THE NEW YORK TIMES  July 3, 1981
RARE CANCER SEEN IN 41 HOMOSEXUALS
By LAWRENCE K. ALTMAN
Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made. The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the diagnoses, mostly in New York City and the San Francisco Bay area, are alerting other physicians who treat large numbers of homosexual men to the problem in an effort to help identify more cases and to reduce the delay in offering chemotherapy treatment......
Dr. Friedman-Kien said he had tested nine of the victims and found severe defects in their immunological systems. The patients had serious malfunctions of two types of cells called T and B cell lymphocytes, which have important roles in fighting infections and cancer. But Dr. Friedman-Kien emphasized that the researchers did not know whether the immunological defects were the underlying problem or had developed secondarily to the infections or drug use.

THE NEW YORK TIMES  May 30, 2011
30 Years In, We Are Still Learning From AIDS
http://www.nytimes.com/2011/05/31/health/31aids.html?pagewanted=1&_r=1&hp
By LAWRENCE K. ALTMAN, M.D.
At first it seemed an oddity: a scattering of reports in the spring and early summer of 1981 that young gay men in New York and California were ill with forms of pneumonia and cancer usually seen only in people with severely weakened immune systems. In hindsight, of course, these announcements were the first official harbingers of AIDS — the catastrophic pandemic that would infect more than 60 million people (and counting) worldwide, killing at least half that number. But at the time, we had little idea what we were dealing with — didn’t know that AIDS was a distinct disease, what caused it, how it could be contracted, or even what to call it.

As AIDS has become entrenched in the United States and elsewhere, a new generation has grown up with little if any knowledge of those dark early days. But they are worth recalling, as a cautionary tale about the effects of the bafflement and fear that can surround an unknown disease and as a reminder of the sweeping changes in medical practice that the epidemic has brought about. Reports of the initial cases were confusing. The first federal announcement, 30 years ago this week, concerned “five young men, all active homosexuals,” with pneumocystis carinii pneumonia, or P.C.P., a disease “almost exclusively limited to severely immunosuppressed patients.” Initial suspicion fell on a known infectious agent, cytomegalovirus.

......It took three years to conclusively identify H.I.V., the virus that causes AIDS, and longer to settle disputed claims for the discovery. When doctors learned that it took about a decade to get sick from AIDS after H.I.V. first entered the body, they realized that people had been unwittingly transmitting the virus for years, spreading it to thousands of people in many countries, who in turn spread it to thousands and ultimately millions more.

Epidemiologists quickly showed that H.I.V. could be transmitted through heterosexual sex; from infected women to their newborns; in transfusions of blood and blood products; and via contaminated needles.

see also HIV/AIDS articles in current issue of Nature
http://www.nature.com/nature/journal/v474/n7349/index.html
AIDS is one of the greatest pandemics in medical history

- Over 20 million people have died from AIDS (Acquired Immune Deficiency Syndrome)
- Not only is this a human tragedy of unimaginable dimensions, it is also a threat to world security because of the potential for political destabilization

GLOBAL REPORT

Global summary of the AIDS epidemic | 2009

<table>
<thead>
<tr>
<th>Number of people living with HIV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>33.3 million [31.4 million–35.3 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>30.8 million [29.2 million–32.6 million]</td>
</tr>
<tr>
<td>Women</td>
<td>15.9 million [14.8 million–17.2 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>2.5 million [1.6 million–3.4 million]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People newly infected with HIV in 2009</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2.6 million [2.3 million–2.8 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>2.2 million [2.0 million–2.4 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>370 000 [230 000–510 000]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIDS deaths in 2009</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.8 million [1.6 million–2.1 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.6 million [1.4 million–1.8 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>260 000 [150 000–360 000]</td>
</tr>
</tbody>
</table>

AIDS is caused by the HIV (human immunodeficiency) retrovirus.


HIV = Human Immunodeficiency Virus  
AIDS= Acquired Immunodeficiency Syndrome

• **Infection with HIV is characterized by a relentless decline in both the numbers and function of lymphocytes called T-helper cells**

• **T helper cells play a central role in coordinating immune responses mediated by both T and B lymphocytes (responsible,respectively for cell mediated (cytotoxic) and humoral (antibody) immunity**

• **HIV infection may produce no symptoms for years, but typically within 10-15 years the weakened immune system loses control over viral replication and AIDS develops**
Over the past couple of decades it has become apparent
• that some individuals escape HIV infection despite being at high risk from repeated exposure to the virus
• and that other people are infected with the virus but progress to AIDS at an unusually slow rate

The Inexplicable Survivors of a Widespread Epidemic

By CAROL POGASH
Published: May 3, 2005

SAN FRANCISCO, April 28 - Before powerful antiviral medicines became available, Kai Brothers lost his partner and many friends to AIDS. Thinking he was next, he quit his job, emptied his 401(k) and waited to die.

Nothing happened.

It has been 16 years since Mr. Brothers learned he was H.I.V. positive. Since then, he has never taken AIDS drugs or had any illnesses associated with the disease. Despite his good

Kai is an “non-progressor” (aka controller): in other words, an HIV infected individual who doesn’t progress to AIDS at the normal rate
There is considerable heterogeneity in the clinical course of HIV infection

http://www.hivcontrollers.org/hivcontrollers

Most HIV-infected individuals have stable viral levels exceeding 10,000 RNA copies/ml

**HIV Controllers:** Plasma viral load (VL)< 2000 RNA copies/ml over a >12 month period without antiviral therapy
Why do some individuals escape HIV infection despite being at high risk for it?

HIV controllers versus progressors: why do some people who contract the virus progress to AIDS at an unusually slow rate?

What are the possible explanations for these observations?
What are the possible explanations for these observations?

• Genetic variants of the virus (see last page of lecture)
• Variation among individuals with respect to other infections
• Variations in life-style (environment)
• Genetic variability among individuals
One question of particular interest: Are there naturally occurring polymorphisms that confer some level of resistance to HIV infection?

These polymorphisms could affect:
• susceptibility to infection to HIV and other pathogens
• rate of progression of the disease
• final disease outcome
• immune response
• response to drug therapy
In the mid-1980’s a group of investigators started a systematic search for genetic polymorphisms that could influence the course of HIV infection.

At this time most investigators were focusing on the genetic variability of the virus itself (that might influence virulence).

These researchers went on a “genetic fishing expedition” to try to find human “resistance alleles”
Systematic search for genetic polymorphisms that could influence the course of HIV infection:

Cohort or group of several hundred individuals at high risk for HIV infection:

- IVD: intravenous drug users
- MSM (homosexual men)
- hemophiliacs who received tainted blood
- some of these high risk individuals were infected with HIV and some were not infected
- blood samples were collected from each -- cell cultures made to supply continuing source of DNA
When the study started, only 1000 human genes had been cloned
• But this was still too many genes to start screening randomly for polymorphisms
• So, the scientists made some judicious choices of candidate genes to focus on

Candidate gene: a gene that, because of its chromosomal location or some other property, becomes a candidate for a particular function, such as disease risk
Different Strategies for connecting a Gene with a Phenotype in (non-model) humans:

Linkage Analysis:
- used in positional cloning of gene mutated in hyperpain (erythermalgia) trait
- the candidate genes were identified based on chromosomal location

Candidate Gene Association Studies:
- Association (in this context) is the tendency of two characters (diseases or other traits, marker alleles such as SNPs) to occur together at non-random frequencies
- The study described in this lecture is an association study: researchers looked for a statistical association between functionally relevant polymorphisms in candidate genes and an decreased or increased susceptibility to HIV infection
- candidate genes were identified as those having a clear biological relationship to the trait in question
Candidate Gene Association Studies:
• These studies do not concern familial inheritance patterns
• Rather they are studies based on a comparison of unrelated affected and unaffected individuals from a population.
• An allele A of a specific gene of interest is said to be associated with a trait if it occurs at a (statistically) significantly higher frequency among affected compared with control individuals.
• Although association studies can be performed for any genetic polymorphism, they are most meaningful when applied to functionally significant variations in genes having a clear biological relation to the trait.

The scientists involved in this study made some judicious choices of candidate genes to focus on:
• chose 50 genes that they whose proteins could potentially influence the HIV life cycle
• systematically examined these genes for allelic variations that correlated with resistance to HIV infection or slow progression of the disease
HITTING THE JACKPOT

Researchers found one gene called CCR5 that showed a statistically significant difference in genotypes among the infected and uninfected cohorts.

CCR5 = CKR5 = CCKR5

Fig. 2. Genotypic markers 37 and HIV-1 infection [G test [39]]. The significance value of the genotype association for each marker is plotted in physical order along each chromosome. The dotted line corresponds to significance at the 1% level for individual tests. The right arrow corresponds to an experiment-wide 1% significance level, estimated with the Bonferroni procedure for multiple samplings [see (43)].
**CCR-5 gene** codes for a transmembrane protein that is involved in signal transduction events stimulated by *chemokines*

- Chemokines are a group of small polypeptides (70-80 amino acids) that induce cells to migrate to the site of inflammation

Investigators found that

- the CCR5 gene is polymorphic
- There is a major variant allele called ΔCCR5 that is missing 32 nucleotides
- Results in a frameshift and truncation of the protein
The frequency of this allele was investigated in a group of individuals who were either
1. infected with HIV or
2. uninfected with HIV but at high risk for HIV because of repeated high risk exposures (IVD, MSM, hemophiliacs) -- *this group may represent resistant individuals*

<table>
<thead>
<tr>
<th>HIGH RISK INDIVIDUALS</th>
<th>CCR5(^+/)CCR5(^{+})</th>
<th>CCR5(^+/)ΔCCR5</th>
<th>ΔCCR5/ΔCCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Infected n=1343</td>
<td>85%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>HIV Uninfected n=667</td>
<td>83%</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- In the general population of American Caucasians, the frequency of ΔCCR5/ΔCCR5 homozygotes is \(~1.2\)%, so we would have expected about 16 HIV-infected individuals to be of this genotype
- That 0% of the HIV infected individuals were homozygous for the mutant allele was statistically significant.

*Another study on 17,214 Europeans*
(from 2000 GSA meeting: S. O’Brien)

*HIV infected*:  
+/- = 3,823  +/Δ =727  Δ/Δ = 1

*Control (NOT at high risk for HIV infection)*
+/- = 10,273  +/Δ =2,221  Δ/Δ = 169
What is surprising about this life-cycle diagram?

Human immunodeficiency virus (HIV) adsorbs to the surface of host T-helper lymphocytes. The HIV envelope glycoproteins undergo a series of interactions with the **CD4 receptor and one or more co-receptors (usually CCR5)**. The culmination of these interactions is the fusing of the HIV outer membrane and the host-cell membrane, leading to virus–host-cell fusion. The viral capsid core then disassembles and viral nucleic acids enter the cytosol in association with virion proteins. A reverse-transcription complex containing the HIV **reverse transcriptase** catalyses complementary DNA synthesis, and the resulting complex containing viral cDNA is transported to the host-cell nucleus. Here, HIV integrase catalyses integration of viral cDNA into host-cell DNA. Expression of the viral DNA produces a precursor polypeptide that is proteolytically processed by HIV protease to give mature structural and functional viral proteins. These proteins assemble with HIV RNA at the cell membrane, from which they bud to release new virions. The targets against which approved anti-HIV agents act are indicated. nNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/ tide reverse transcriptase inhibitor.
HUH?
CCR5 receptor for HIV?
CD4 receptor for HIV?

Entry of an animal virus into a cell
• To enter animal cells, viruses must recognize and bind to specific proteins encoded by the host cell genome and displayed on the surface of the cell
• The host is an unwitting collaborator in the sense that these cell surface proteins have roles in normal host processes

The virus co-opts the receptor for its own purposes:
• A protein on the surface of the virus particle binds to the cell surface”receptor”
• the virus envelope fuses with the cell membrane and the entire virus particle enters the cell
Entry of the HIV virus into a host cell involves two different cell-surface receptors on target cells called CD4 and CCR5.

CD4 is the cell-surface receptor involved in T cell antigen recognition.

When the viral protein gp120 (knobs in this diagram) contact the CD4 and CCR5 proteins on the surface of a lymphocyte, an associated viral protein anchored to the surface of the virus shoots out a harpoonlike projection that pierces the host cell’s membrane. This stretches out the harpoon protein between the virus and the cell; when the two ends of the protein snap back towards each other, the membrane surrounding the virus particle fuses with the membrane of the cell.
The following study was performed on a group of HIV-positive Danish homosexual men who showed different phenotypes with respect to the progression of the disease.

<table>
<thead>
<tr>
<th>Population</th>
<th>CCR5+/CCR5⁺</th>
<th>CCR5+/ΔCCR5</th>
<th>ΔCCR5/ΔCCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Danish population</td>
<td>81 %</td>
<td>18 %</td>
<td>1%</td>
</tr>
<tr>
<td>HIV Infected: long-term, slow progression</td>
<td>34%</td>
<td>66%</td>
<td>0%</td>
</tr>
<tr>
<td>HIV Infected: normal progression</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Look at this table again

What about the blue-highlighted individuals?
They are homozygous for the wild-type allele

<table>
<thead>
<tr>
<th>HIGH RISK INDIVIDUALS</th>
<th>CCR5⁺/CCR5⁺</th>
<th>CCR5⁺/ΔCCR5</th>
<th>ΔCCR5/ΔCCR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Infected n=1343</td>
<td>85%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>HIV Uninfected n=667</td>
<td>83%</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Does the fact that 83% of uninfected high risk individuals are +/+ undercut the argument the the mutation confers resistance?
This figure shows factors associated with HIV-1 susceptibility and rapid disease progression (left) or with HIV-1 resistance and slow progression. RANTES: codes for chemokine (ligand) that binds to CCR5 receptor protein

- See last few pages of lecture for specific examples of polymorphisms in the major histocompatibility (MHC aka HLA) genes influencing susceptibility to HIV infection and progression to AIDS
The identification of naturally occurring CCR5 mutations has inspired scientists to address the CCR5 molecule as a promising target to prevent or limit HIV infection in vivo.

Inhibitor-drugs and antibodies that are able to counteract HIV at its major portal of entry are presently undergoing evaluation in clinical trials or have even been licensed for therapy.

**Anti-CCR5 strategies working at target cell surface**

**CCR5: From Natural Resistance to a New Anti-HIV Strategy**

*Viruses 2010, 2, 574-600*  doi:10.3390/v2020574
An alternative to the above strategies:
Direct manipulation of the CCR5 gene via gene therapy

Some interesting web sites:
http://www.wiley.com/legacy/wileychi/genmed/clinical/

What does zinc-finger nuclease (ZFN) gene therapy involve?

- An artificial protein construct combining two different inventions of mother nature:
  - sequence-specific DNA binding motif (the zinc finger)
  - endonuclease domain lifted from a restriction enzyme (Fok I)

- DNA repair systems that fix up breaks in the DNA backbone that occur naturally (nuclease activity or exposure to X-rays) or unnaturally (due to ZFN nucleases)

http://www.compozrzfn.com/
• The zinc finger is one of the most common conserved domains in the human genome – which contains ZF domains in over 700 proteins (~2% of human genes)
• Among the zinc finger domains, C2H2 type zinc finger is constituted by two cysteines and two histidines
• These amino acid residues can bind a zinc ion, forming a globular domain
• The C2H2 zinc finger domains are often found in DNA-binding proteins where the domains can mediate sequence-specific DNA binding.
Figure 1 A diagram of ZFN-induced indel mutations. A full ZFN target site consists of two “half-sites” separated by a 5–6 bp spacer. Each half-site contains a 9 bp sequence that can be recognized by a 3-finger zinc finger array. A ZFN consists of a zinc finger array fused to a nuclease domain. A heterodimeric pair of ZFNs binds to the left and right half sites and induces a double strand DNA break (DSB) in the spacer. Cells utilize non-homologous end joining (NHEJ) machinery to repair the DSB, an error-prone process that can lead to random insertions or deletions (indels) at the target site.
Mechanism of nonhomologous end joining (NHEJ). This mechanism is error prone.

http://web.mit.edu/engelward_lab/animations/NHEJ.html
Schematic of the CCR5 coding region showing the genomic sequences targeted by CCR5 ZNFs

Dimerization activates the nuclease activity of the FokI domain and cleavage of both strands occurs

Each set of 4 zinc fingers recognizes 12 base pairs so that the effective recognition site is 24 base pairs – long enough to occur just once in a genome
Figure 8. ZFN-mediated directed mutagenesis in human cells. (A) Targeted disruption of the CCR5 gene by NHEJ (mutagenic repair) using engineered ZFNs. Cells are transfected with ZFNs alone. CCR5 (m) depicts mutant CCR5 gene. (B) Targeted disruption of the CCR5 gene by ZFN-induced homology-directed repair. In this experiment, cells are transfected with both ZFN and CCR5Δ32 (or mutant CCR5 DNA).
Proof of principle using a mouse model

hematopoietic stem/progenitor cells (HSPCs)
Phase 1 Dose Escalation Study of Autologous T-cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases in HIV-Infected Patients

This study is currently recruiting participants.

Verified by Sangamo Biosciences, February 2011

First Received: January 6, 2010  Last Updated: February 22, 2011  History of Changes

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Sangamo Biosciences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information provided by</td>
<td>Sangamo Biosciences</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01044654</td>
</tr>
</tbody>
</table>

Purpose

This research study is being carried out to study a new way to possibly treat HIV. This agent is called a “Zinc Finger Nuclease” or ZFN for short. ZFNs are proteins that can delete another protein named CCR5. This CCR5 protein is required for certain types of HIV (CCR5 tropic) to enter into and infect your T-cells. T cells are one of the white blood cells used by the body to fight HIV. The most important of these are called CD4 T-cells.

Some people are born without CCR5 on their T-cells. These people remain healthy and are resistant to infection with HIV. Other people have a low number of CCR5 on their T-cells, and their HIV disease is less severe and is slower to cause disease (AIDS).

Even with no detectable levels of HIV in the blood, HIV remains in some tissues in the body, primarily the gut tissue. HIV infects the CD4+ T-cells including in the blood and gut. The new treatment to be studied will involve removing white blood cells from the blood that contains CD4+ T-cells. These mononuclear CD4+ T-cells are then genetically modified by the ZFNs to be resistant to infection by HIV by removing the CCR5 gene from the surface of the CD4+ T cell where HIV enters the cell.

Additional genetically modified cells are manufactured and then re-infused back into you. Researchers hope that these genetically modified cells will be resistant to infection by HIV and will be able to reseed additional resistant CD4+ T-cells in your body.

Laboratory studies have shown that when CD4+ T-cells are modified with ZFNs, HIV is prevented from killing the CD4+ T-cells. On the basis of these laboratory results, this is the potential that ZFNs may work in humans infected with HIV and improve their immune system by allowing their CD4+ T-cells to survive longer.

The purpose of this research study is to find out whether “zinc finger” modified CD4+ T-cells are safe to give to humans and find how “zinc finger” modified T-cell affects HIV.
Sangamo BioSciences Announces Presentation of Positive Clinical Data From Novel ZFN Therapeutic Approach for the Treatment of HIV/AIDS at Conference for Retroviral and Opportunistic Infections


RICHMOND, Calif., Feb. 28, 2011 /PRNewswire/ -- Sangamo BioSciences, Inc. (Nasdaq: SGMO) announced today the presentation of positive preliminary clinical data from its Phase 1 trial (SB-728-902). The trial is being conducted in immunologic non-responders, HIV-infected subjects who are currently on highly active antiretroviral therapy (HAART) and have undetectable levels of virus but suboptimal CD4+ T-cell counts. The study is designed to evaluate safety and clinical outcomes of Sangamo's zinc finger nuclease (ZFN)-generated CCR5-modified, autologous T-cell product (SB-728-T) for the treatment of HIV/AIDS. CCR5 is the major co-receptor used by HIV to infect cells of the immune system.

"These compelling data provide a mechanistic 'proof of concept' for this novel approach to HIV therapy which shows the most promise of any yet tested," stated Carl June M.D., Director of Translational Research at the Abramson Family Cancer Research Institute at the University of Pennsylvania School of Medicine, and an investigator in a second SB-728-T Phase 1 trial that is led by Pablo Tebas, M.D. at the University of Pennsylvania.

"From a single infusion of ZFN-modified cells, substantial and sustained increases in total CD4+ T-cell counts were observed in most subjects. This improvement is greater than we have seen in any previous adoptive T-cell approach. The data are consistent with CCR5-ZFN-modified T-cells being resistant to HIV infection and having a selective advantage in the presence of the virus — just as we saw in the preclinical studies. This is very encouraging as we continue to evaluate the drug in HIV-infected subjects with active infections."

SCID: (genetic) severe combined immunodeficiency
Fig. 1. Principle of ZFN-assisted gene targeting in zygotes. Zygotes collected from wild-type mice are coinjected into the pronucleus and cytoplasm with DNA of a gene targeting vector and mRNAs for the expression of a pair of gene specific zinc-finger nucleases (ZFN1/2). HR of the targeting vector with the target site results in a knockout (KO) or knock-in (KI) allele. Manipulated zygotes are subsequently transferred into pseudopregnant females to recover mutant mice.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Function/role in HIV disease</th>
<th>Variants</th>
<th>Influence on HIV disease</th>
<th>Grading of genetic and molecular evidence*</th>
<th>Protection from bias1</th>
<th>Biological credibility1</th>
<th>Relevance**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5-CCR2 focus</td>
<td>Chemokine receptors; co-receptor of HIV-1 (CCR5)</td>
<td>CCR5 A32, CCR5 3037-T, CCR5 P1, CCR2 V64I, derived haplotypes</td>
<td>Protection (CCR5 A32, CCR5 3037-T, CCR5 P1, CCR2 V64I; derived haplotypes)</td>
<td>1-3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>HLA</td>
<td>MHC acquired immunity</td>
<td>HLA A, B, C, homozygotic, or selected HLA B alleles</td>
<td>Protection or progression depending on allele</td>
<td>1-3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>TRIM5α</td>
<td>Innate immunity; HIV-1 restriction</td>
<td>Multiple non-synonymous variants</td>
<td>Neutral effect on HIV-1; effect on other retroviruses (N=MLV)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>KIR</td>
<td>Innate immunity; regulation of NK cell response</td>
<td>Specific KIR-HLA associations</td>
<td>Protection or progression depending on the specific association</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CXCL12 (SDF-1)</td>
<td>Ligand of CXCR4</td>
<td>3'UTR SDF1-3'A</td>
<td>Neutral or progression</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>TSG101</td>
<td>Vascular protein sorting required for HIV-1 budding</td>
<td>Various haplotypes of promoter: -1831&gt;C, and intronic 1813&gt;A&gt;C</td>
<td>Protection or progression depending on haplotype</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CCL5 (RANTES)</td>
<td>Ligand of CCR5</td>
<td>Various haplotypes of promoter: -401G&gt;A, -282G&gt;C and intronic 1113&gt;T&gt;C</td>
<td>Protection or progression depending on haplotype</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IL-10</td>
<td>Anti-inflammatory cytokine</td>
<td>Promoter -592&gt;C&gt;A</td>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CCL3L1 (MIP1α)</td>
<td>Ligand of CCR5</td>
<td>Variable gene copy number</td>
<td>Progression associated with low-copy number</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CXCR1</td>
<td>Fractalkine receptor minor HIV-1 co-receptor</td>
<td>T280M</td>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>APOBEC3G</td>
<td>Intrinsically acquired immunity; HIV-1 DNA hypermutation</td>
<td>H186R or expression polymorphism</td>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CCL3 (MIP1β)</td>
<td>Ligand of CCR5</td>
<td>Intronic 459C&gt;T</td>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IL-4</td>
<td>Pleiotropic cytokine</td>
<td>Promoter -509&gt;C&gt;T</td>
<td>Conflicting</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Grading of genetic and molecular evidence: 1 = strong evidence; 2 = moderate evidence; 3 = weak evidence. **Insufficient evidence for grading. **Relevance: 1 = major; 2 = moderate; 3 = minor.
The Class 1 HLA genes are highly polymorphic and different alleles confer different levels of resistance to HIV progression to AIDS

- 300 HLA-A alleles
- 600 HLA-B alleles
- > 100 HLA-C alleles

The class 1 HLA proteins are expressed on the surface of most somatic cells

The HLA complex is the same as MHC (major histocompatibility complex)
Cytotoxic T cell  Killer T cells, also known as cytotoxic T cells, police the human body, looking for cells showing signs of infection and destroying them.

In the following diagram, a virus enters a cell. Viral and other peptides are processed by the cell and are "passed" out to the outside of the cell, held on the outside by HLA protein

A cytotoxic T cell then binds to this cell via an interaction between CD8, TCR, and HLA. If the peptide presented to the cytotoxic T cell by HLA fits the cleft in TCR, then a chemical signal is triggered within the T cell which causes it to attack and destroy the infected cell

CD8 cell surface protein  The CD8 protein comes secondary to the CD4 protein in the story of HIV infection, but CD8 and CD4 are quite closely related in that they are cell surface proteins found predominantly on T cells, and they both bind to HLA protein on other cells. CD8 is ordinarily found on the surface of killer T cells (as opposed to CD4, ordinarily found on the surface of helper T cells). CD8 binds to HLA class I on some other cell - which, as the diagram below shows, allows the T cell receptor protein to dock to HLA-I and check the antigen ("Ag") which HLA is presenting.
Genetic Variants of the Virus:

- Virologist estimate that an infected individual may produce as many as $10^9$ virus particles per day.
- As with other viral RNA replicases, reverse transcriptases lack proof-reading abilities due to a lack of 3’-5’ exonuclease activity.
- In the case of HIV, copying errors occur at a rate of $1 \times 10^{-5}$ to $1 \times 10^{-4}$.
- Couple this mutation rate with the persistent nature of the infection and the large number of particles produced: tremendous opportunity for the production of viral genetic diversity.
- Explains the rapid evolution of multi-drug resistance.