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AIDS Education and Training Center

May 13-14, 2011  
Orlando, FL

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## **Innate Immunity, CD4 Cell Count and Elite Controllers**

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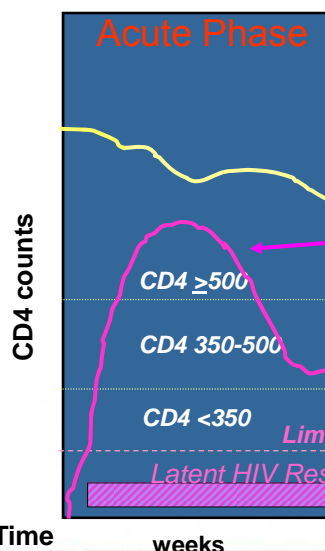
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# 1. Understanding definitions and concepts

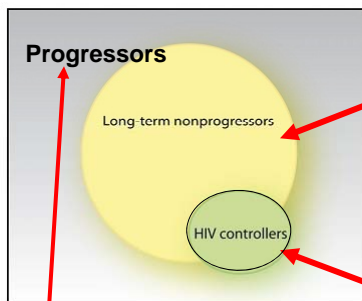
## Course of Untreated HIV Infection



- Initial control of virus replication and viral setpoint are important determinants of subsequent disease outcome.
- Without HAART most HIV infected persons exhibit variable but progressive decline in CD4 T cells and ongoing virus replication. They are designated as **Chronic Progressors**
- A small proportion exhibit spontaneous and durable control of virus replication with lack of disease progression in the absence of HAART and are designated as **Virologic Controllers**
- Some manifest low level viremia but maintain their CD4 T cells in absence of HAART, designated **Viremic Controllers (include LTNP)**

Plasma HIV RNA copies/ml

## Elite Controllers, LTNP and Chronic Progressors



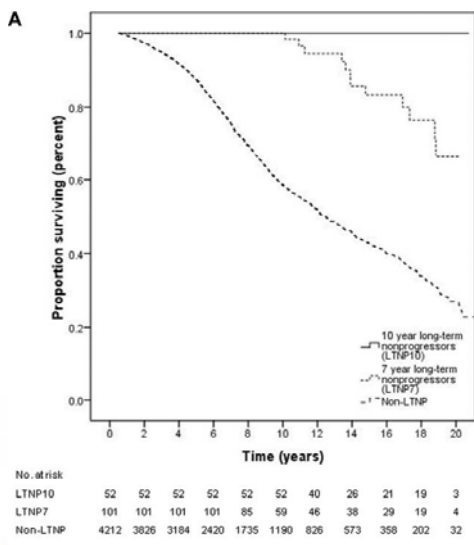
- LTNP: ~5% of HIV+ population
- Definition based on CD4 control for 7-10 years without HAART
- VL usually <2,000 HIV RNA copies/ml
- Most ultimately show CD4 decline; better survival if stable for >10 years

- Elite Controllers (EC):  $\leq 1\%$  of HIV+
- Maintain durable HIV control to <50 copies/mL without HAART
- Rarely progress
- Also known as HIV controllers

- Non-controllers or Chronic Progressors: > 90% of HIV+
- Inability to control virus; VL >10,000 copies/mL without HAART
- With early HAART many progressors achieve characteristics of EC but virus rebounds if HAART is discontinued

Deeks SG and Walker BD: *Immunity* 27:1286, 2007

## Survival Analysis, LTNP

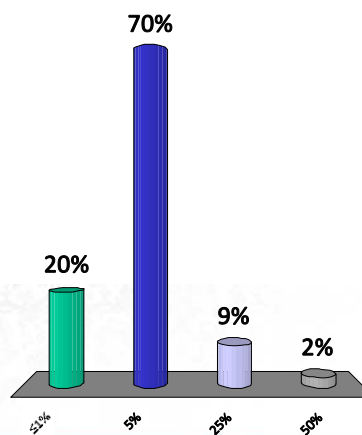


Kaplan-Meier analysis of time to death for 7- and 10-year long-term nonprogressors (LTNP7s and LTNP10s, respectively) and non-LTNPs

(Okulicz, JF et al, *JID* 200:1714-23, 2009)

**Approximate percentage of HIV infected persons that are classified as LTNP is:**

- A.  $\leq 1\%$
- B. 5%
- C. 25%
- D. 50%



## Our Common Goal: to Cure AIDS

- “Cure” means that patient remains healthy without the need to take ARV medications
- There are two desirable scenarios of cure for AIDS which would permit discontinuation of ARV drugs
  - Sterilizing cure: Permanent eradication of virus
  - Functional cure: Permanent suppression of viral replication despite inability to eradicate virus

## Elite Controllers as Models for Achieving Functional Cure

- **Understanding the mechanisms that allow elite controllers to maintain undetectable viremia over a long period of time would**
  - help to develop strategies for a functional cure for HIV infection
  - help to establish correlates of immune protection and evaluation of effective HIV vaccines



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## Complete or Near Complete HIV Control: Epidemiologic Factors are Not Revealing ...

- **Route of HIV acquisition is not a strong predictor of immunologic non progression**
- **Gender is also not a limiting factor, with both male and female HIV controllers**
- **Ethnicity: Identified in multiple ethnicities**
- **Race, geographic location, and/or viral subtype -potential impact on immunologic and virologic outcomes remains unknown**



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## Possible Virologic and Host Factors Involved in HIV Control

- **Is it the Virus?**
  - Mutations/defective virus
  - Viral fitness
  - Virus reservoir
- **Is it the Host Genetics ?**
  - HLA
  - Anti-viral host restriction factors
- **Is it the Quality of Immune Defenses?**
  - Innate immunity
  - Cytotoxic CD8 T cells
  - CD4 T cells
  - Neutralizing antibody



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## Factors Associated with Virologic Control

## Intrinsic Virologic Factors are Rarely Implicated in Virologic Controllers

- **Attenuated virus:** Incidence of infection with defective virus is very rare; famous Australian (Sydney Blood Bank) cohort infected with Nef deletion mutant-some have since progressed
- **Replication defective virus:** Most EC are infected with pathogenic virus but some manifest a high frequency of replication defective virus
- **Defects in viral fitness** are attributed to escape mutations in fitness-critical viral epitopes that cannot be compensated and point to a robust immune system



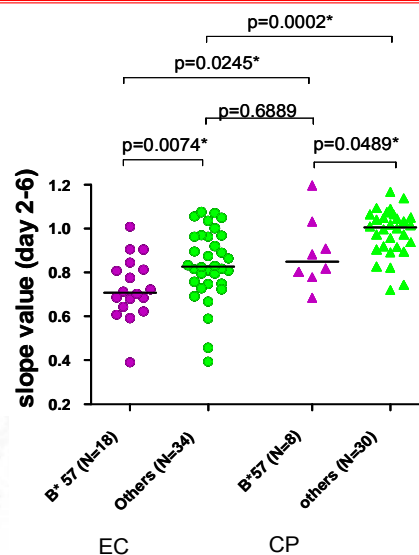
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## HLA Influences Viral Replication Capacity



Miura, Brockman et al, JVI 2009



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## Virus Reservoirs

- The stable elite controllers' HIV reservoir is extremely low, but does not differ from those of long-term suppressed patients under antiretroviral therapy initiated at the time of the primary infection
- The HIV reservoir is strongly linked to the host's MHC alleles and CD8-specific T cells



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## Host Factors in HIV Control



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## Host Factors in HIV Control

- **Known factors**
  - Chemokine family: CCR5 polymorphisms: delta 32 allele homozygosity prevents acquisition of HIV, and heterozygosity assoc with delayed progression to AIDS
  - MHC locus: HLA-B5701, and to a lesser extent HLA-B27 are associated with protection from progressive HIV disease (*Kiepiela et al., Nature 432: 769-775, 2004*)
- **Not yet established**
  - Host restriction factors: Apobec3G, Trim5a, tetherin, others-role in LTNP/EC not yet defined



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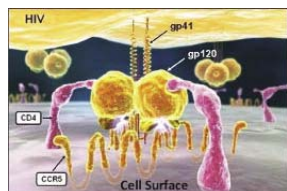
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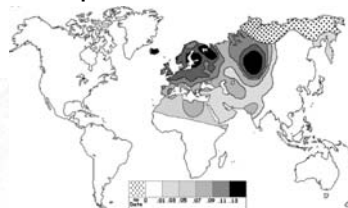
## An example of functional cure: the Berlin patient

- In 2007, a patient was given a stem cell transplant with the CCR5 $\Delta$ 32/ $\Delta$ 32 mutation for treatment of relapse of AML
- 3 years after transplant, CD4 T-cell numbers have returned to the normal range of healthy patients whereas HIV RNA and DNA remain continuously undetectable in plasma and PBMC



CD4-CCR5-HIV interaction (Atreya et al, THURJ, 2009)

The molecule CCR5 is a co-receptor necessary for HIV to enter the CD4 T cells



Geographic distribution of the CCR5- $\Delta$ 32 allele (Faure et al, Virology Journal, 2008)



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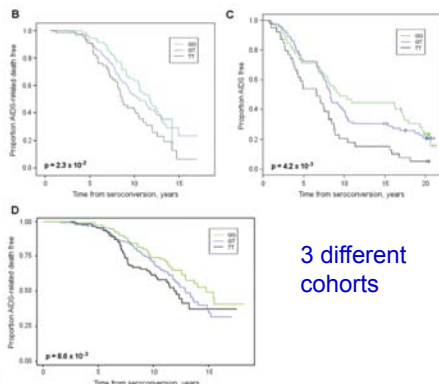
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## CXCR6 Affects Non-Progression to AIDS (Study in LTNP, excluding EC)

**Chemokine receptor CXCR6:**

- is a minor HIV-1 coreceptor and mediator of inflammation
- involved in the trafficking of effector T cells and in the activation and homeostasis of natural killer T cells



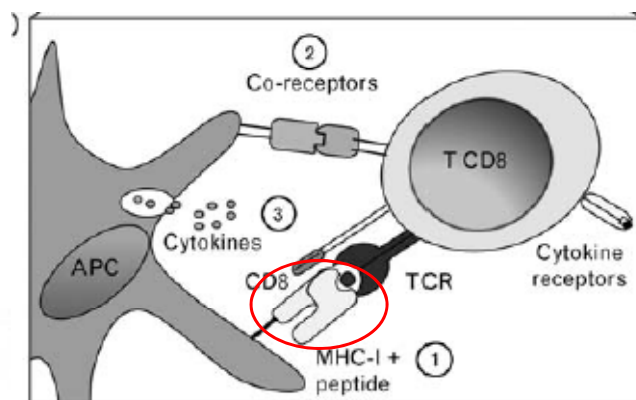
3 different cohorts

- Analysis of the single nucleotide polymorphism rs2234358 in the CXCR6 gene reveals that the genotype GG associates with slower disease progression and is more common in LTNP
- This is a new chemokine receptor genetic variant in Chromosome 3 and regulates CXCR6 expression

Limou et al, JID 2010

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## Determinants of CD8+ T cell responses in control of HIV replication



HLA molecules present antigen peptides

Adapted from Appay V: Current Opinion in HIV and AIDS 2011, 6:157-162

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SCIENCE VOL 330 10 DECEMBER 2010

# The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation

The International HIV Controllers Study\*†

Infectious and inflammatory diseases have repeatedly shown strong genetic associations within the major histocompatibility complex (MHC); however, the basis for these associations remains elusive. To define host genetic effects on the outcome of a chronic viral infection, we performed genome-wide association analysis in a multiethnic cohort of HIV-1 controllers and progressors, and we analyzed the effects of individual amino acids within the classical human leukocyte antigen (HLA) proteins. We identified >300 genome-wide significant single-nucleotide polymorphisms (SNPs) within the MHC and none elsewhere. Specific amino acids in the *HLA-B* peptide binding groove, as well as an independent *HLA-C* effect, explain the SNP associations and reconcile both protective and risk *HLA* alleles. These results implicate the nature of the HLA-viral peptide interaction as the major factor modulating durable control of HIV infection.

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## More on HLA: The Nature of the HLA-Viral Peptide Interaction is a Relevant Factor Modulating Durable Control of HIV Infection

Significance of the “protective” polymorphisms in the HLA locus: the example of the HLA-B protein.

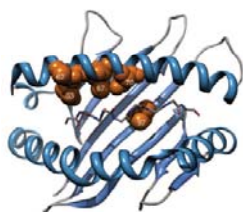


Fig. 4. Three-dimensional ribbon representation of the HLA-B protein based on Protein Data Bank entry 2bwp (30), highlighting amino acid positions 62, 63, 67, 70, and 97 lining the peptide binding pocket. The peptide backbone of the epitope is also displayed. This figure was prepared with UCSF Chimera (32).

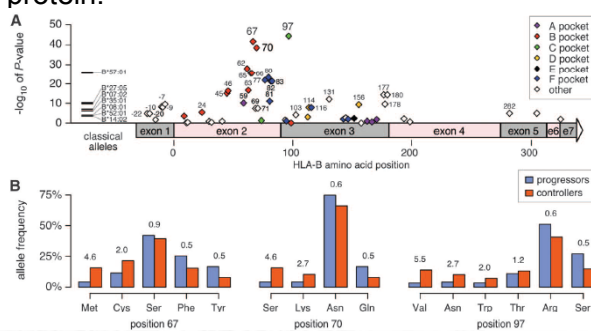


Fig. 3. Associations at amino acids in *HLA-B* in the European sample. (A) Association results for all variable amino acid positions, as calculated by the omnibus test. Colors denote conventional pocket positions. *P* values for significant classical *HLA-B* alleles are shown for comparison. (B) Marked allele frequency differences between controllers and progressors for amino acids at positions 67, 70, and 97. Numbers above the bars indicate odds ratios values >1 indicate a protective effect. (C) Associa-

Specific amino acids in the HLA-B peptide binding groove affect HLA class I peptide presentation, explaining the SNP associations with HIV-1 control

Pereyra et al, Science 2010

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## Possible Virologic and Host Factors Involved in HIV Control

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- **Is it the Host Genetics ?**
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- **Is it the quality of Immune Defenses?**
  - Innate immunity
  - Cytotoxic CD8 T cells
  - CD4 T cells
  - Neutralizing antibody



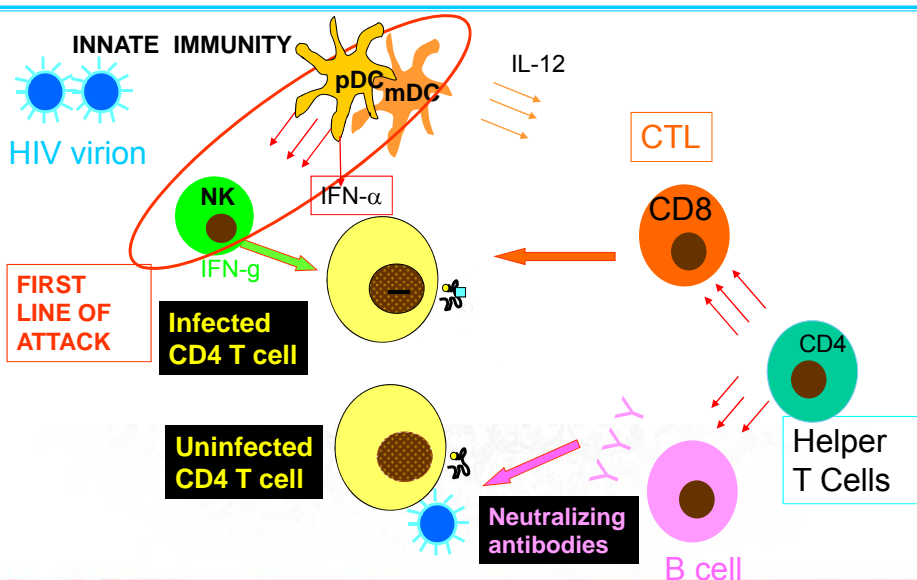
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## Host Virus Interaction: Components of Antiviral Immunity



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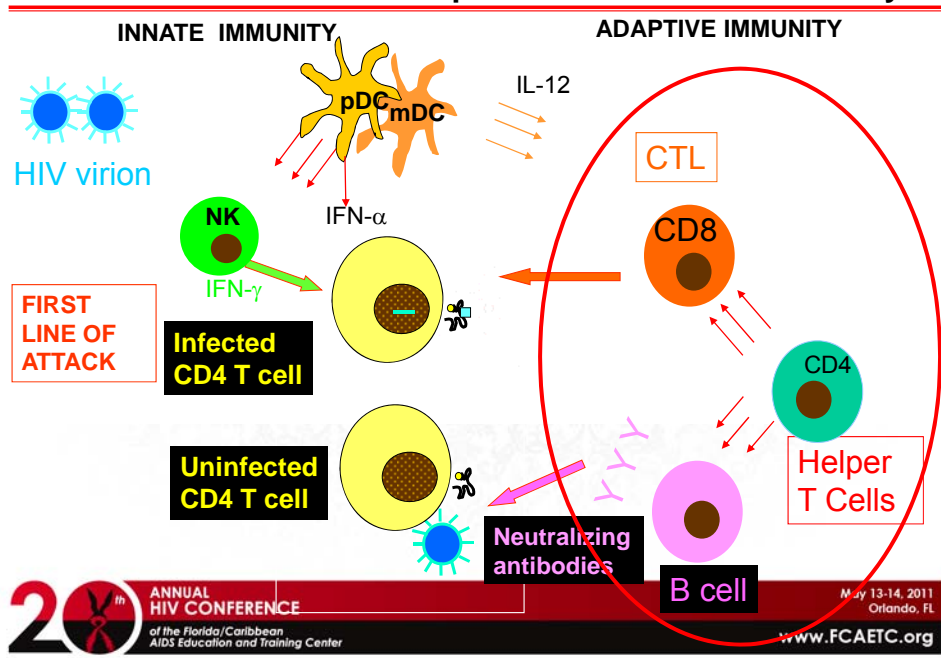
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## Host Factors: Innate Immunity

- Natural Killer cells: KIR3DS1 an activating NK cell receptor, and KIR3DL1 an inhibitory receptor confer added protection to HLA B57 (*Martin et al., Nat. Genet. 39: 733-740, 2007*)
- pDC are higher in LTNP (*Soumelis et al., Blood: 98: 906-912, 2001*)
- No definitive correlation has been made between innate immunity by standard immunologic measures with viral control



## Host Virus Interaction: Components of Antiviral Immunity



## Host Factors: Adaptive Immunity

- **Strong associations have been seen with**
  - Adaptive CD8 T cell immune responses. This is the most consistent antiviral mechanism linked to virologic control
  - Adaptive CD4 T cell immune responses (50%)
- **Antibody responses have not been strongly associated with virologic control**



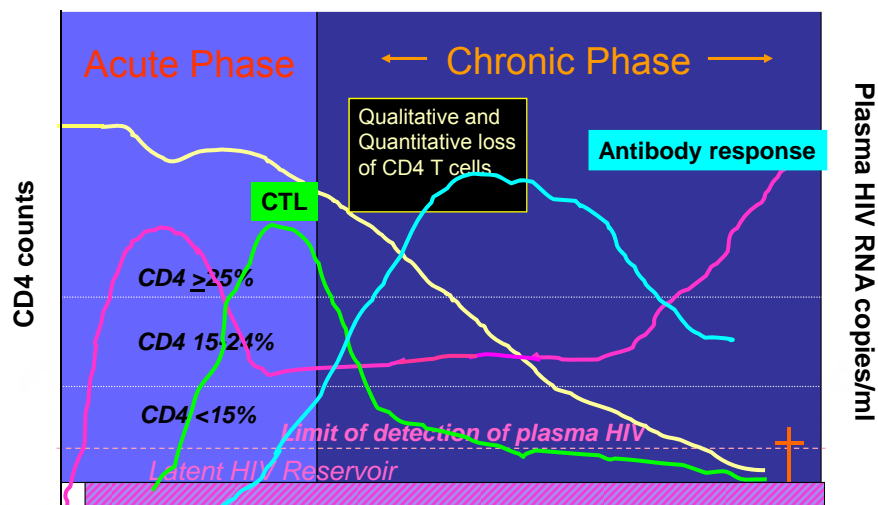
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## Adaptive Immune Responses in Natural “Immune Control” of HIV



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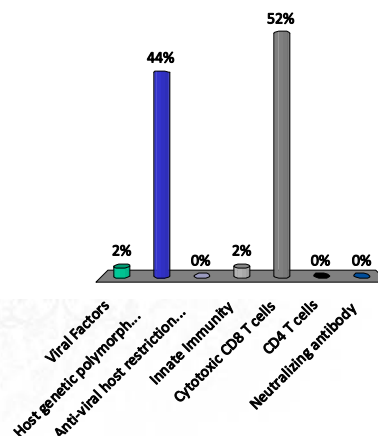
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## Identify the most well established factors for determining virus control in Elite Controllers

- A. Viral Factors
- B. Host genetic polymorphisms influencing virus entry or HLA
- C. Anti-viral host restriction factors
- D. Innate Immunity
- E. Cytotoxic CD8 T cells
- F. CD4 T cells
- G. Neutralizing antibody



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## Antiviral Functions of CD8 T Cells are Better in Elite Controllers

- Proliferation upon encounter with HIV antigens and the ability to produce the cytolytic protein perforin (*Migueles et al., 2002*). HIV specific CD8 T cell proliferation seen only in EC and not in aviremic patients on suppressive HAART regimens
- Polyfunctional cytokine response: interferon-g, MIP-1b, TNF-a, interleukin-2, and/or CD107a (*Betts et al., 2006; Zimmerli et al., 2005*). Polyfunctional T cells are seen in blood and mucosal tissues (*Ferre, 2009*)
- HIV inhibition: freshly isolated CD8+ T cells of HIV controllers have higher capacities to inhibit HIV replication in infected autologous CD4+ T cells (*Saez- Cirion et al, 2007*)

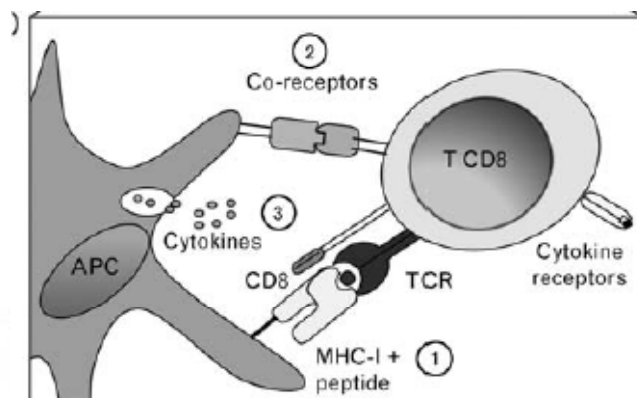


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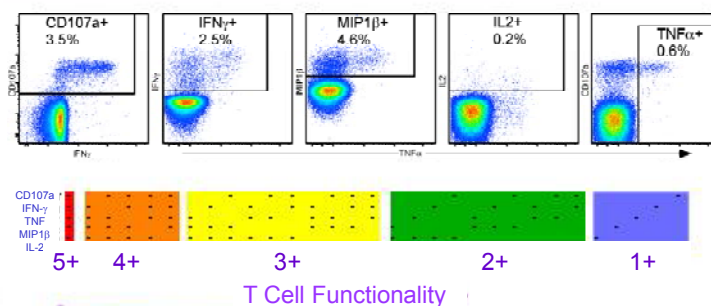
## Determinants of CD8+ T cell responses in control of HIV replication



Adapted from Appay V: Current Opinion in HIV and AIDS 2011, 6:157-162

## Qualitative T cell responses: Intracellular Cytokines

### Flow Cytometric Quantification of 5 T Cell Functions

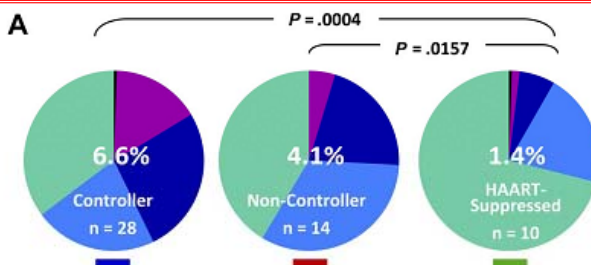


Signature of a "protective immune response":

**Polyfunctional T cells**

**Loss of polyfunctionality = poor immune response**

## HIV Gag-specific Polyfunctional Mucosal CD8 T cells



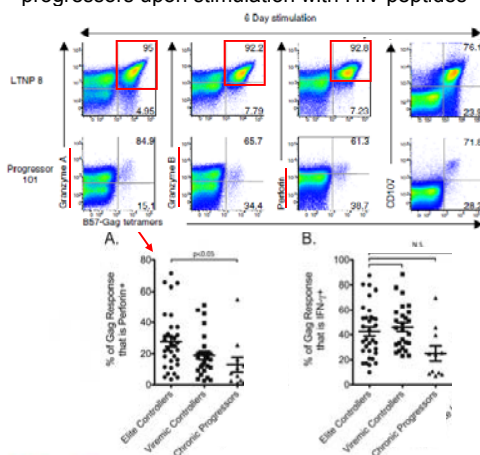
**HIV Gag-specific polyfunctional CD8<sub>T</sub> cell responses.** (A) The overall polyfunctionality of the mucosal CD8<sub>T</sub> cell response can be visualized with pie charts in which each slice represents a different functional category: black indicates 5 functions; purple, 4 functions; dark blue, 3 functions; light blue, 2 functions; green, 1 function. The number in the center of each pie represents the median total percentage of cells responding in any way to Gag stimulation. Elite and viremic controllers are combined into a single "controller" category. NC indicates noncontroller; HAART, HAART-suppressed. Statistical differences between groups are indicated above pie charts.

Ferre, A.L. et al. *Blood* 113: 3978–3989, 2009

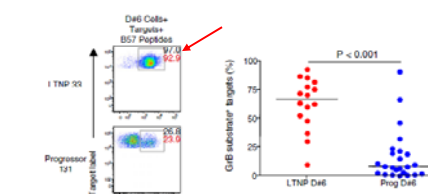
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## Granule-exocytosis-mediated cytotoxicity as a correlate of immunologic control of HIV

Cytotoxic granule content in LTNP and progressors upon stimulation with HIV peptides



Cytotoxic activity of HIV-specific CTL in LTNP vs. progressors

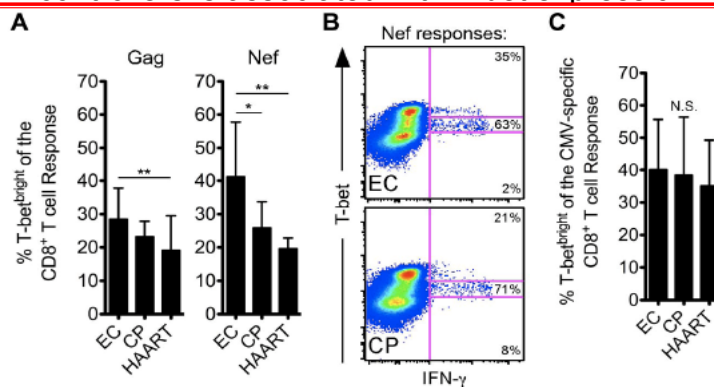


Migueles, S.A. et al. *Immunity* 29, 1009–1021, 2008

Perforin upregulation in HIV-specific Ag-stimulated CTL in EC vs. progressors

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## Increased HIV-specific CD8 T-cell response in HIV elite controllers is associated with T-bet expression



HIV-specific CD8<sup>+</sup> T cells from ECs express higher amounts of T-bet than CPs after short-term stimulation. (A) The fraction of Gag- or Nef-specific CD8<sup>+</sup> T cells, as identified by staining for IFN- $\gamma$ , TNF $\alpha$ , or CD107a, that fell within the T-bet bright gate was determined for all ECs, CPs, and HAART subjects. (B) Representative flow cytometric plots from ECs and CPs showing the fraction of the Nef-specific response that fell within the 3 T-bet gates. Events shown have been gated on CD8<sup>+</sup> T cells. (C) The fraction of CMV-specific CD8<sup>+</sup> T cells that fell within the T-bet bright gate was determined for all ECs, CPs, and HAART subjects as in panel A. (A-C) Statistical analysis was carried out using 1-way ANOVA (nonparametric; Kruskal-Wallis) followed by a Dunn test for multiple comparisons. \*P < .05; \*\*P < .01. Bars represent the means and error bars indicate SDs.

Hersperger et al. *Blood* 117:3799-808, 2011

## CD4 T Cells in HIV Infection

- CD4 cells are the major target cells for HIV infection
- CD4 cells of elite controllers do not show reduced susceptibility to infection (*Rabi et al. J Virol, 2011*)
- Several subsets of CD4 T cells exist and are the major immune cells that provide essential help to and regulation of function of other immune cells

## CD4 T cells: Role in Adaptive Immunity Against HIV

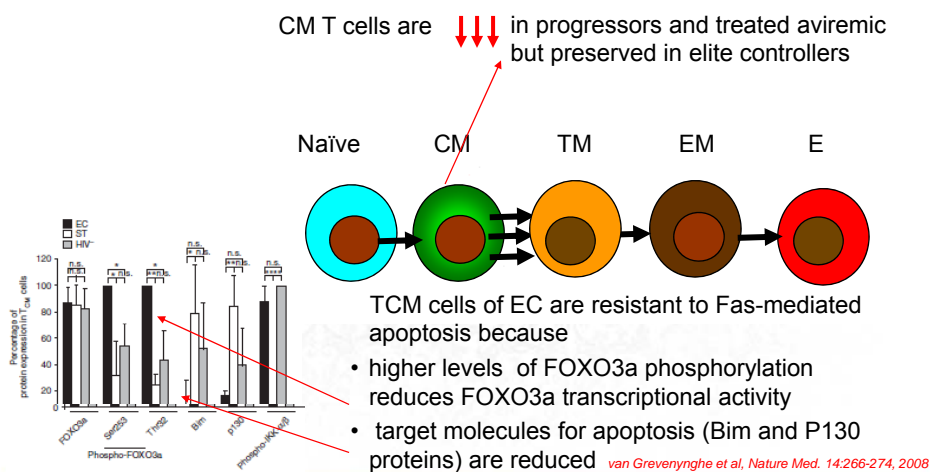
- CD4 T cells provide important helper function to T cells and B cells
- EC patients show antigen-specific CD4 T cell proliferation and polyfunctional responses
- EC CD4 T cells do not show immune exhaustion markers (CTLA4 and PD-1); virus replication upregulates these markers
- HIV-specific CD4 T cells will likely be an important component of an effective HIV vaccine



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## CD4 T cell differentiation subsets: Loss of Central Memory (CM) cells



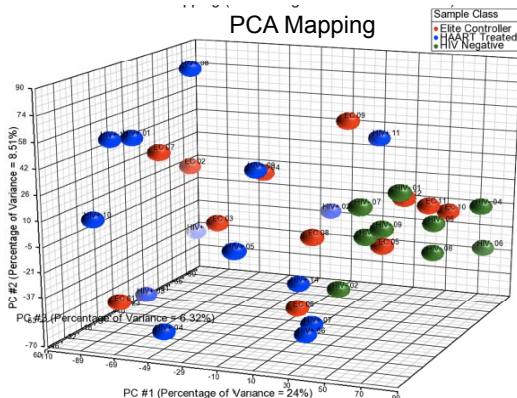


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## Transcriptional Profiling of CD4 T Cells Identifies Distinct Subgroups of HIV-1 Elite Controllers

Comparison of gene expression signatures for individuals from EC, progressor and HIV neg. groups: principal component analysis (PCA) of microarray transcripts



Transcriptional profiling of CD4 T cells is not homogeneous among individuals and identifies distinct subgroups of EC.

Indeed, CD4 gene profile of some EC clusters with progressors: these EC have lower CD4 count.

CD4 gene profile of some other EC clusters with HIV neg: these EC have higher CD4 count.

Vigneault et al., J Virol 2011



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## Summary of CD4 and CD8 T cells: Potential Mechanism for Virus Control in HIV “Controllers”

Mechanism	Evidence
<b>Adaptive Immune Response</b>	
HIV-specific CD8 <sup>+</sup> T cells	Controllers are enriched certain class I HLA alleles and often have CD8 <sup>+</sup> T cells that produce multiple cytokines and/or proliferate in response to HIV peptides
HIV-specific CD4 <sup>+</sup> T cells	Controllers often have CD4 <sup>+</sup> T cells that express high amounts of HIV-specific IL-2 and interferon- $\gamma$ in response to HIV peptides

Saez-Cirion, A. et al., Trends Immun 2007



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## What is the Role of Immune Activation in HIV Disease Progression

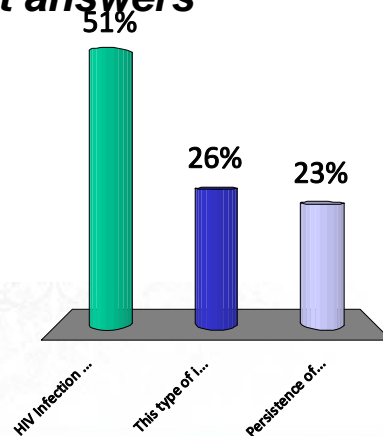


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## Audience Response-3 Immune Activation in HIV *Indicate correct answers*

1. HIV Infection is associated with generalized persistent immune activation
2. This type of immune activation is bad because it leads to destruction of immune cells by apoptosis
3. Persistence of this type of immune activation is good because it makes killer CD8 T cells do their job



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## Generalized Immune Activation is... Not Good

- Immune activation is marked by excessive frequency of HLADR+ CD38+ CD8 T cells
- Frequency of activated CD8 T cells are a better predictor of disease progression than loss of CD4 T cells or increase in virus load or virus tropism

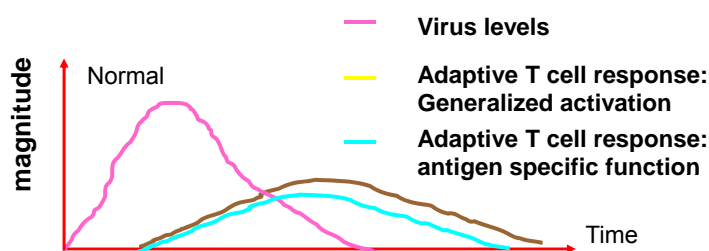
(Giorgi,J, 1993)



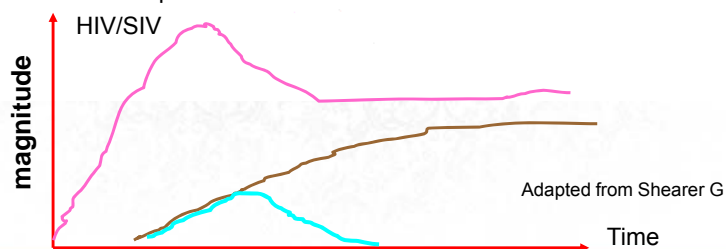
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### Normal response to viral infections



Aberrant immune activation- immune activation persists even though HIV specific immune response wanes



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## Generalized Immune Activation: What Causes it and Why is it so Bad?

### **Exact cause not confirmed; most likely causes:**

- **HIV and its proteins drive aberrant immune activation**
  - Stimulation of innate immune system
  - Direct and Indirect stimulation of T and B cells
  - Failure of immunoregulation (ie, loss of T-regulatory cells)
- **HIV induced gut damage leads to microbial translocation**
  - Bacterial products drive immune activation of innate and adaptive immune system

### **It is detrimental to host:**

- **Results in quantitative and qualitative loss of immunity by exacerbating HIV replication, causing immune exhaustion and apoptotic cell death**



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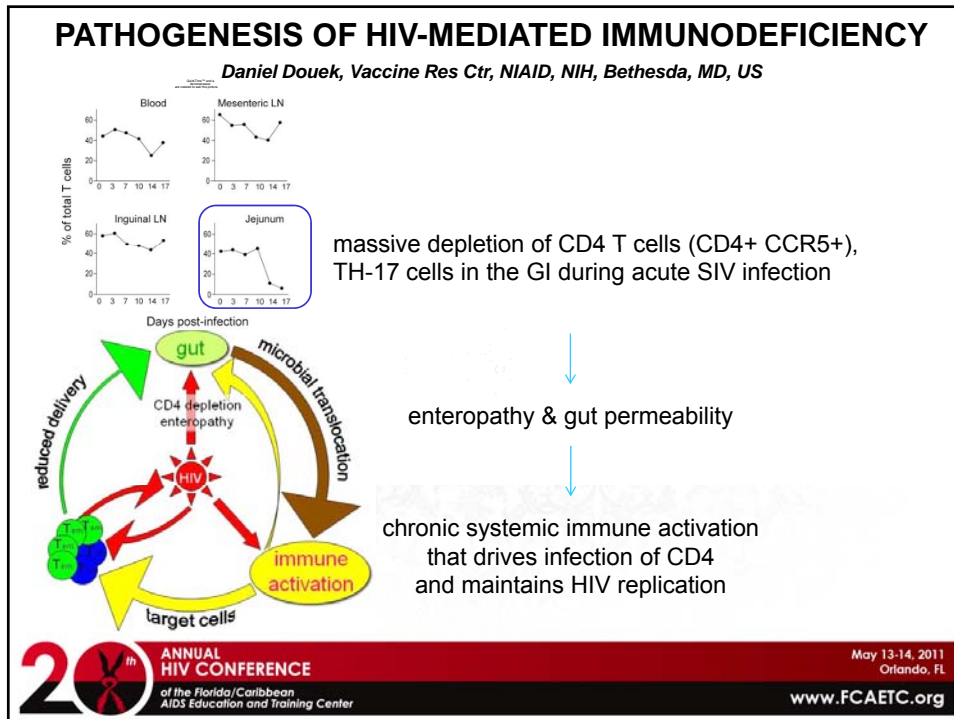
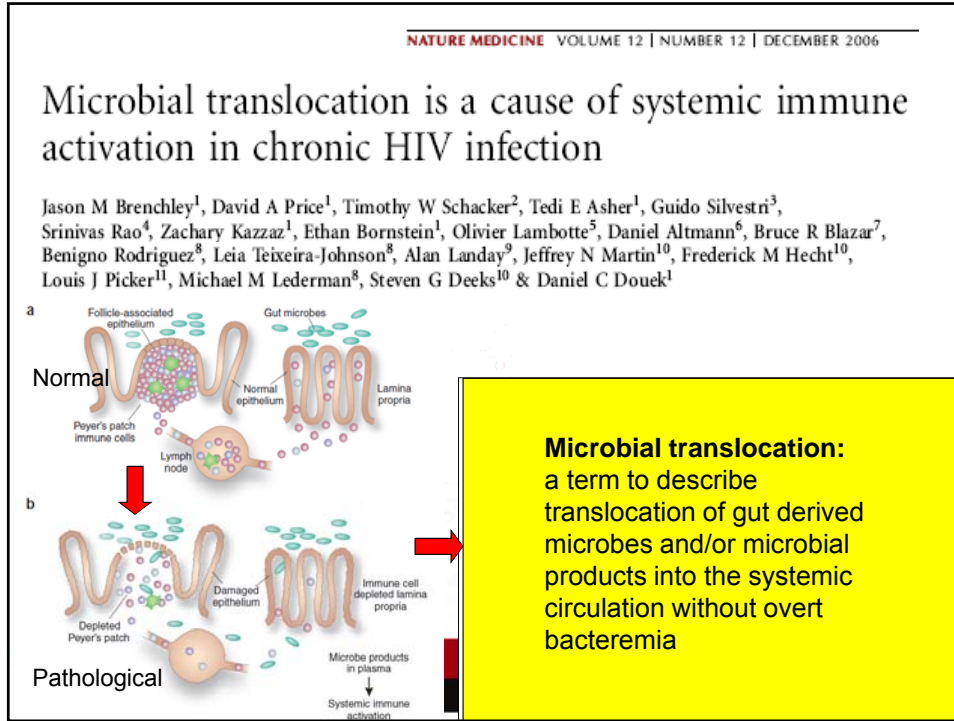
## HIV and the Gut

- **Gastrointestinal tract is the most prominent early site of virus replication (1-3 weeks post infection)**
- **Rapid and extensive depletion of CCR5+ CD4 T cells in the gut occurs within days of primary HIV infection. TH-17 subset is wiped out, also B cells; gut pathology important driver of HIV disease pathogenesis**



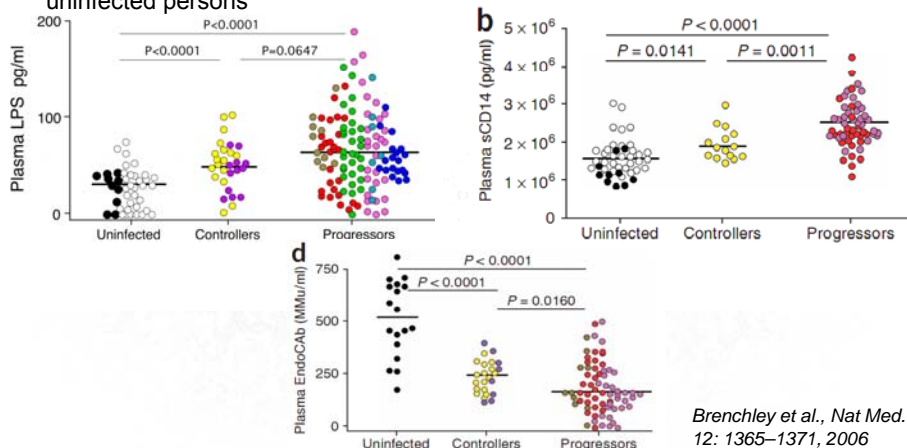
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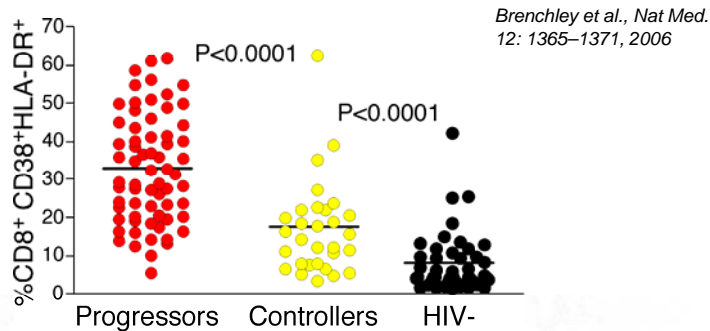


## Microbial Translocation is Lower in Elite Controllers than in Progressors

But elite controllers manifest higher levels of microbial translocation than uninfected persons



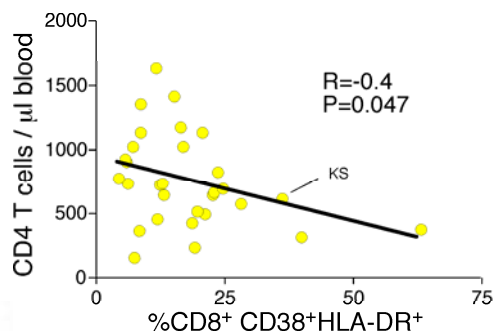
## Do Elite Controllers have Evidence of Immune Activation?



Elite controllers have lower frequencies of activated T cells compared to Progressors (but higher than uninfected individuals)

## Immune Activation in Elite Controllers

Are low levels of immune activation detrimental in Elite Controllers?



Slow CD4 T cell depletion can occur in association with T cell activation



Hunt, P.W. et al. *J. Infect. Dis.* 197:126–133, 2008

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## Elite Controllers: Summary -1

- EC are natural viremic controllers and generally do not experience the depletion of CD4+ T cells seen in progressive HIV-1 infection except in association with immune activation
- The long term EC status (>10yrs) is a promising model for functional cure; most manifest strong antiviral cell-mediated immunity, favorable host genetics and low HIV reservoirs
- EC also have a lower degree of mucosal CD4+ T cell depletion and lower levels of microbial translocation than patients with progressive disease



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## Elite Controllers

### Summary-2: Immune Mechanisms

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- Polyfunctional CD8+T cell responses to HIV-1 stimulation are seen in primary HIV-1 infection. These responses are lost in patients who become progressors, but are maintained in EC
- Primary CD8+ T cells from EC (but not progressors) are capable of suppressing HIV-1 replication in autologous CD4+ T cells
- Patients on HAART have comparable viral loads to EC, but do not have the effective granzyme B-mediated killing of HIV-1-infected CD4+ T cells that is seen in EC
- A definable immunologic marker for durable control or a protective host genotype has still not been defined



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## Elite Controllers: Summary 3

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- Eventually, only a small proportion (elite long-term nonprogressors) might represent models of functional cure with long-term virus undetectability and stable immune competence
- Continued study of mechanisms of virus control through comprehensive approaches is important for the development of strategies for achieving a state of EC (ie functional cure) in chronic progressors
- Therapeutic or vaccine strategies may be successful in accomplishing this goal



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# Thank you



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