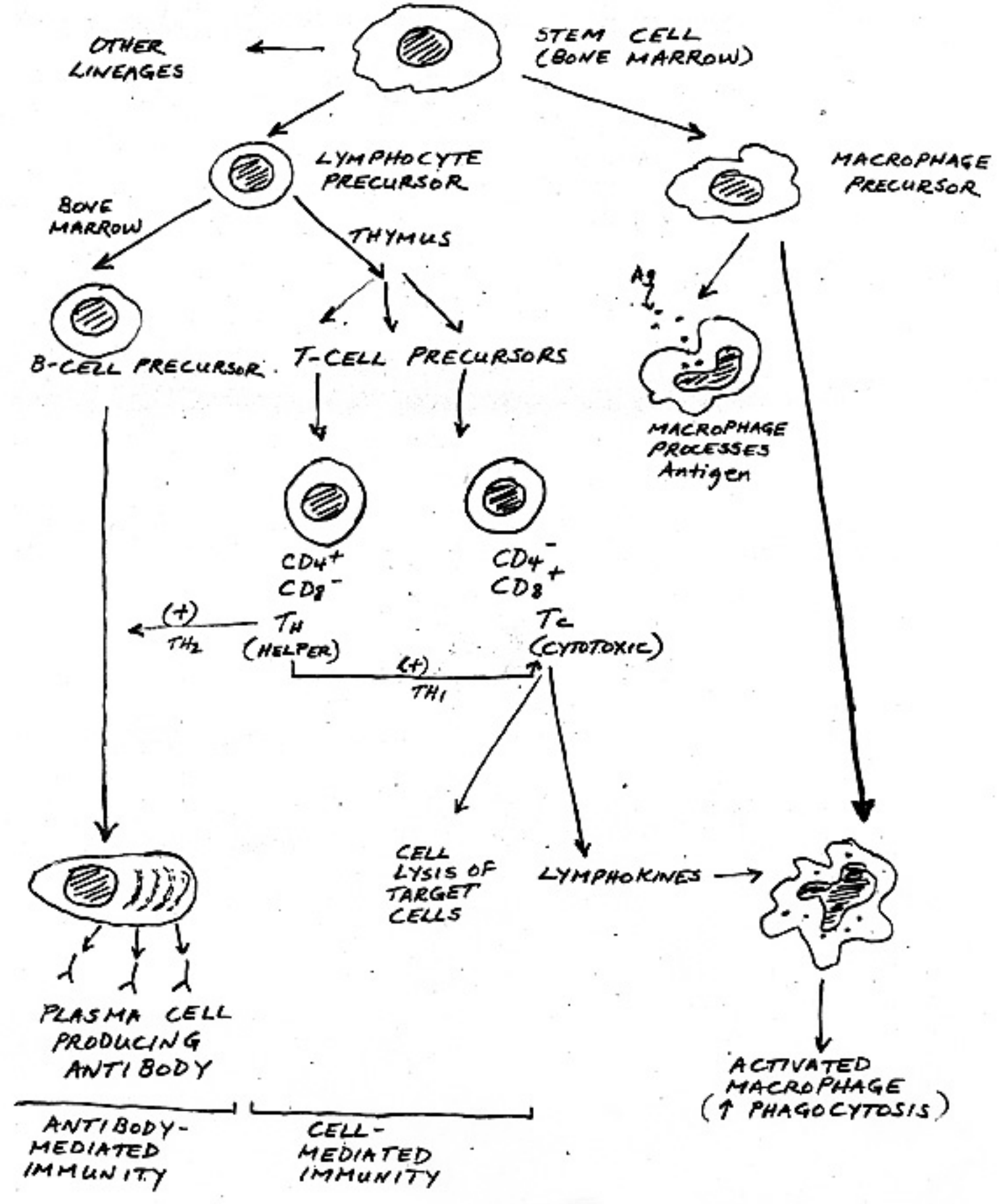
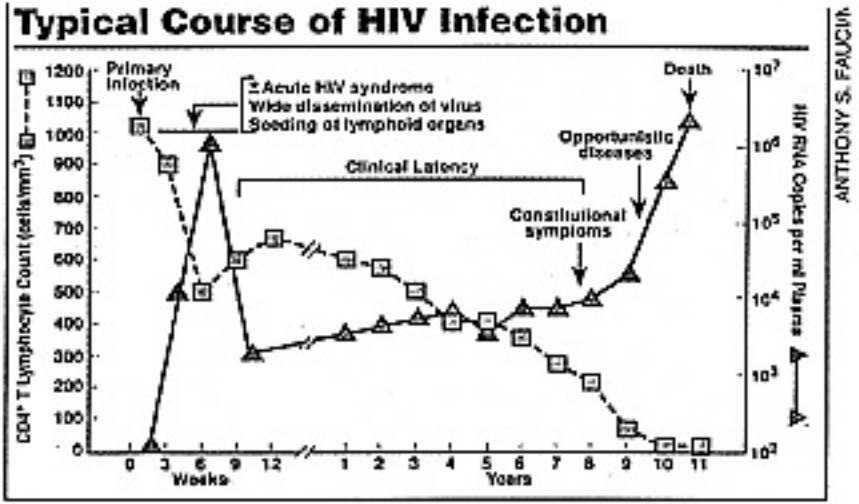
DEVELOPMENTAL PATHWAYS OF T- AND B-CELLS FROM STEM CELLS





A higher low. HIV levels *(triangles)* spike, then drop—but do not bottom out as previously thought. Instead, they rise steadily as CD4s (*squares*) decline.

Science 272:1884 June 28, 1996.

Questions and Answers: HIV is the Cause of AIDS

What is AIDS?

AIDS stands for acquired immunodeficiency syndrome. A diagnosis of AIDS is made by a physician using certain clinical or laboratory standards.

What causes AIDS?

AIDS is caused by infection with a virus called human immunodeficiency virus (HIV). This virus is passed from one person to another through blood-to-blood and sexual contact. In addition, infected pregnant women can pass HIV to their babies during pregnancy or delivery, as well as through breast feeding. People with HIV have what is called HIV infection. Most of these people will develop AIDS as a result of their HIV infection.

What body fluids transmit HIV?

These body fluids have been proven to spread HIV:

- blood
- semen
- vaginal fluid
- breast milk
- other body fluids containing blood

These are additional body fluids that may transmit the virus that health care workers may come into contact with:

- fluid surrounding the brain and the spinal cord
- fluid surrounding bone joints
- fluid surrounding an unborn baby

How does HIV cause AIDS?

HIV destroys a certain kind of blood cells--CD4+ T cells (helper cells)--which are crucial to the normal function of the human immune system. In fact, loss of these cells in people with HIV is an extremely powerful predictor of the development of AIDS. Studies of thousands of people have revealed that most people infected with HIV carry the virus for years before enough damage is done to the immune system for AIDS to develop. However,

recently developed sensitive tests have shown a strong connection between the amount of HIV in the blood and the decline in CD4+ T cell numbers and the development of AIDS. Reducing the amount of virus in the body with anti-HIV drugs can slow this immune destruction.

An author indicated in a recently published book that AIDS is caused by HHV-6 rather than HIV. Is this true?

No, this is not true. Both HHV-6 and HIV infect the same kind of cells in a person's body. These cells are called CD4+ T cells (helper cells). However, AIDS will **not** develop in someone who is not infected with HIV. Infection with HHV-6 does not lead to infection with HIV. HHV-6, one of the eight known human herpesviruses, is common throughout the world, with over 90% of adults in many populations being infected. Most people are infected with HHV-6 between the ages of 6 months and 2 years old, soon after they lose their mother's antibodies. HHV-6 is the cause of roseola [ro ZEE o la], a usually mild childhood disease that is also called exanthem subitum [eg ZAN them SUBI tum] or sixth disease. Approximately 30% of all children get roseola, usually before 2 years of age.

Why do some people make statements that HIV does not cause AIDS?

The epidemic of HIV and AIDS has attracted much attention both within and outside the medical and scientific communities. Much of this attention comes from the many social issues--homosexuality, drug use, poverty--related to this disease. Although the scientific evidence is overwhelming and compelling that HIV is the cause of AIDS, the disease process is not yet completely understood.. This incomplete understanding has led some persons to make statements that AIDS is not caused by an infectious agent or is caused by a virus that is not HIV. This is not only misleading, but may have dangerous consequences. Before the discovery of HIV, evidence from epidemiologic studies involving tracing of patients' sex partners and cases occurring in persons receiving transfusions of blood or blood clotting products had clearly indicated that the underlying cause of the condition was an infectious agent. Infection with HV has been the sole common factor shared by AIDS cases throughout the world among homosexual men, transfusion recipients, persons with hemophilia, sex partners of infected persons, children born to infected women, and occupationally exposed health care workers. Recommendations to prevent HIV involve guidance to avoid or modify behaviors that pose a risk of transmitting the virus as well as the use of tests to screen donors of blood and organs.

The inescapable conclusion of more than 15 years of scientific research is that people, if exposed to HIV through sexual contact or injecting drug use, may become infected with HIV. If they become infected, most will eventually develop AIDS.

How can I get more information about AIDS?

CDC operates a free telephone service that is available 24-hour, 7 days a week. You can contact the CDC National STD and AIDS Hotlines at 1-800-342-2437. Service for Spanish-speaking audiences and the Deaf are also available.

Basic Statistics

The following data are summarized from the CDC semiannual *HIV/AIDS Surveillance Report*. Numbers are based on AIDS cases reported to CDC through **June 2001**.

For a more complete understanding of the current surveillance trends, you may download a PDF file of the *HIV/AIDS Surveillance Report* or request a free copy of the HIV/AIDS Surveillance Report by calling the CDC National Prevention Information Network at 1-800-458-5231.

Cumulative AIDS Cases

The cumulative number of AIDS cases reported to CDC is **793,026**. Adult and adolescent AIDS cases total **784,032** with **649,186** cases in males and **134,845** cases in females. Through the same time period, **8,994** AIDS cases were reported in children under age 13.

Total deaths of persons reported with AIDS are **457,667**, including **452,111** adults and adolescents, and **5,168** children under age 15, and 388 persons whose age at death is unknown.

Cumulative Cases by Age

Of the total AIDS cases reported through June 2001, patients' ages at time of diagnosis were distributed as follows:

Age	# of Cumulative AIDS Cases
Under 5:	6,928
Ages 5 to 12:	2,066
Ages 13 to 19:	4,219
Ages 20 to 24:	27,880
Ages 25 to 29:	103,085
Ages 30 to 34:	175,343
Ages 35 to 39:	177,759
Ages 40 to 44:	131,718
Ages 45 to 49:	77,152
Ages 50 to 54:	40,972
Ages 55 to 59:	22,423
Ages 60 to 64:	12,415
Ages 65 or older:	11,065

Cumulative Cases by Race/Ethnicity

Race or ethnicity of persons reported with AIDS as of June 2001 was:

Race or Ethnicity	# of Cumulative AIDS Cases
White, not Hispanic	337,035
Black, not Hispanic	301,784
Hispanic	145,220
Asian/Pacific Islander	5,922
American Indian/Alaska Native	2,433
Race/ethnicity unknown	632

Cases by Exposure Category

Following is the distribution of reported AIDS cases among adults and adolescents by exposure category. A breakdown by sex is provided where appropriate. The categories and totals are:

Exposure Category	Male	Female	Total*
Men who have sex with men	361,867	-	361,867
Injecting Drug Use	142,888	54,203	197,091
Men who have sex with men and inject drugs	50,066	-	50,066
Hemophilia/coagulation disorder	4,949	285	5,234
Heterosexual contact	30,956	54,782	85,738
Recipient of blood transfusion, blood components, or tissue	5,031	3,863	8,894
Risk not reported or identified	53,429	21,712	75,142

* Includes 3 persons whose sex is inknown.

The distribution of reported AIDS cases among children* by exposure categories follows:

Exposure Category	# of AIDS Cases
Hemophilia/coagulation disorder	237
Mother with or at risk for HIV infection	8,207
Receipt of blood transfusion, blood components, or tissue	382
Risk not reported or identified	168

* The term "children" refers to persons under age 13 at the time of diagnosis.

Areas Reporting Most Cases

The 10 leading states or territories reporting the highest number of cumulative AIDS cases among residents as of June 2001 are as follows:

State/Territory	# of Cumulative AIDS Cases
New York	144,106
California	121,831
Florida	83,005
Texas	55,292
New Jersey	43,017
Illinois	25,665
Puerto Rico	25,459
Pennsylvania	25,264
Georgia	23,575
Maryland	22,432

The 10 leading metropolitan statistical areas reporting the highest number of cumulative AIDS cases among residents as of June 2001 are as follows:

Metropolitan Area	# of Cumulative AIDS Cases
New York City	122,062
Los Angeles	42,796
San Francisco	28,212
Miami	24,838
Washington, DC	24,029
Chicago	22,217
Philadelphia	19,605
Houston	19,582
Newark	17,472
Atlanta	16,423

International Statistics

According to the Joint United Nations Programme on HIV/AIDS, as of **the end of 2001**, the following trends of the worldwide epidemic (or pandemic) of HIV are evident:

- Today, **40 million people are estimated to be living with HIV/AIDS**. Of these, 37.2 million are adults. 17.6 million are women, and 2.7 million are children under 15.
- During 2001, **AIDS caused the deaths of an estimated 3 million people**, including 1.1 million women and 580,000 children under 15.

- Women are becoming increasingly affected by HIV. Approximately **48%, or 17.6 million**, of the 37.2 million adults living with HIV or AIDS worldwide are women.
- The overwhelming majority of people with HIV - approximately 95% of the global total - now live in the developing world.

For current statistics on the number of reported AIDS cases in North, Central, and South America, please contact the Pan American Health Organization (PAHO) which is the regional office for the Americas of the World Health Organization at 525 23rd Street, N.W., Washington, D.C. 20037, telephone: 202-861-4346.

Other international web sites available are the World Health Organization (WHO) and the United States Agency for International Development (USAID).

Please enter your name and e-mail address to be notified of future basic statistics on HIV/AIDS.

Name: _____ **E-mail Address:** _____ Enter

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Last Revised: February 28, 2002
Centers for Disease Control & Prevention
National Center for HIV, STD, and TB Prevention
Divisions of HIV/AIDS Prevention
Please send comments/suggestions/requests to: hivmail@cdc.gov

CDC's Goals for HIV Prevention

Overarching National Goal

Reduce the number of new HIV infections in the United States from an estimated 40,000 to 20,000 per year by 2005, focusing particularly on eliminating racial and ethnic disparities in new HIV infections.

1. By 2005, decrease by at least 50% the number of persons in the United States at high risk for acquiring or transmitting HIV infection by delivering targeted, sustained and evidence-based HIV prevention interventions.

2. By 2005, through voluntary counseling and testing, increase from the current estimated 70% to 95% the proportion of HIV-infected people in the United States who know they are infected.

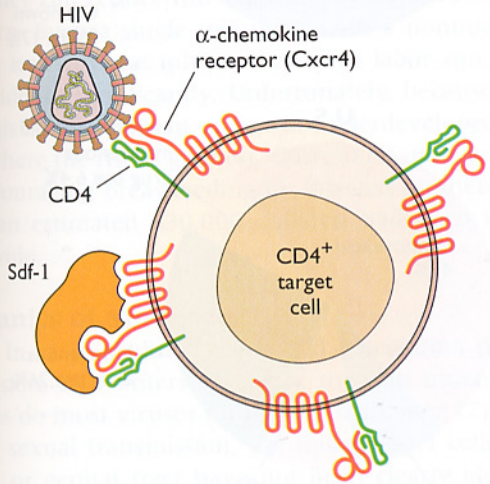
3. By 2005, increase from the current estimated 50% to 80% the proportion of HIV-infected people in the United States who are linked to appropriate prevention, care and treatment services.

4. By 2005, strengthen the capacity nationwide to monitor the epidemic, develop and implement effective HIV prevention interventions and evaluate prevention programs.

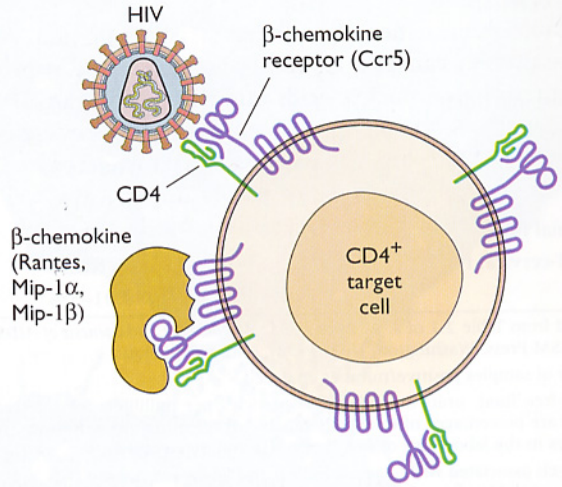
International Goal

5. Assist in reducing HIV transmission and improving HIV/AIDS care and support in partnership with resource-constrained countries.

Figure 18.6 Coreceptors for macrophage/monocyte- and T-cell-tropic strains of HIV-1. Cxcr4 is the major coreceptor for T-cell-tropic strains; entry of such strains is inhibited by the receptor's natural ligand, Sdf-1. Ccr5 is the major coreceptor for macrophage/monocyte (M)-tropic strains, and their entry is inhibited by the receptor's natural ligands, Rantes, Mip-1α, and Mip-1β. Primary T cells and monocytes express both coreceptors; primary T cells are susceptible to both strains, but monocytes can be infected only by M-tropic strains for reasons that are not yet clear. Adapted from Fig. 3 of A. S. Fauci, *Nature* **384:** 529–533, 1996, with permission.



T-cell-line-tropic strain of HIV-1



Macrophage-tropic strain of HIV-1

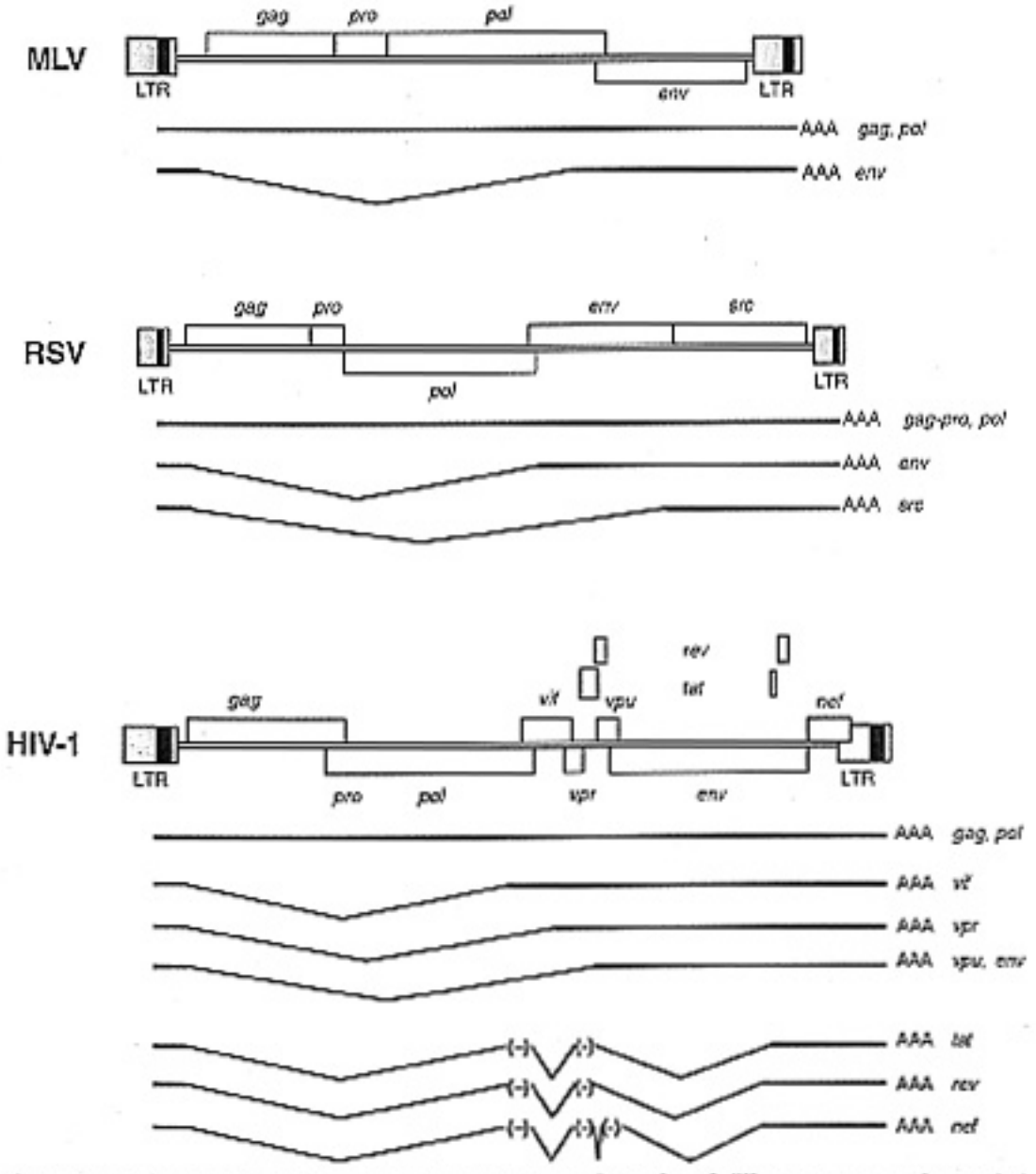


Figure 17 Alternative splicing patterns in retroviruses. Examples of different patterns of retroviral splicing include the single splicing event that generates the MLV *env* RNA, alternative splicing of RSV responsible for *env* and *src* RNAs, and the multiple alternative splicing events characteristic of complex retroviruses such as HIV-1. HIV-1 splicing complexity is increased by the alternative use of small, noncoding, central exons (denoted in parentheses).

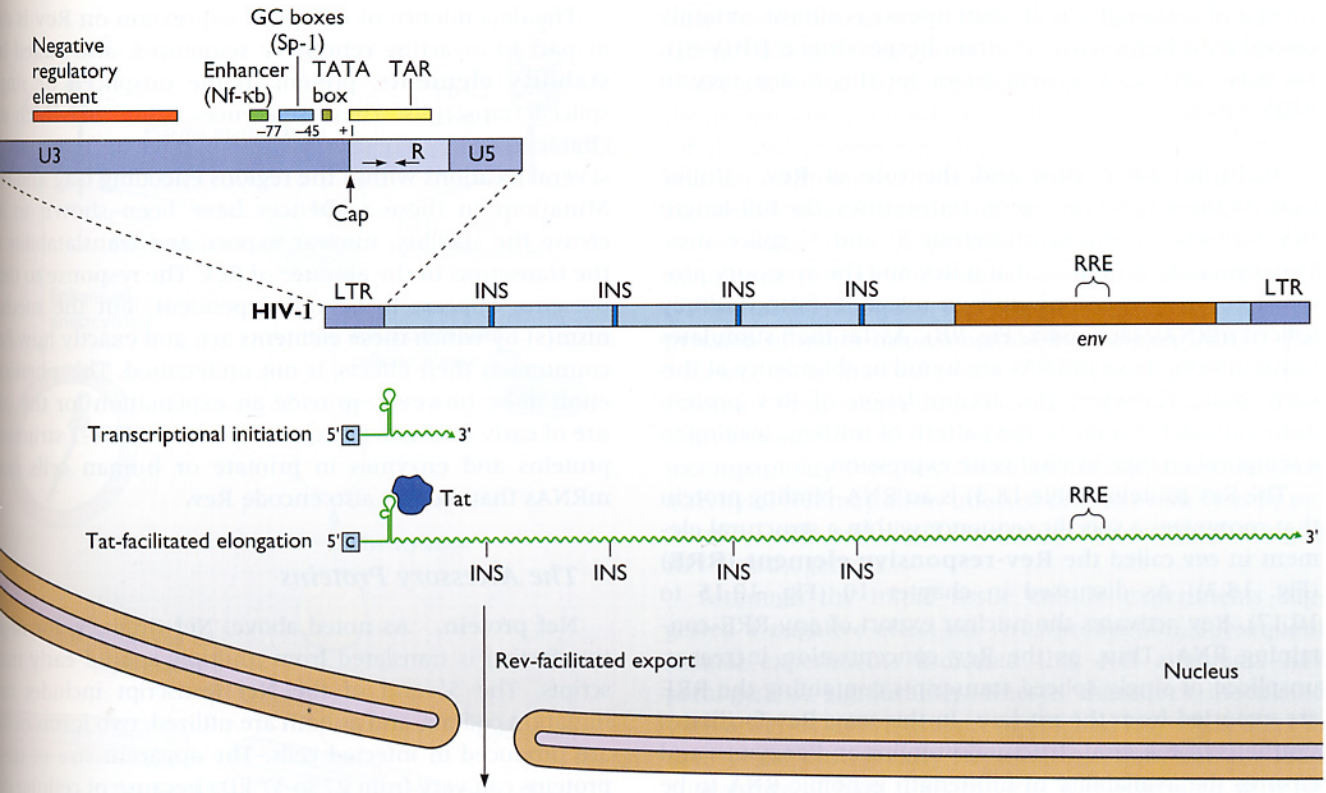


Figure 18.3 Mechanisms of *tat* activation. Some regulatory elements in the HIV LTR are depicted in the expanded section at the top. The numbers refer to positions relative to the initiation of transcription (cap site). The opposing arrows in R represent a palindromic sequence that folds into a stem-loop structure in the transcribed mRNA to which Tat binds (center). Tat is required for efficient elongation during HIV-1 RNA synthesis. The position of the RRE in the *env* transcript and the presence of *cis*-acting repressive sequences, also known as instability elements (INS), are also illustrated.

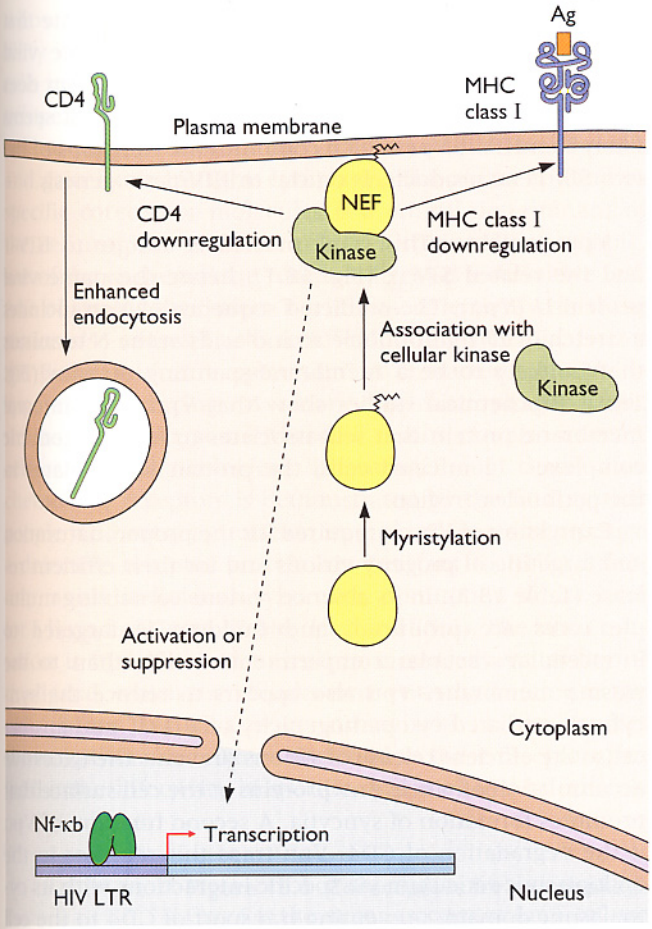


Figure 18.5 Intracellular functions attributed to Nef. Nef is myristylated posttranslationally; the jagged protrusion represents myristic acid covalently linked to the glycine residue at position 2 in Nef. Myristylation enables Nef to attach to cell membranes and interact with a cellular serine kinase and perhaps other cellular proteins. The cytoplasmic domain of CD4 contains the target sequences for Nef-mediated downregulation. Nef reduces cell surface expression of CD4 by enhancing endocytosis; major histocompatibility complex class I expression is also reduced. By an unknown mechanism, Nef increases the activity of the cellular transcriptional activator Nf-κb and perhaps other cellular transcription proteins, thereby augmenting expression directed by the viral LTR. Nef has also been reported to suppress viral gene expression.

virus replication in these cells, hence the name "n factor." Multiple functions have been attributed (Table 18.3; Fig. 18.5), and it is now clear that Ne pleiotropic effects on infected cells. The functions r for the Nef protein vary for different strains of th and with different cell types. Nef has been shown crease cell surface expression of CD4 as a result o action with the cytoplasmic portion of this i membrane protein and induction of its endocytos lysosomal degradation). Nef also decreases cell surf pression of major histocompatibility complex (MH I molecules in infected primary lymphocytes. As a cytotoxic lymphocyte response against viral infect quires recognition of viral epitopes presented by ma tocompatibility complex class I molecules, this inh activity of Nef may allow infected cells to evade lysi totoxic T cells and could be a major factor contribu HIV-1 pathogenesis.

Although the initial tissue culture experimen gested a negative effect on virus production, subs animal experiments indicated that Nef augmen pathogenesis significantly. Rhesus macaques ino with a Nef-defective mutant of SIV had low virus their blood during early stages of infection, and th appearance of high titers of virus was associated w version of the mutation. More importantly, macaques inoculated with a virus strain containing tion of *nef* did not progress to clinical disease and fact immune to subsequent challenge with w virus. The observation that *nef* had been deleted i isolates from some individuals who remained as matic for long periods and from transfusion recipie did not develop AIDS also suggests that this viral can contribute significantly to pathogenesis. Initia that intentional deletion of *nef* might facilitate the opment of a vaccine strain for humans were dashe it was discovered that newborns of the female ma who had been immunized with the *nef*-minus strai developed an AIDS-like disease.

Vif protein. Vif stands for viral infectivity fact protein (Table 18.3; Fig. 18.4) accumulates in th