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Overview of HIV/AIDS, 1999

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RESUMEN

La epidemia del HIV-I está dada por tres distintas familias de virus con mecanismos de transmisión y características propias. El estado actual de la epidemia, de acuerdo al Programa de Naciones Unidas para el SIDA, estima que hay 33.4 millones de personas que viven con el complejo HIV/SIDA y cada día ocurren alrededor de 16,000 nuevas infecciones (la mitad en personas menores de 25 años). Se estima que en 1998 la enfermedad afectó alrededor de 590,000 niños.

En el presente trabajo se hace una revisión de la patogénesis de la enfermedad, su historia natural, así como de las principales características que tiene la terapia antirretroviral, revisando aspectos como adherencia, toxicidad, alteraciones en pacientes con dislipidemia y disglicemia hasta pacientes con lipodistrofia.

PALABRAS GUÍA: *HIV/SIDA, epidemiología HIV/SIDA, tratamiento y prevención de HIV/SIDA.*

ORIGINS OF THE HIV EPIDEMIC

Several immunodeficiency viruses (all members of the lentivirus family) exist in nature, including the simian immunodeficiency virus (SIV) in primates, the feline immunodeficiency virus (FIV) in cats, and the bovine immunodeficiency virus (BIV) in cattle.[1]

Two distinct human immunodeficiency virus infections have been established in humans, caused respectively by human immunodeficiency virus type 1 (HIV-1) and human immunodeficiency virus type 2 (HIV-2). Both can be transmitted horizontally (during sexual intercourse, sharing of drug injection equipment, or from exposure of mucous membranes to contagious body fluids) and vertically (from infected mothers to developing fetuses or to breast-feeding infants). HIV-2 is associated with a markedly smaller epidemic than HIV-1, spreads more slowly than HIV-1 by heterosexual transmission, leads to severe disease in a smaller proportion of infected individuals than does HIV-1, and requires more time for infection to progress to AIDS than does HIV-1.[2-7]

The genetic sequence of HIV-2 is identical to an SIV strain found in sooty mangabeys (SIVstm), with the natural range of sooty mangabeys overlapping areas of major HIV-2 endemicity in western equatorial Africa (including Guinea-Bissau, Equatorial Guinea, Sierra Leone, and Liberia).[8-10]

How was HIV-2 transmitted from primates to humans? Sooty mangabeys are a source of "bush meat," and are also killed because of the crop damage they inflict. Infant mangabeys orphaned during hunting of adults may also be brought into homes as pets. It is thought that bites from domestic pets or exposure to blood during butchering are the likely means by which SIV crossed from primates to humans. At least six independent transmissions of SIVstm to humans have been documented, resulting in subsequent evolution of HIV-2 in the human hosts it has infected. HIV-2 can thus be thought of as a zoonosis: an infection transmitted from animals to humans under natural conditions.[9]

In contrast to the relatively small HIV-2 epidemic, HIV-1 has spread rapidly across the world. The HIV-1

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epidemic actually consists of three distinct families of viruses with independent transmissions (figure 1). The largest and first identified is the HIV-1 M group ("Main"), responsible for the vast majority of HIV infections worldwide. The M parent strain has further evolved into 11 sub-families or clades, identified as A-K. A second HIV-1 family is the HIV-1 O group ("Outlier"), named for the fact that serologic tests for HIV-1 M group strains did not detect these viruses. While O group infections have been identified in North America and Western Europe, their spread has largely been restricted to western equatorial Africa, including Gabon, Cameroon and Equatorial Guinea. Recently a third HIV-1 family known as the N group ("non-M / non-O") has been identified in three persons, all of whom have lived in Cameroon.[11]

What is the source of HIV-1? Genetic sequencing has shown that HIV-1 is most closely related to SIV strains found in chimpanzees (*Pan troglodytes*). However, our limited knowledge of SIV infections in chimpanzees in the wild has made it difficult to ascertain which subspecies of chimpanzees transmitted SIV to humans (only four chimps infected with SIV have been identified). Through additional genetic sequence analysis, the subspecies *Pan troglodytes troglodytes* has recently been identified as the source of all three known human HIV-1 strains.[12]

The geographic range *of P. t. troglodytes* is western equatorial Africa, including Cameroon, Equatorial Guinea, Gabon and the Congo. On the border of the Congo and the present Democratic Republic of the Congo (formerly Zaire, and before that the Belgian Congo) is the city of Kinshasa (formerly Leopoldville, Belgian Congo). In 1959 an adult Bantu male in Leopoldville died from an unidentified illness, and plasma specimens saved for future investigation were subsequently found to be HIV seropositive. However, it was not until the late 1990's that molecular biological techniques permitted a comparison of gene sequences from this specimen (known as ZR-59) with genetic maps of known HIV-1 M clades. As can be seen in figure 2, by three different methods of genetic sequence analysis ZR 59 is located in the center of the starburst pattern of HIV-1 M differentiation, suggesting that ZR 59 was obtained soon after HIV-1 M entered the human family and before further evolution into clades occurred (figure 3 for a summary of relationships between SIV's and HIV's).[13]

Because chimpanzees are taken into homes as pets and are also a target of the bush meat trade, HIV-1 was probably transmitted to humans through the same

Figure 1

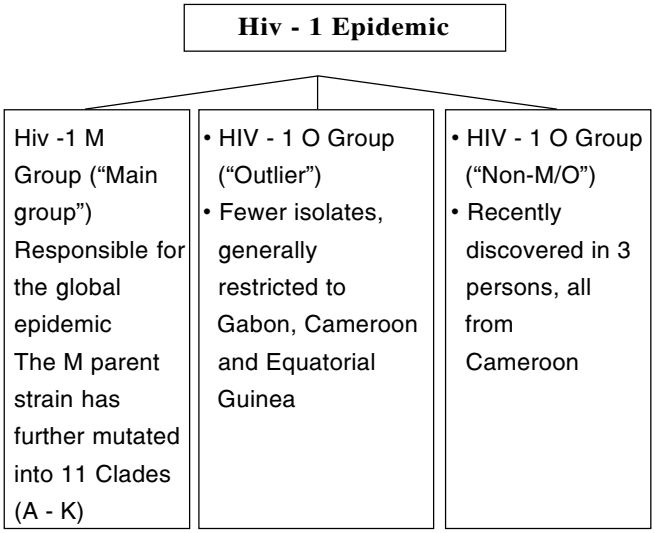


Figure 2
Phylogenetic analyses of ZR-59 (genetic sequences obtained from plasma collected in 1959 from an adult Bantu male living in Leopoldville, Belgian Congo (now Kinshasha, Republic of Congo. Zhu T et al, Nature 1998;391:594-7

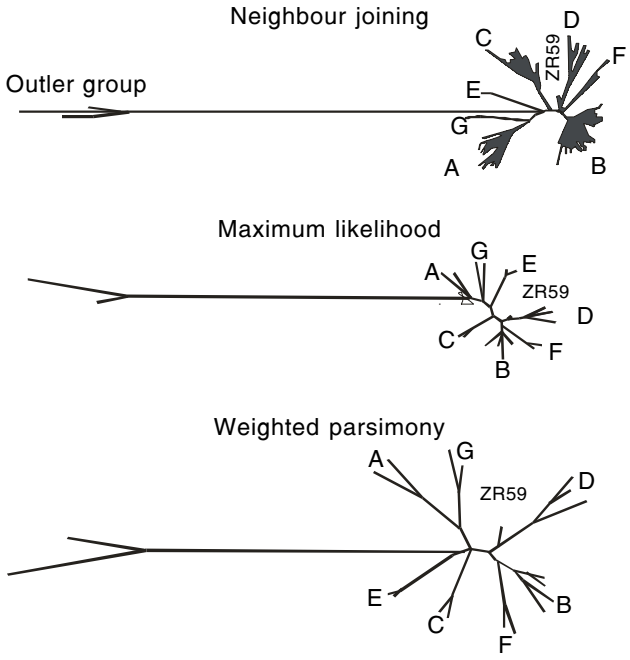
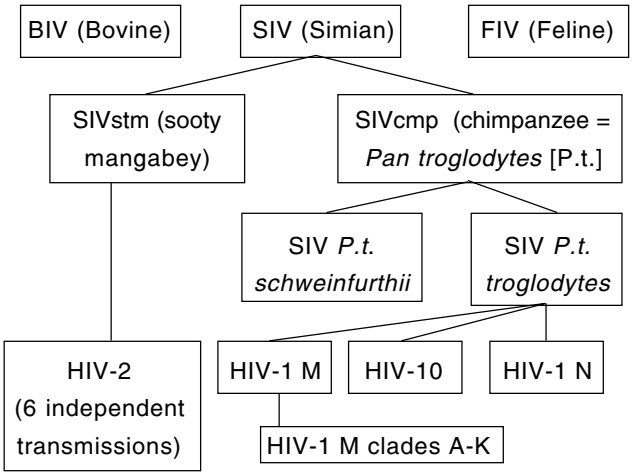


Figure 3
Retroviruses associated with immunodeficiency



means as occurred with HIV-2. That there have been three independent transmissions of HIV-1 suggests that chimps are potentially an ongoing source of new HIV-1 transmissions. Unfortunately, the number of these animals in the wild is dropping due to their popularity as a source of meat, possibly threatening them with extinction. This is of concern not only to conservationists, but also to human virologists and immunologists who are anxious to learn how chimpanzees —98.5 percent genetically similar to human beings— are able to control SIV infection without developing disease, while HIV-1 infection is virtually universally devastating to the human immune system.[9,14]

CURRENT STATUS OF THE GLOBAL EPIDEMIC

Initially identified in 1981 among gay men in Los Angeles, New York and San Francisco, the HIV-1 epidemic has since spread to virtually every country in the world.[15-17] In 1998 UNAIDS estimated that 33.4 million persons were living with HIV/AIDS, with 16,000 new infections occurring every day (half of them in persons under 25 years of age). In 1998 this translated to a total of 5.8 million new infections, including 590,000 in children.

Among HIV-1 clades, B is the most common in the Americas, Western Europe and in Southeast Asia (along with clade E), while other clades, especially C, are dominant in Africa and India. Africa is by far the hardest hit region of the world, accounting for two-thirds of global infections. By 1998 34 million Africans had been infected, with 12 million deaths by the end of 1998 (4 million infections in 1998 alone, with 5,500 AIDS funerals occurring in Africa each day). The countries of southern Africa, including Namibia, Botswana, Zambia, Zimbabwe, Lesotho, Swaziland and South Africa, have either the highest prevalences or the most rapidly rising infection rates in the world, with as many as 25-35 percent of adults being infected.

Ninety percent of new HIV infections occur in developing countries, but only 10 percent of infected persons are aware of their HIV-positive status. Globally 2.3 million AIDS deaths occurred in 1997, a 50 percent increase from 1996, accounting for the fact that in 1997 AIDS surpassed malaria as the number two infectious killer. In 1998, AIDS was the number one killer in Africa, the number one infectious killer in the world, and the number 4 cause of death worldwide (displacing Tuberculosis from position 4 to position 8).[18]

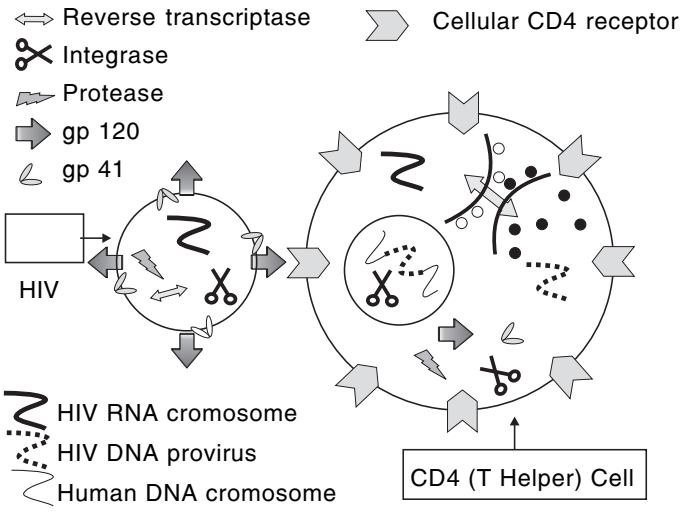
HIV PATHOGENESIS

HIV can be imagined as a single-stranded, RNA chromosome packaged in a protein-lipid envelope along with several enzymatic proteins. As a rather simple life form, HIV does not have the capacity to replicate by itself because it cannot synthesize protein. This makes HIV an obligate parasite, depending on the cells it infects to synthesize its structural and enzymatic proteins.

The human cellular membrane is an effective barrier against numerous infections, including most viruses. However, two external proteins of HIV (gp120 and gp41) interact with the CD4 receptor on certain lymphocytes (known as T-helper or CD4 cells), allowing HIV to enter and replicate. [Gp stands for "glycosylated (glucosed) protein," while the associated number denotes the relative size of each molecule.] Gp41 is the so-called "transmembrane" protein, while gp120 is the external envelope protein.

As the virus approaches a CD4 cell, gp120 fits into a cleft on the surface of the CD4 receptor (figure 4). This interaction leads to a conformational change in the relationship between the CD4 receptor, gp120, and gp41. In this sequence of events, gp41 "snaps open" from a so-called "coiled spring" confirmation, analogous to the manner in which the influenza virus has a surface protein which acts like a harpoon to penetrate the membrane of the cell which it will infect. Part of gp41 is thus known as the "fusion protein", and its penetration of the CD4 membrane initiates fusion

Figure 4

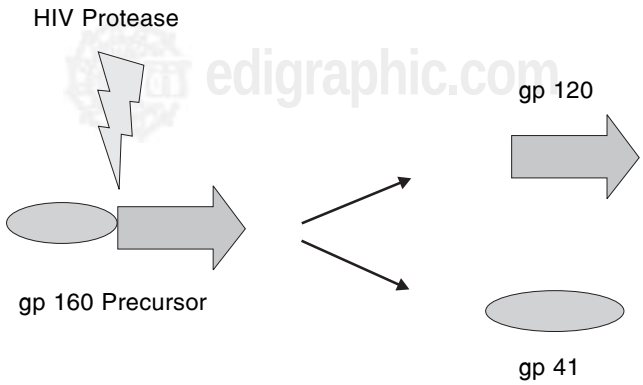


of cell membrane with viral envelope. In the end, viral components which were previously extracellular are now brought into the cytoplasm of the cell (One of the newest drugs in the anti-HIV armamentarium is a compound known as T-20, the first drug in the category of HIV fusion inhibitors. T-20 mimics the structure of the gp41 fusion protein and at appropriate plasma levels anneals to it, preventing the interaction between gp41 and the CD4 receptor. In a phase I trial of T-20, which must be administered intravenously or subcutaneously, a dose-dependent inhibition of HIV plasma levels has been observed.[19] Although the mode of administration of T-20 makes it less practical than agents available by mouth, this represents an important "proof of concept" which may possibly be developed into more bioavailable drugs).

Once the HIV single-stranded RNA chromosome has been brought into the CD4 cell's cytoplasm, genetic information contained in the viral chromosome will be used to direct synthesis of viral proteins by the cell's ribosomes. A transcription of this genetic information from RNA to DNA format must first occur, since cellular ribosomes require that protein synthesis (translation) be directed by messenger RNA which has been transcribed from nuclear DNA.

To accomplish the transcription step, HIV possesses an enzymatic protein known as reverse transcriptase. After reading the letters of the RNA strand, reverse transcriptase will employ DNA nucleosides already present in the cytoplasm to construct a new, single-stranded DNA chromosome which contains the same

Figure 5



information present in the RNA strand, but now in a form recognizable by the cell. Reverse transcriptase will then add a complementary second strand of DNA, creating a double-stranded HIV DNA provirus which will provide the blueprint for production of viral proteins.

The provirus will next be transported to the nucleus by another viral enzyme known as integrase, which will (in most cases) randomly splice the provirus into one of the double-stranded DNA human chromosomes. This integration of viral genetic information into human DNA is a characteristic feature of retroviruses, and accounts for the difficulty which has been encountered in trying to eradicate HIV from infected individuals. If an infected cell with integrated viral genetic information were to divide and replicate, it would pass on the viral chromosomes as part of its genetic inheritance. (It has been estimated that approximately one percent of human genes can be attributed to retroviral infections in our distant past).

Once the provirus has been integrated into the cellular chromosome, the information is in a latent form, much as we might consider an unread book on a library shelf. However, under the influence of cellular activation —which can result from vaccination, from coinfections, or from other stimuli such as cytokines— this genetic information can be used by the cell to manufacture HIV proteins.

Some viral proteins are produced as immature "preproteins" which must be cleaved to create functional subunits. One example is the gp160 precursor that must be cleaved by the viral protease to produce functional gp41 and gp120 envelope proteins (figure 5). In the absence of the protease function, viruses will bud from the surface of the cell but they will be replication incompetent.

Table 1
Antiretroviral Agents

Reverse Transcriptase Inhibitors (RTI's)

Nucleoside Analogs (NRTI's, "nukes")	Non-Nucleoside Analogs (NNRTI's, "non-nukes")	Protease Inhibitors (PI's)
AZT,ZDV (Retrovir®)	delavirdine (Rescriptor®)	saquinavir (Fortavase®)
ddI (Videx®)	nevirapine (viramune®)	indinavir (Crixivan®)
ddC (Hivid®)	efavirenz (Sustiva®)	ritonavir (norvir®)
3TC (Eoivir®)		nelfinavir (viracept®)
d4T (ZeritR)		amprenavir (Agenerase®)
ibacavir (Ziagen®)		

At the present time there are 3 broad targets for therapy against HIV. The first targets the infection of CD4 cells by HIV through fusion inhibitors (T-20), as already discussed. Second, reverse transcriptase inhibitors impede the transcription process either by direct inhibition of the reverse transcriptase (by non-nucleoside analogue reverse transcriptase inhibitors [NNRTI's]), or by making the elongation of the transcribed DNA strand impossible by substituting physically modified letters of the genetic code (nucleoside analogue reverse transcriptase inhibitors [NRTI's]). Finally, protease inhibitors (PI's) inhibit the final cleavage step, leading to replication-incompetent viral progeny (table 1 for a summary of antiretroviral drugs).

In addition to the CD4 receptor, HIV must also use one of several possible cellular co-receptors to infect CD4 cells. Most sexual transmissions of HIV-1 involve viruses which target CCR5 co-receptors, and they are therefore known as R5 viruses. When R5 viruses infect lymphocytes in tissue culture, multinucleated giant cells are not produced, and thus they are known as non-syncytium inducing (NSI) strains. NSI strains tend to predominate in early infection and are preferentially transmitted during sexual contact. In contrast, cells which use the CXCR4 co-receptor, known as X4 viruses, arise by a single amino acid mutation in the gp120 envelope protein. X4 viruses are associated with more rapid clinical progression, and often evolve from R5 strains as HIV disease progresses.[20] Research is ongoing to block the various co-receptors as an additional therapeutic strategy.

NATURAL HISTORY FOLLOWING INFECTION

Following exposure to HIV (for example, following sexual intercourse with an infected partner), HIV first associates with dendritic cells (Langerhans cells) present in the genital submucosal tissue which possess CD4 and CCR5 co-receptors.[21] Dendritic cells pass HIV infection to nearby CD4 lymphocytes which are then transported to regional lymph nodes and to the vascular system, quickly spreading virus throughout the body and across the blood brain barrier within days to weeks of becoming infected.[22, 23] During these first few weeks, high levels of viral replication are associated with very high "virus loads" (virus levels in the bloodstream), frequently exceeding several million virus particles/mL. During this period manifestations of the acute HIV infection (also known as the acute retroviral infection) can be observed.[24,25] Symptoms and signs may include fever, rash, adenopathy, sore throat, ulceration of the genitals or GI tract (from mouth to anus), muscle or joint pain, diarrhea, nausea and vomiting, liver and spleen enlargement, oral yeast infections, weight loss, and central nervous system symptoms which may include headache, cognitive impairment, nerve palsies, aseptic meningitis and even

psychosis. The rash of the acute HIV syndrome is a macular, nonpainful, nonpruritic rash (5-10 mm) present especially on the trunk; the rash may be evanescent and present for only hours or a few days. In the oral cavity erythema, tonsillar exudates and well delineated ulcerations of the bucal mucosa or tongue may be seen. In some series, patients presenting with odynophagia have undergone endoscopy to reveal similar, well delineated esophageal ulcerations from which HIV particles have been isolated.[26,27]

Following this initial level of very high viremia, during the next 6-12 months a titanic struggle ensues between the particular virus with which a patient is infected and the genetically determined immune system of the host. The result of this encounter is a reduction in the initially very high virus load to some subsequently lower viral "set point," the level of which is remarkably stable over the next 10 years in the absence of therapy. Observational natural history studies indicate that the initial viral set point determines the prognosis for each HIV-infected individual, with higher set points being associated with more rapid progression from HIV infection to an AIDS diagnosis (figure 6).[28,29]

Changes in the CD4 count are also commonly observed, with a dip being seen during the acute retroviral syndrome, followed by a reversion almost to baseline when the viral set point is achieved. Thereafter a gradual depletion of CD4 cells is commonly seen at a rate of approximately 10 percent per year — or in absolute terms, approximately 60-80 cells/mL per year. As can be seen in figure 7, as the CD4 count declines thresholds are reached for increasingly serious opportunistic dis-

Figure 7
Opportunistic disease thresholds with declining CD4 counts

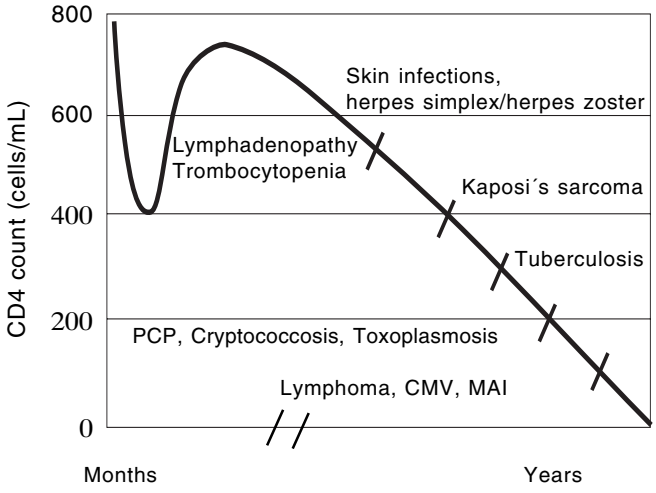


Figure 6
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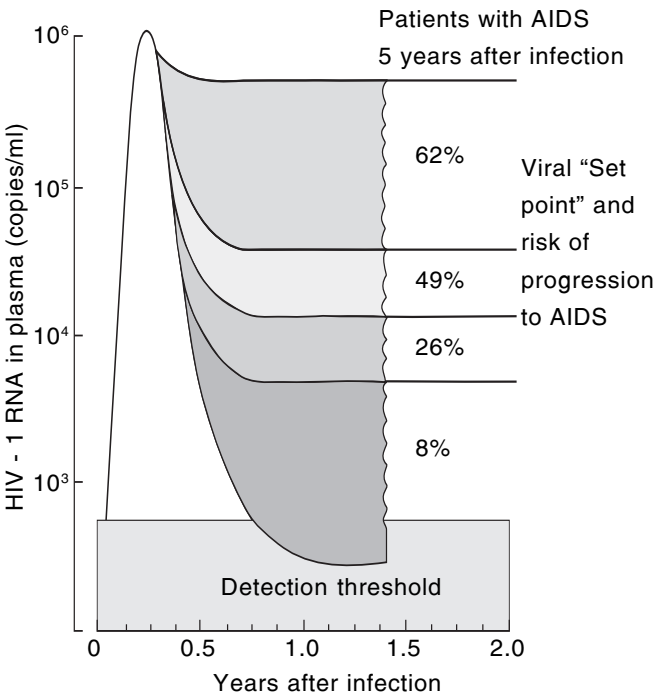


Figure 8
Likelihood of developing AIDS within 3 years

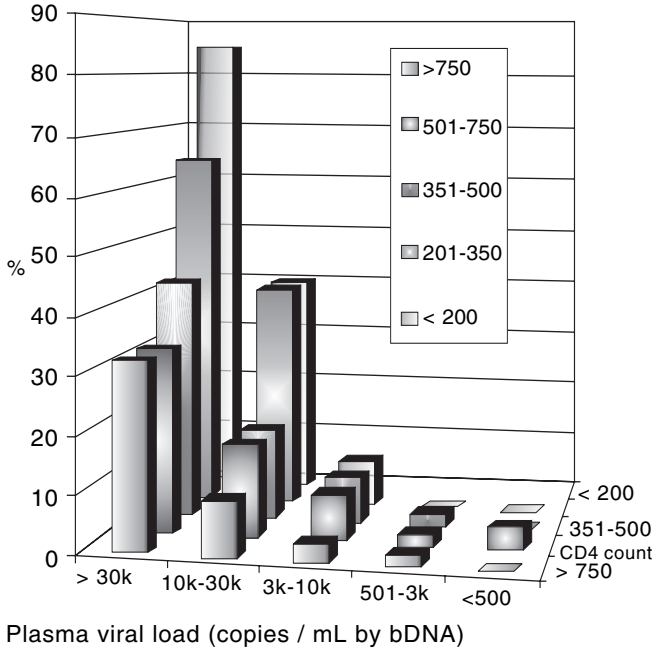


Figure 9
Average progression: 10 years from infection to AIDS diagnosis

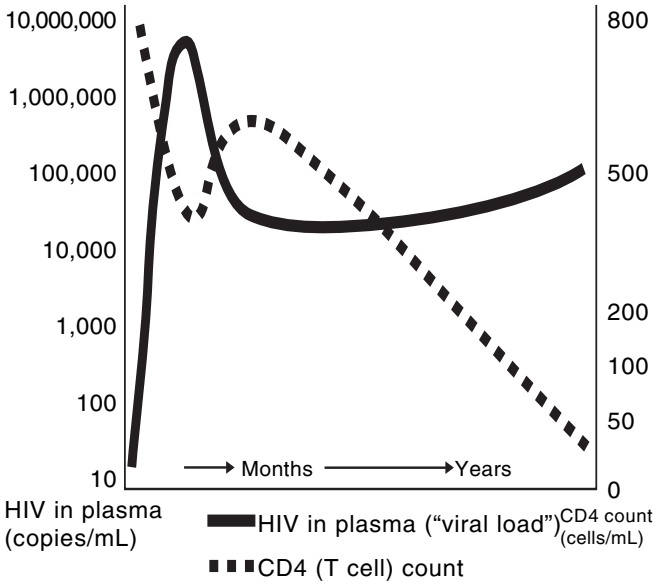
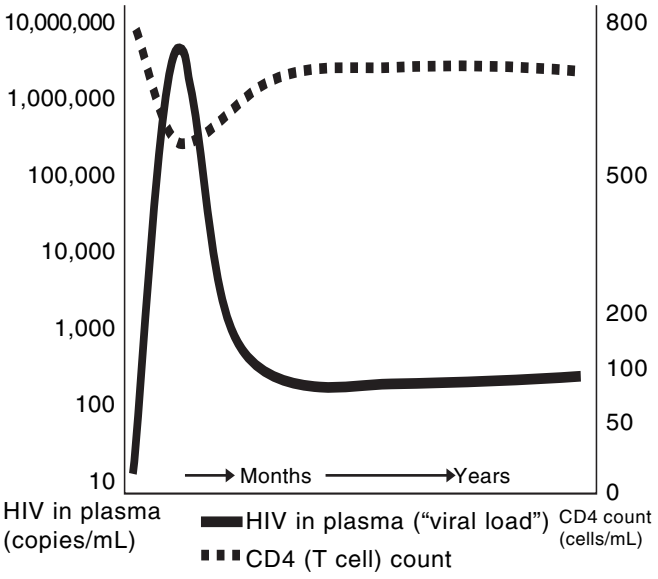


Figure 10
Non progressors: normal CD4 count, low detectable viral load



eases. The level of 200 cells/mL is an important benchmark as it denotes the level at which PCP (*Pneumocystis carinii* pneumonia) prophylaxis is indicated. Patients with CD4 counts < 50 are at the highest risk of dying.

Numerous natural history studies have helped to clarify the relationship between CD4 count and viral load as they both relate to the risk of progression to an AIDS diagnosis.[30,31] As can be seen in figure 8, patients with high viral loads and low CD4 counts are at the highest risk of progressing, whereas those with low viral loads and high CD4 counts are not. These observations have led to current recommendations regarding initiation of antiretroviral therapy. While minor differences exist between various agencies issuing these recommendations, a CD4 count between 350 and 500 should lead to a recommendation to initiate therapy, as should a viral load greater than 5,000-20,000 (depending upon the particular assay used to measure the virus load).[32]

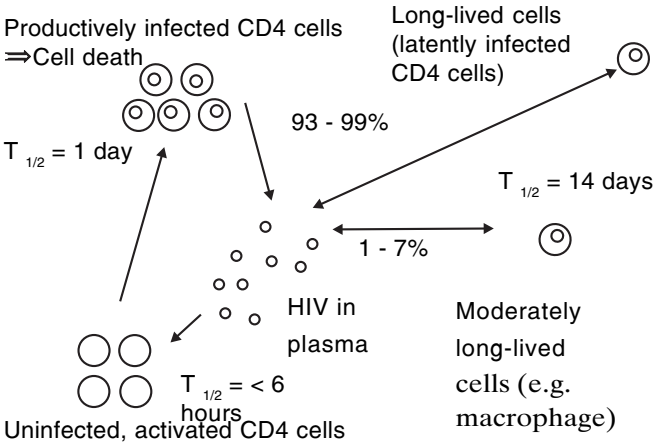
Several patterns of progression from HIV infection to an AIDS diagnosis can be seen, with the idealized "average" patient progressing to an AIDS diagnosis within 10 years following infection (as can be seen in figure 9). However, as seen in figure 10, extremely rapid progression has also been observed, with only months to a year or two between HIV-infection and the development of an AIDS diagnosis or death.[33-37] These individuals generally have persistently high viral loads and CD4 counts that do not recover following the acute retroviral infection.

In contrast, very rare individuals known as long-term nonprogressors are able to maintain normal CD4 counts and very low but usually detectable viral loads in the absence of antiretroviral therapy, with some individuals being observed to not progress for 15-18 years following infection.[38]

When viral particles are released from an infected CD4 cell their plasma half-life is approximately six hours (figure 11).[39] During this period they have the opportunity to infect activated CD4 cells, allowing for another viral replication cycle to recur with subsequent death of the host CD4 cells. HIV is also able to infect and replicate within circulating macrophages, a longer-lived cell population (half-life approximately two weeks) which can produce new virions without being killed in the process. Finally, very rare CD4 cells with integrated HIV genetic information undergo a transition from activation to latency, with a subsequent lifespan that may be 30 years or more. This pool of latently infected cells appears to be established by the time symptoms of the acute retroviral syndrome are observed, making it unlikely that even when therapy is initiated very early the formation of this pool can be prevented.

Studies of chronically infected patients have shown that despite several years of undetectable plasma viremia, stimulation of these latently infected cells (with

Figure 11
Modified from Perelson et al, Science 1996;271:1582-6



radiation or antigens) can lead to the production of replication competent viruses.[40] These latently infected cells which serve as potential "embers" for re-kindling active HIV replication have led to the conclusion that antiretroviral therapy alone —at least with the potency of currently available therapies— are not likely to eradicate HIV from infected individuals.

IS ERADICATION OF THE LATENT POOL NECESSARY?

Because plasma viremia quickly rebounds when antiretroviral therapy is discontinued –even after maintaining control for several years– it is apparent that suppression of HIV replication by currently available antiretroviral agents does not provide a long-term suppression of viremia, nor does it stimulate an innate immune response which can control viremia in the absence of treatment. However, data from a number of sources are increasingly providing a glimpse of situations in which the human immune system is able to control HIV replication in an ongoing manner.

Two populations have provided particular insight into the possibility that HIV-specific human immune responses can control HIV replication in the absence of therapy. These include long-term nonprogressors (described above) as well as acutely-infected patients who are treated aggressively with antiretroviral therapy.

When CD4 and CD8 lymphocytes of some long-term nonprogressors are isolated and exposed to HIV proteins in the laboratory, they proliferate, suggesting have been programmed to respond to HIV. These HIV-specific CD4 and CD8 lymphocytes are thought to play a very active role in maintaining control of viremia in long-term nonprogressors.

In contrast, chronically infected individuals in whom these same studies are performed do not demonstrate a response to HIV proteins. It appears likely that in most individuals HIV-specific CD4 and CD8 lymphocytes which are produced and are in an activated state during the acute retroviral syndrome become preferential sites for HIV infection and subsequent cell death.

What if antiretroviral therapy were initiated at the time of the initial production of these HIV-specific cells? A study of patients with the acute retroviral syndrome (high levels of plasma viremia in the absence of positive HIV antibody tests) who were treated with aggressive antiretroviral therapy demonstrated the induction and expansion of such HIV-specific immune responses.

This potential capacity to use highly active antiretroviral therapy (HAART) to control HIV replication and protect the population of HIV-sensitized CD4 and CD8 lymphocytes makes identifying patients with the acute retroviral syndrome a clinical priority. The most important aspect of making such a diagnosis is keeping the acute retroviral infection in the differential diagnosis of syndromes consistent with this condition. In one retrospective study of all patients presenting with symptoms which led medical personnel to test for infectious mononucleosis by sending a heterophile antibody (monospot test), approximately 1 percent appeared to have been undergoing the acute retroviral syndrome.[41]

While viral load testing to identify the acute retroviral syndrome is one context in which it is appropriate to use this assay to make the diagnosis of HIV infection, it is important to recognize that these highly sensitive tests can also lead to false positive results if they are applied to HIV-uninfected populations. [42] For this reason, either a qualitative HIV viral load assay (developed for this circumstance) should be used, or the quantitative viral load can be used but with a censoring of lower values (for example, considering as positive only results greater than 25,000 copies per mL).

ANTIRETROVIRAL THERAPY IN CHRONICALLY INFECTED PATIENTS

Long-term data now make it clear that the use of potent, combination antiretroviral therapy has dramatically changed the prognosis for HIV-infected pa-

tients. In the United States, a two-thirds decrease in AIDS mortality has been observed since 1996, and the number of new AIDS diagnoses made each year has continued to decline since the same date.[43-45] Unfortunately, the number of new HIV infections occurring each year has not declined, suggesting that our therapies are more successful than our preventive methods.

It is now evident that when HAART is successful and plasma viremia can be maintained at very low levels (<20-50 copies per mL, depending upon the particular assay being used), prevention of resistance to drugs is possible, as is long-term clinical stabilization with often gradual but continuous increases in CD4 counts.

CD4 counts which increase during therapy are also associated with evidence for increased CD4 functional capacity as manifested by a decrease in opportunistic infections and in the possibility of discontinuing prophylaxis or maintenance therapy for various opportunistic infections when the CD4 count has been elevated for several months.[46] Immune reconstitution syndromes against such antigens as mycobacteria, cytomegalovirus and hepatitis B also provide evidence of increasing immunologic strength and diversity as the CD4 repertoire is reconstituted.[47-50]

As a result of these benefits, many HIV-infected individuals are experiencing a higher quality of life, often undergoing a change from viewing one's futures as curtailed and declining to having to make decisions about possibly discontinuing disability benefits and going back to work or school as one's capacities are re-established.

While the benefits of antiretroviral therapy have been impressive, it is also clear that these drugs do not work in everyone, that adherence to complex and often burdensome regimens can be quite difficult, and that new and sometimes serious side effects are being observed.

ADHERENCE

The need to be to be faithful to what can be quite challenging schedules of medication administration is one of the Achilles' heels of antiretroviral therapy. Some medications must be separated from each other, some must be taken with food while others must be taken before or after food, some need to be refrigerated, some are taken as many as three times daily. Numerous medications can easily lead to very large pill burdens, with one protease inhibitor (amprenavir) requiring 16 tablets daily. It is well known that adherence to medication schedules for other chronic illnesses such as hypertension and diabetes can be quite variable, but unfortunately in the case of HIV, the result of even brief nonadherence may be drug resistance. Developing resistance to one drug in a therapeutic category often leads to cross-resistance to other drugs of the same type. This is the reason that initiating and changing therapeutic regimens for HIV-infected patients must be done from a strategic perspective, with second and third tier regimens being anticipated in advance.

DRUG TOXICITIES

At the same time that decreased morbidity and mortality from HIV have been observed, increasing drug toxicities have also been noted. While these have been seen with the greatest incidence in patients who have used protease inhibitors, even the nucleoside reverse transcriptase inhibitors have been associated with these complications.

DYSLIPIDEMIAS AND DYSGLYCEMIA

Increases in blood glucose and lipid levels (including LDL-cholesterol and triglycerides) have been observed in patients on HAART. Anecdotal cases have demonstrated acute coronary events in some individuals with elevated lipids, although population-based studies have so far not suggested an increased incidence above that which might be expected given other risk factors. Nevertheless, increases in cholesterol, triglyceride and glucose must be monitored and managed clinically, with options including the addition of lipid-lowering agents, use of hypoglycemics, and possibly moving away from protease inhibitors.[51-56]

LIPODYSTROPHIES

The accumulation or loss of fat deposits, sometimes occurring simultaneously, has also been observed in patients on antiretroviral therapy. This can include the accumulation of fat in the dorsocervical area ("buffalo hump") or in the omentum (leading to sometimes significant increases in abdominal girth known as " protease paunch" or "crix belly"), as well as the loss of subcutaneous fat in the facial muscles, buttocks, and in the extremities (where decreasing circumference and increasing prominence of blood vessels can be observed). [57,58] While not life-threatening, these changes in body image can be psychologically discomforting to many individuals who want to maintain their ability to swim in public, exercise at the gym, etc. Possible

treatments for increasing fat accumulation have included liposuction, the use of human growth hormone, and changing antiretroviral drug regimens.[59] Patients who are not already having difficulty with adherence may have an increased disincentive to use them when they result in such disfigurement. In addition, individuals who have not disclosed their HIV-positive status in certain situations may be "outed" by their changing physiognomy.

POSTEXPOSURE PROPHYLAXIS

Retrospective, uncontrolled data evaluating health care workers from North America and Europe who had taken AZT monotherapy following occupational exposure to HIV infection have suggested that this intervention is associated with a 79 percent decreased risk of seroconversion.[60] This report led to widespread availability of AZT monotherapy in such circumstances, although the rising prevalence of antiretroviral resistance, especially in heavily treated patients, has in many cases led to the recommendation that two or three drugs be used routinely following occupational exposure to HIV-infected body fluids.[61]

In contrast to the situation in health-care workers where at least some data is available, there are no data on the efficacy of providing a brief antiretroviral regimen to prevent establishment of HIV infection in persons who have had non-occupational exposure to HIV through sexual intercourse, injection drug use, or following mucous membranes contact with potentially infected bodily fluids. However, because of evidence suggesting a benefit for these regimens following occupational exposure, patients who present with a history of non-occupational exposure are increasingly being offered similar regimens by health-care workers. No uniform guidelines yet exist, and studies are ongoing to determine the efficacy of such interventions, the time period within which therapy must be initiated, possible diversion of resources from other modes of prevention and HIV treatment, as well as the impact of these interventions on reduction of risky behaviors.[62-66]

One concern is that making such protocols widely available could lead to an increase in the prevalence of drug resistance as a result of noncompletion of or nonadherence to the prescribed antiretroviral regimen. Even though therapies are usually administered for only a four-week period, even in the case of well-informed health-care workers who know their source patients were HIV-infected, in some studies up 78 percent have not completed their treatment course, with some developing serious side effects including nephrolithiasis, hepatitis, and pancytopenia.[67-69]

In addition, public health officials reasonably worry that postexposure prophylaxis (PEP) could be misunderstood as "a morning-after pill that cures HIV," leading to a decrease in personal behaviors which diminish the risk of becoming HIV-infected. Any PEP intervention should be accompanied by counseling and educational programs that stress the need to modify behavior to prevent such exposures from occurring again.[70]

ABSTRACT

The HIV-1 epidemic actually consists of three distinct families of viruses with independent transmissions, and their characteristics. The current status of the global epidemic indicated that in 1998 UNAIDS estimated that 33.4 million persons were living with HIV/AIDS, with 16,000 new infections occurring every day (half of them in persons under 25 years of age). In 1998 this disease included 590,000 children.

This work also analyzed the HIV pathogenesis, the natural history infection and main characteristics of the antiretroviral therapies, since adherence, drug toxicities, dyslipidemias and dysglycemia disorders; to lipodystrophies postexposure prophylaxis.

KEY WORDS: *HIV/AIDS, HIV/AIDS epidemiology, treatment and prevention, HIV/AIDS.*

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