



A Gleam of Hope

Long-term non-progressors
HIV-exposed non-seroconverters

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Background

- ◆ Rapid Progressors, ~10%, 2-3 years
- ◆ Typical Progressors, ~80%, <10 years
- ◆ Long-term non-progressors, >10 years
 - Varying definitions of LTNP: ~0.8%-10%
- ◆ HIV-exposed non-seroconverters
 - Impossible to measure the frequency



Hypothesis

- ◆ What is learned through the study of LTNPs and non-converters may lead to advances extending the life expectancy of HIV-positive people or preventing seroconversion entirely by inducing a similar immunity to that naturally possessed by non-seroconverters.



Methods

- ◆ Medical Literature
- ◆ Press Releases, current and past
- ◆ AIDS research organization publications
- ◆ Clinical trial data
- ◆ Biochemical test data
- ◆ Anecdotal evidence



Factors Influencing Infection and Progression

- ◆ Route of exposure and quantity of virus
- ◆ Phenotype (virulence) of virus
- ◆ Host polymorphism in coreceptors
- ◆ Capacity of host immune system
- ◆ Other genetic factors affecting host immunity
- ◆ A *combination* of these factors



Long-term non-progressors



- ◆ Less virulent HIV virus
- ◆ Mutant form of HIV virus
- ◆ “Superman” immune system hypothesis
 - Cytotoxic T Lymphocyte activity
 - CD-8 cells and alpha-defensins -1, -2, -3
 - HLA B*5701



HLA B*5701

- ◆ Human Leukocyte Antigen
- ◆ HLA proteins attach to virus fragments in infected cells, bring to cell surface and present to CD-8 cells (cytotoxic T lymphocytes) that destroy the infected cell
- ◆ Present in 85% of LTNPs
 - Only true for a very strict definition of LTNPs

HIV-exposed non-converters

- ◆ Discordant Partners (HIV-/HIV+)
- ◆ HIV- infants from HIV+ mothers
- ◆ Exposed health workers
- ◆ Exposed sex workers, extremely high risk
 - Women from Nairobi, Kenya among the first discovered: 25% - 95% of clients infected. Similar cases found in Gambian women.



Cytotoxic T Lymphocytes

- ◆ Recognize infected cells and destroy them before HIV buds from cell and infects others
- ◆ Discordant partner trials: HIV- partner had CTL response against partner's HIV virus, but did not seroconvert (41-45% of cases)
- ◆ Virus exposure induces HIV-immunity without infection



CCR-5



- ◆ HIV-coreceptor on surface of CD-4 cell
- ◆ CCR-5 mutant gene causes 32bp deletion
- ◆ Causes no phenotypic abnormality
- ◆ HIV cannot enter cells of individuals who are homozygous for the CCR-5 mutation
- ◆ Rare: 1% Caucasians homozygous mutant



Potential Solutions and Conclusions

- ◆ Analysis of how LTNPs and non-seroconverters effectively control the HIV virus may lead to therapeutic interventions
- ◆ Cell-mediated vs. antibody response
 - Determined by genetics, dose of virus and route of infection
 - Engineer a prophylactic vaccine to promote response