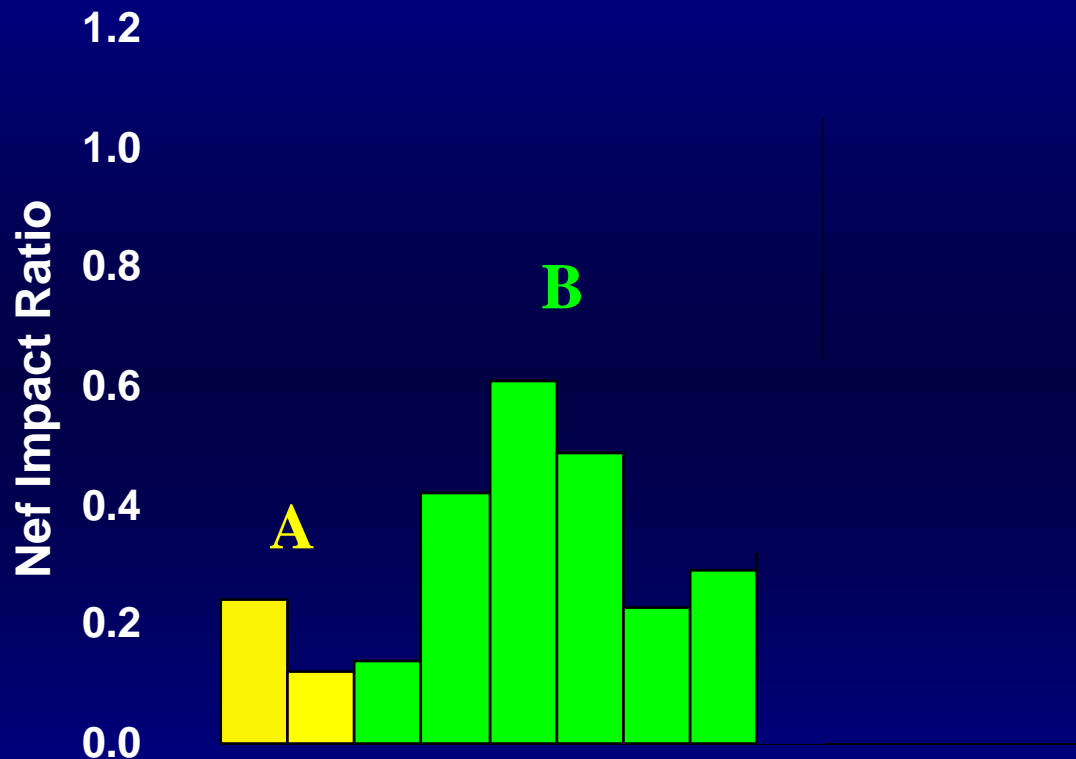
# The impact of Nef on CTL antiviral activity can vary dramatically



$$\text{Nef Impact Ratio} = (6.3 - 3.2) \div (6.3 - 2.6) = 0.84$$

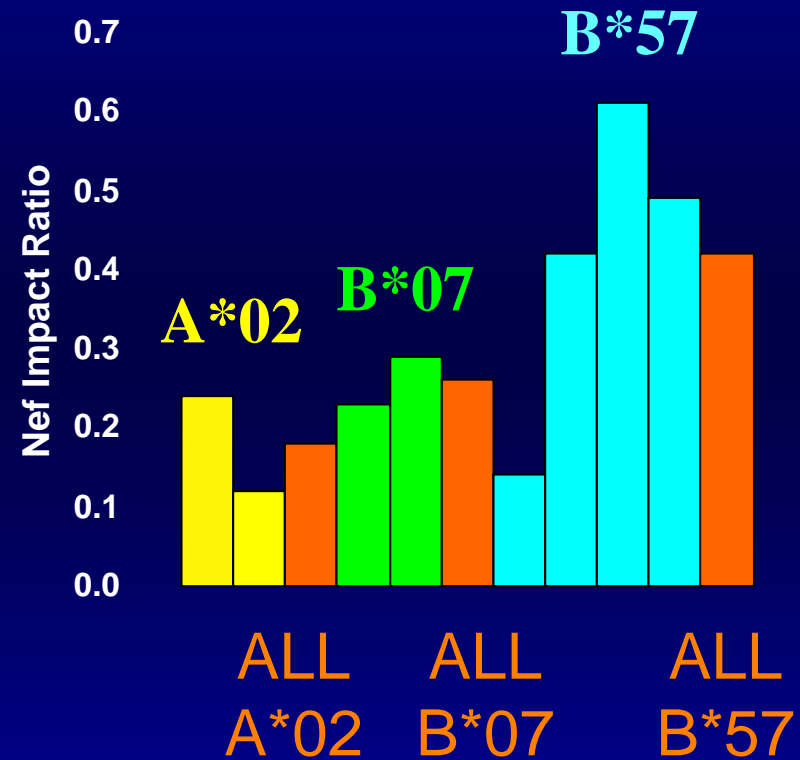
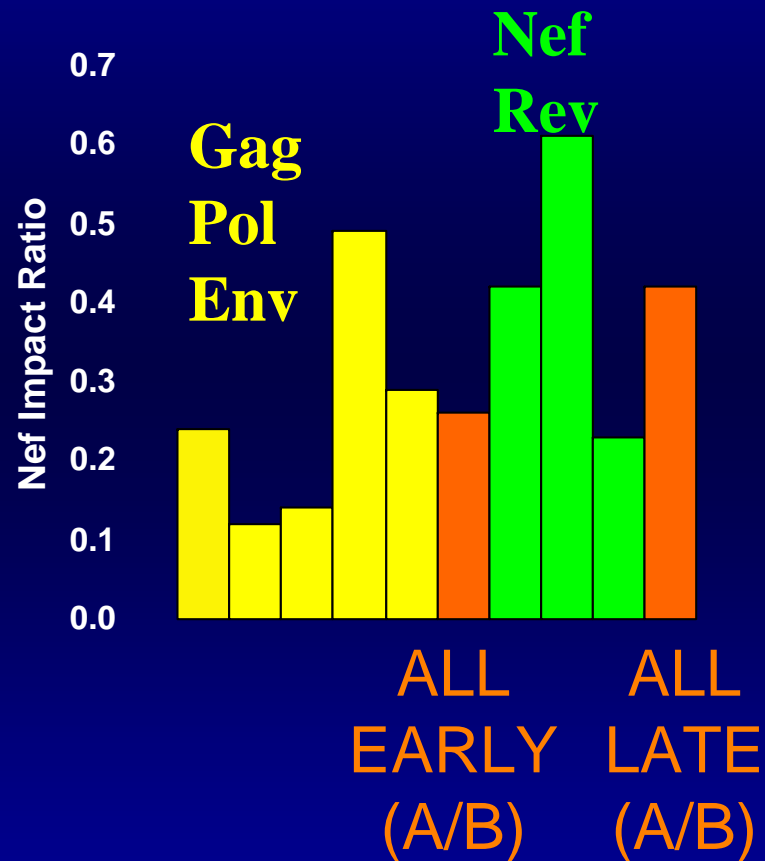
Adapted from S. Adnan and O.O. Yang et al. Blood 2006, 108:3414

# Nef does not affect the antiviral activity of HLA-I C-restricted CTL



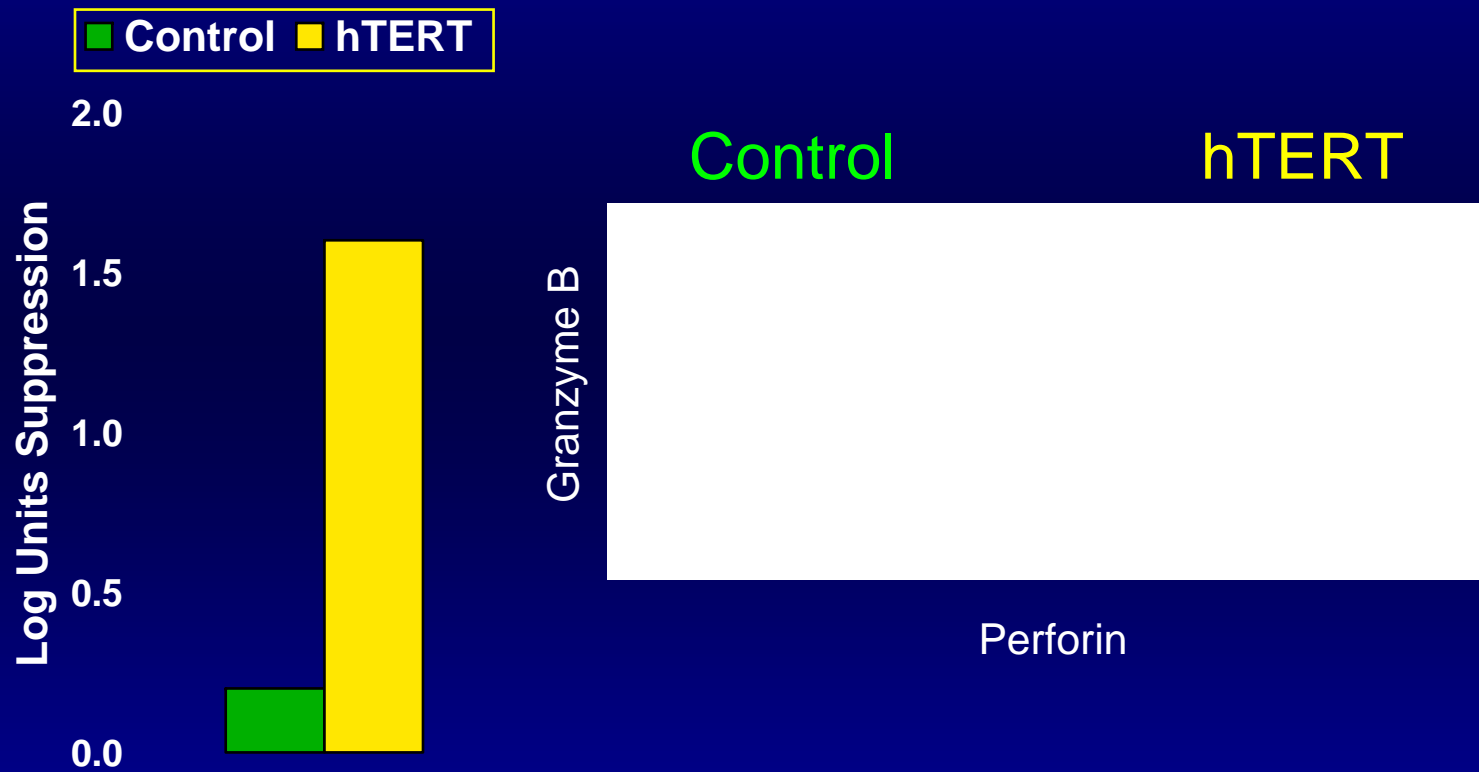
Adapted from S. Adnan and O.O. Yang et al. Blood 2006, 108:3414

# Other epitope factors may also affect Nef susceptibility (?)



(Unpublished data)

# HIV-1-specific CTL lose antiviral function with senescence



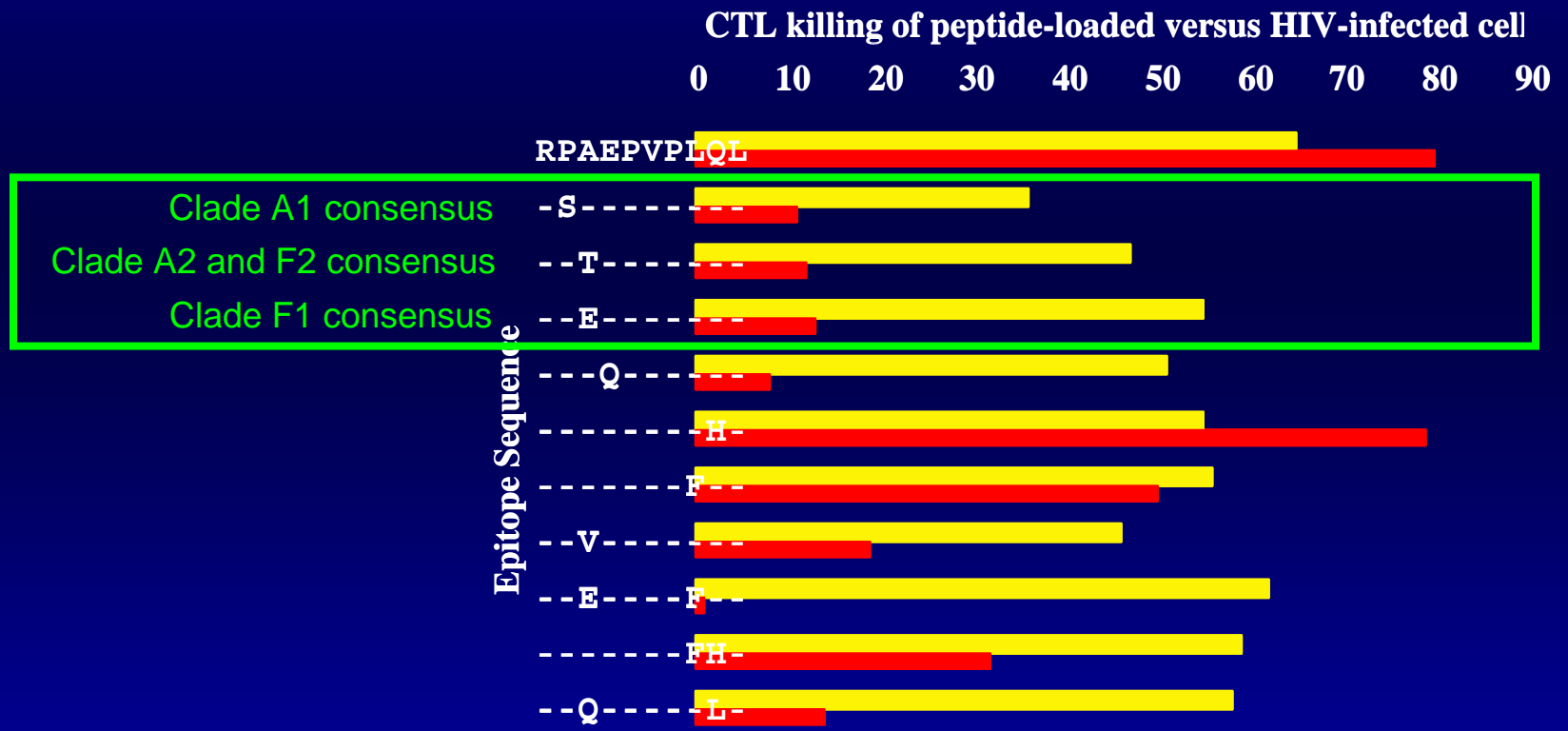
Adapted from M. Dagarag  
and O.O. Yang et al. *J Virol*  
2003, 77:3077

From O.O. Yang and C. Uittenbogaart  
et al. *Virology* 2004, 332:16

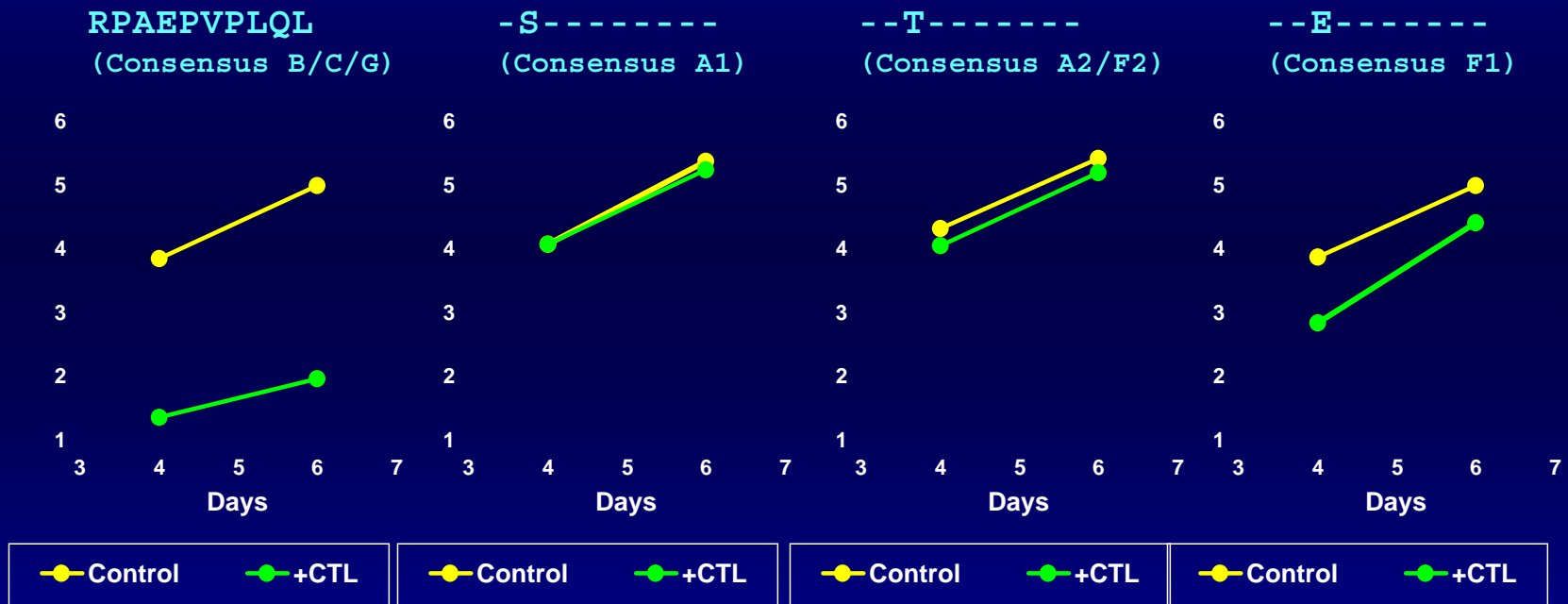
# Summary of factors determining CTL antiviral efficiency

- Epitope levels (adequacy for recognition)
- Epitope kinetics (timing of recognition in relation to viral production)
- Impact of Nef-mediated HLA-I downregulation
- Effector status of CTL
- *What is the relative importance of these factors???*

# An example that antiviral assays can give different results than standard CTL assays (Implications for escape and cross-clade studies?)



# CTL detection does not predict virus suppression



# Implications for analysis of current vaccine trials?

- ELISpot is the major validated surrogate marker for CTL immunogenicity of vaccines
- Most likely, ELISpot responses are *necessary but not sufficient* to reflect the antiviral activity of CTL (recognition of infected cells)
- If current vaccine trials fail to demonstrate clinical benefit despite “immunogenicity,” it may be premature to discount a CTL-based vaccine approach based on lack of protection in vaccine “responders”

**A more important question about  
HIV-1-specific CTL:**

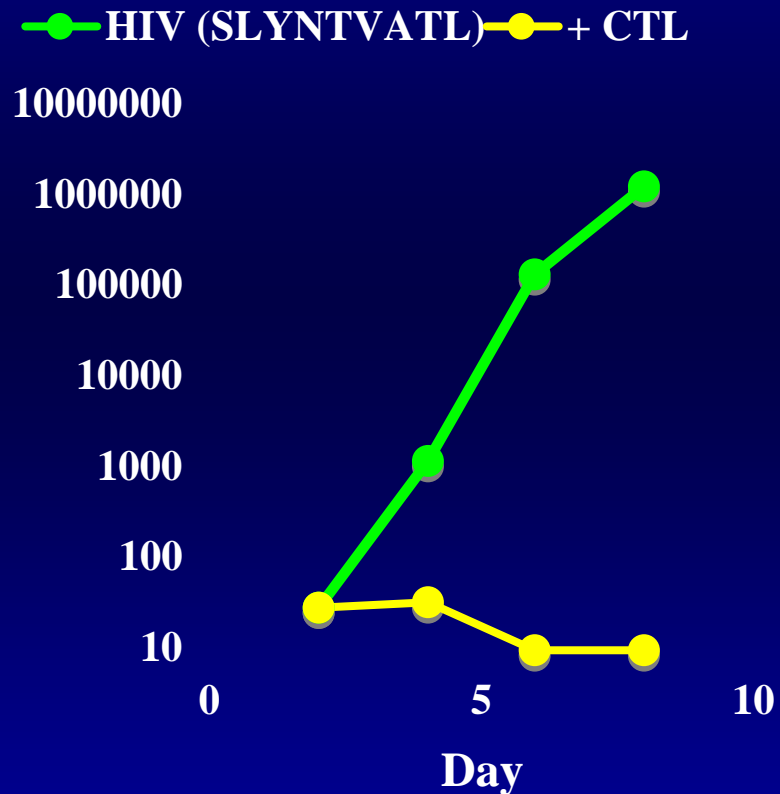
**Why do they fail *in vivo*?**

## **Multiple mechanisms have been observed and proposed to explain failure *in vivo***

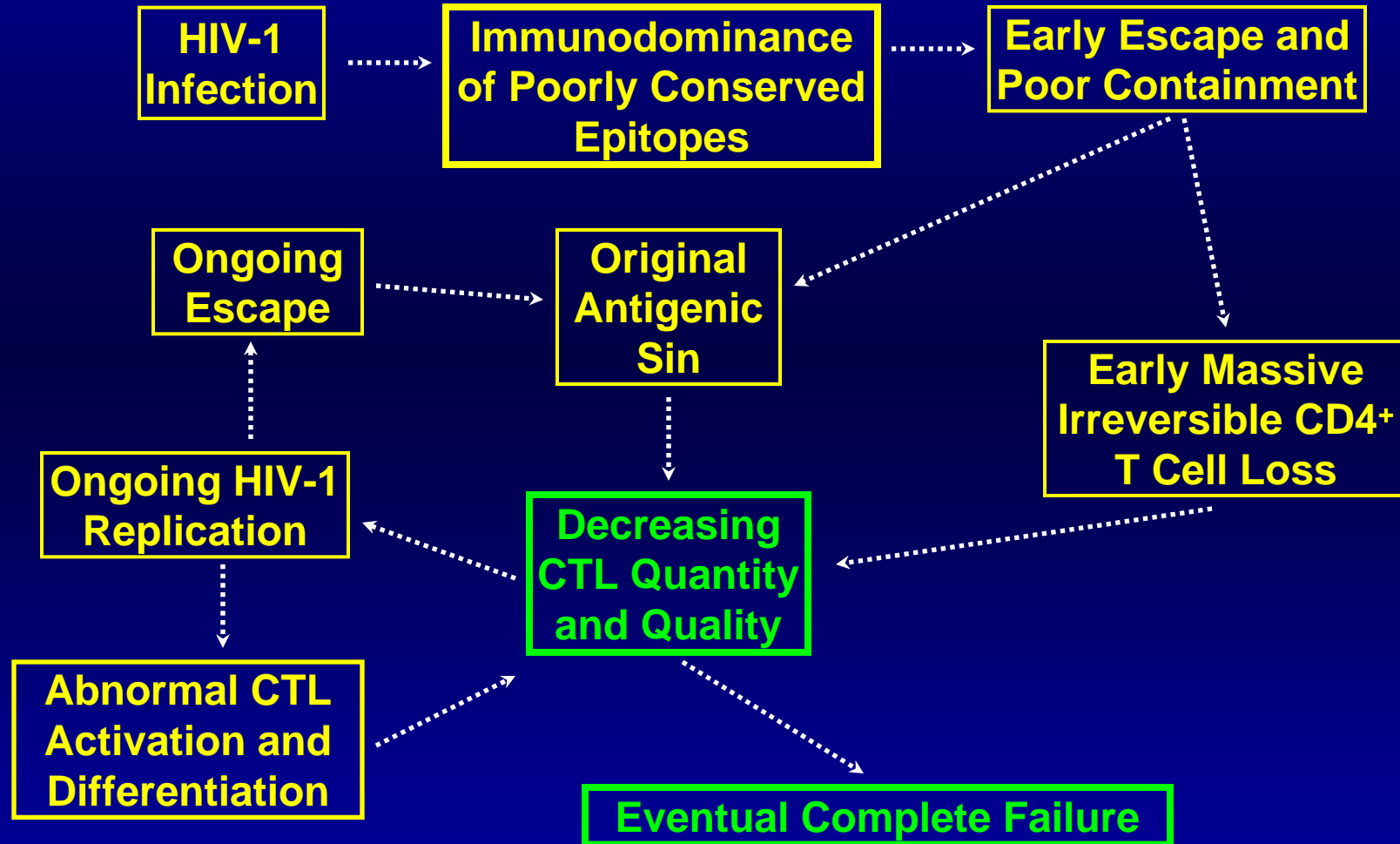
- Abnormal differentiation and activation
- Exhaustion/senescence
- Hypofunctional profile
- Lack of CD4 help
- Epitope escape mutation

***Can a single process explain these diverse events (Ockham's razor)???***

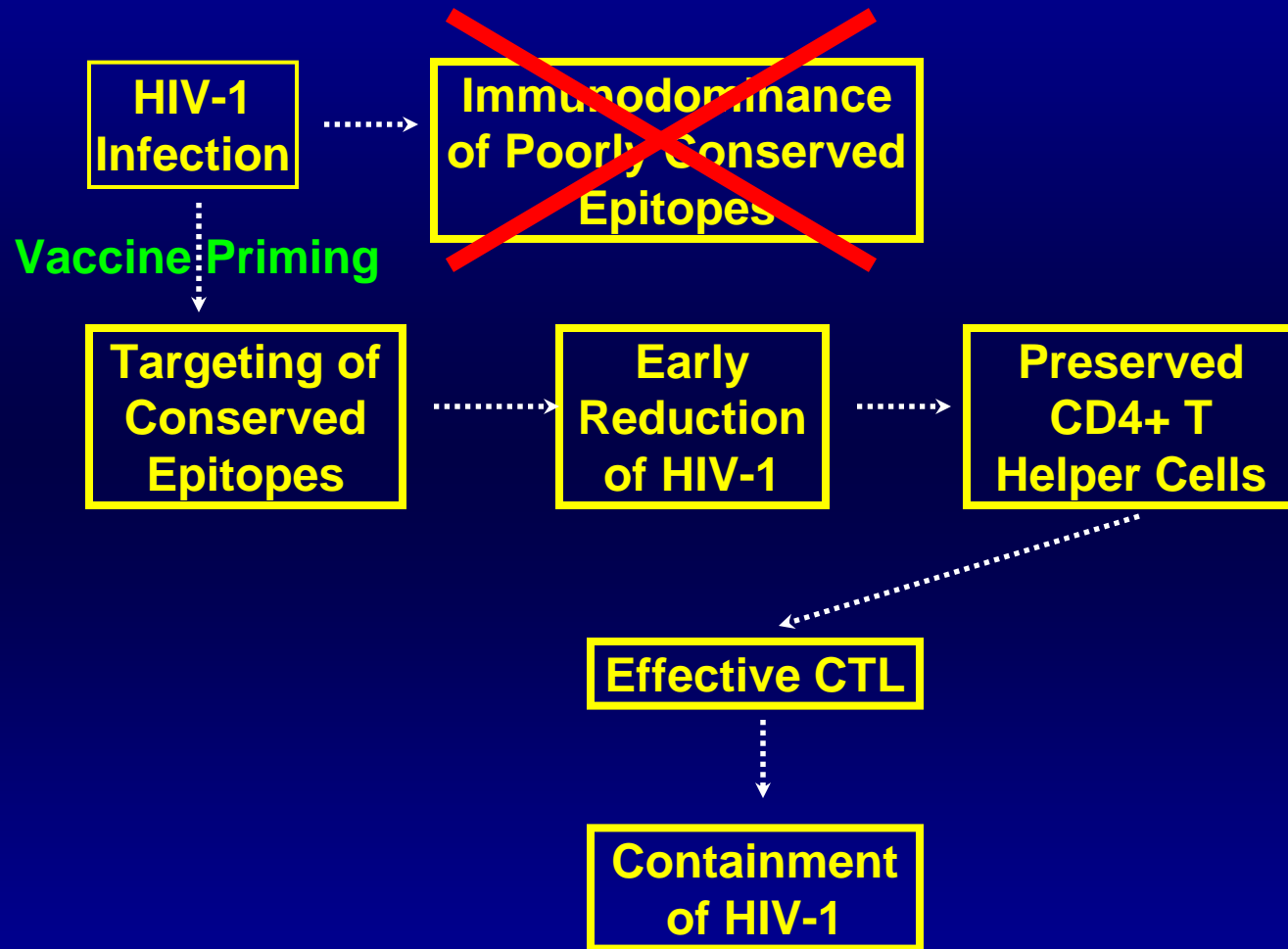
# Single amino acid changes in epitopes can allow HIV-1 to completely avoid CTL



# A hypothesis....



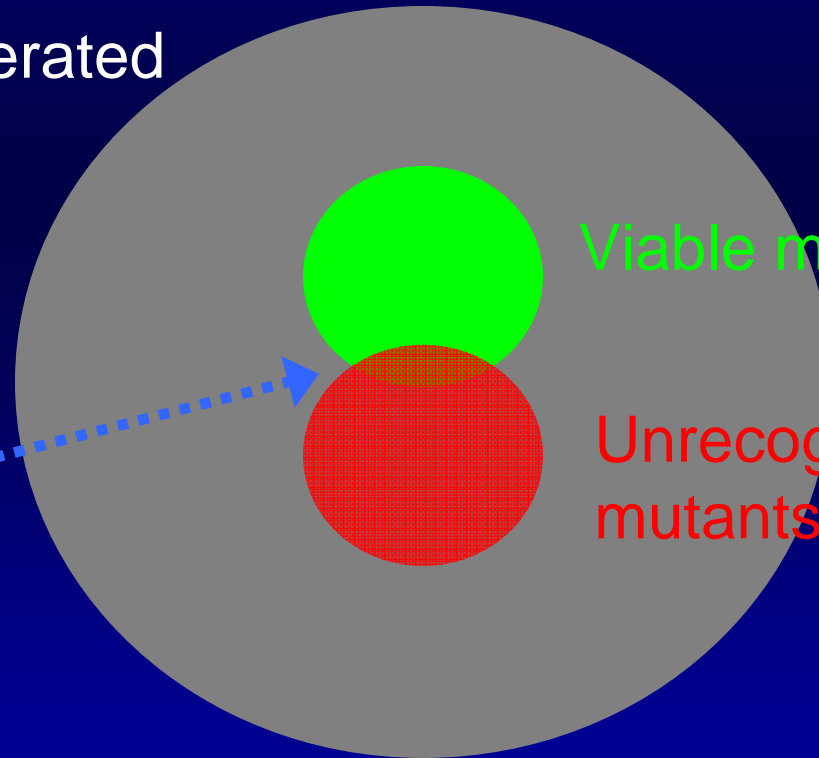
# A hypothesis....



# What strategies can prevent escape?

All randomly generated  
epitope mutants

Escape  
Mutants



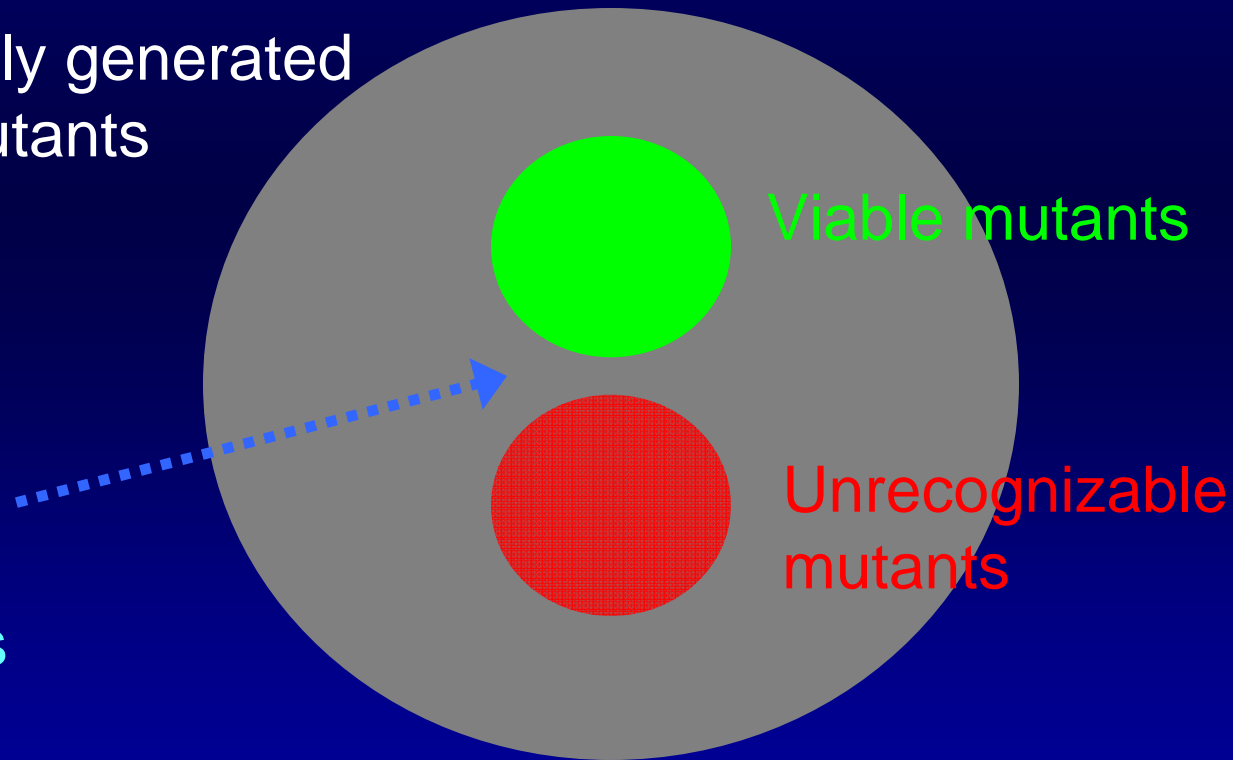
Viable mutants

Unrecognizable  
mutants

# A mutation must be *both* non-recognized *and* viable to allow escape

All randomly generated epitope mutants

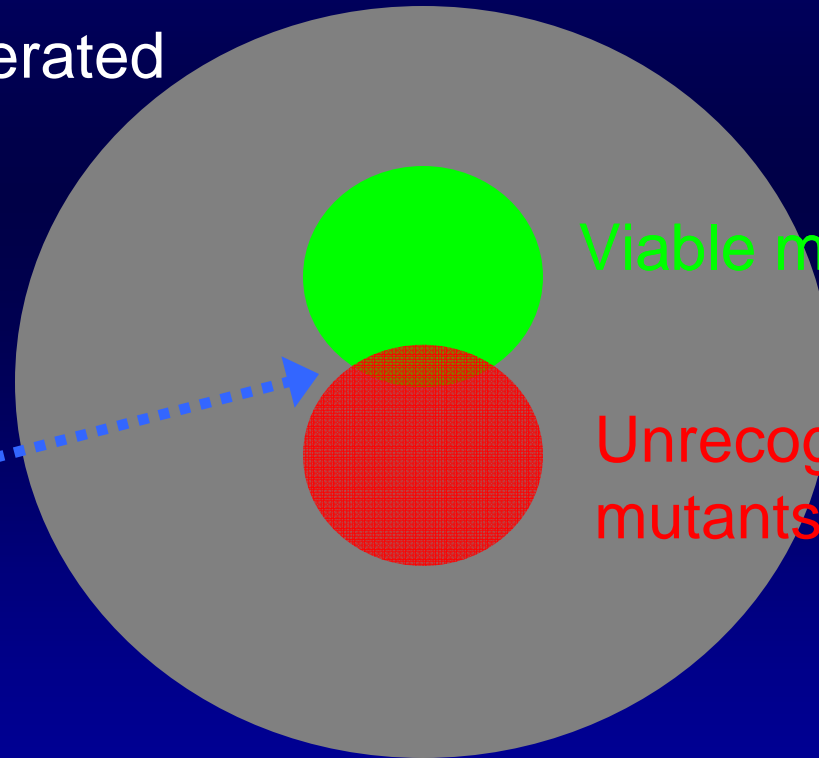
No  
Escape  
Mutants



# Bypassing immunodominance to focus CTL on very constrained epitopes?

All randomly generated epitope mutants

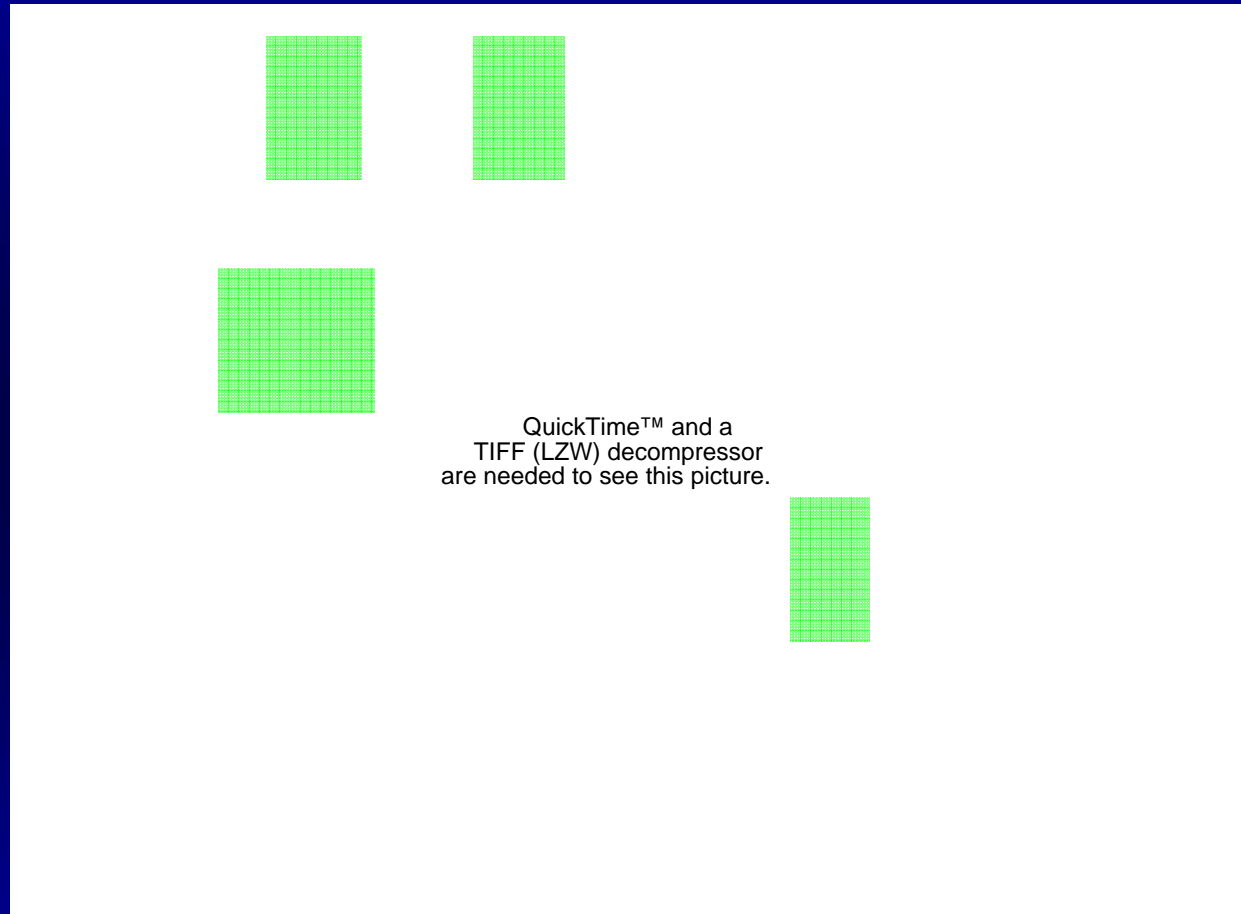
Escape Mutants



Viable mutants

Unrecognizable mutants

# Focus immunity on constrained sequences?



From entropy calculations generously provided by B Korber

# Acknowledgments

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