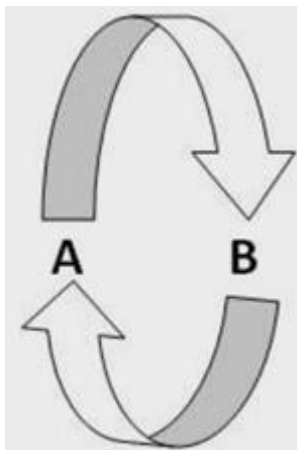


HIV infection: A disease with characteristics of positive feedback systems

HIV infection and many other infections caused by a wide variety of microorganisms have a mutually enhancing relationship that is characteristic of positive feedback systems.

Although the reciprocal enhancing effects of HIV and other infections have been frequently described since the late 1980s, it is useful to explicitly recognize these as positive feedback systems as this highlights the implications they have for treatment of individuals and for control of the epidemic. Explicitly recognizing the positive feedback characteristic of HIV disease also provides a way of looking at pathogenesis that can suggest further studies, both clinical and laboratory, that might advance our understanding of mechanisms of disease acquisition.

This is an illustration of positive feedback. **A** stimulates **B** which in turn stimulates **A**. In this way the effects of A and B are increased.



The infections associated with the immunological disorders of HIV disease are generally, but not solely, caused by microorganisms that replicate within cells. Many of the organisms that cause these infections survive in healthy people without causing disease, prevented from doing so by a competent immune system. When the immune system fails these infectious agents start to divide. They may then cause disease. An additional effect of some of these active infections is to accelerate the replication of HIV. Several mechanisms are responsible for this effect, which can then result in further immunological deterioration.

In addition, co-infection with many of the pathogens that also affect individuals with intact immune systems can also promote HIV replication.

Not all co-infections result in a more rapid progression of HIV disease. Many have no effect and a few have even been reported to cause a temporary improvement of HIV disease. This may be the case with measles, scrub typhus and a form of transfusion associated hepatitis. But more often, when an effect of a co-infection has been noted, it has been to promote HIV disease progression.

Different co-infections can therefore affect the course of HIV disease in different ways. Some may have no impact on the course of HIV disease; a few may possibly cause a temporary amelioration. Those that are able to accelerate it are highly prevalent in HIV infected individuals.

Worldwide, viruses of the herpes family are probably the most important of the co-infections that interact with HIV in a mutually enhancing fashion. . Virtually all adults are infected with some of these viruses that usually exist in a latent or dormant state. They are readily activated in the setting of HIV infection and then promote further HIV replication by a number of different mechanisms.

In developing nations a range of different endemic infections, depending on geography, may be just as important; many can also accelerate HIV disease progression. Conversely, HIV infection can promote progression of some endemic infections.

Several different mechanisms have been uncovered that can explain the effects of co-infections on promoting HIV replication. With such a wide range of infections, the precise ways in which each do this will vary in detail.

However there is one characteristic possessed by all HIV potentiating infections. This is their ability to add to the immune activation that is a feature of progressive HIV disease.

By now I think it is generally accepted that chronic immune activation not only results from HIV infection but is a major contributor to the pathogenesis of HIV disease. A state of sustained high level immune activation is the basis of the chronic inflammation and immunologic deterioration characteristic of progressive HIV disease.

But what exactly is immune activation?

Immune activation refers to those changes that take place in the immune system when exposed to an infectious agent that allow it to eliminate or control the infection. Essentially, the immune system is activated from a resting state to fight an infection. Generally this process will last for days until the infection is overcome, and usually but not always, is followed by a lifelong immunity to the infectious agent.

However in progressive HIV disease the immune system continues to be activated at a high level and it is this sustained immune activation that eventually results in disease. An activated state of the immune system is characterized by differentiation of precursor immune system cells. Differentiation is the process by which these cells develop specialized functions. Examples of cells that have acquired specialized functions are those that produce specific antibodies, or those with the ability to kill other cells infected with specific microorganisms. Proliferation of immune system cells is an

important characteristic of an activated state. This is usually a short-term response subsiding with control of the infection that stimulated it. But in progressive HIV disease, proliferation is sustained, probably with episodic cycles of further accelerations, and this continued proliferation contributes to the loss of immune system cells.

These cellular changes, differentiation and proliferation, are associated with the secretion of a variety of cytokines. Cytokines are molecules that can change the behaviour of cells by binding to specific receptors on their surfaces, for example, causing them to divide. Once released, cytokines not only attach to receptors on other cells but can also come back and attach to the receptors on the cell that produced it.

The cytokines that are released have widespread effects. Importantly, they include those that are associated with inflammatory changes, - the pro-inflammatory cytokines. With respect to positive feedback, pro-inflammatory cytokines including IL-6 and TNF alpha are able to accelerate HIV replication.

A part of the immune system, the innate immune system, responds immediately to infection by recognizing molecular patterns common to different organisms. The more familiar adaptive immune system responds to specific characteristics unique to each organism.

The innate immune system is also activated in untreated HIV infection. Interestingly effects of activation of innate immunity were recognized very early in the epidemic, even before HIV was discovered, and so are among the earliest recognized AIDS related immunological abnormalities. Activated innate immunity is responsible for the large amounts of alpha interferon in the circulation of people with untreated HIV/AIDS, first noted in 1981, the year this disease first came to our attentionⁱ. At that time the origin of this endogenous interferon was not known. For a period, elevated levels of beta 2- microglobulin were regarded as an adverse prognostic marker. This molecule can be regarded as a surrogate marker for interferon. The association of interferon with abnormalities characteristic of this disease – including low CD4 numbers was also reported in the first 2-3 years of the epidemicⁱⁱ. Over twenty years later mechanisms have been discovered that can explain the participation of interferon in the disease processⁱⁱⁱ.

Interferon appearing in the circulation in untreated HIV disease may even be the first marker of immune activation noted, although not recognized as such when first observed

The changes that occur on activation of the immune system are associated with many other markers that can be measured. Different molecules appear on the surface of activated cells. These can be detected and measured, as can the cytokines associated with immune activation.

These measurements can tell us the extent of immune activation. Importantly, the degree of immune activation parallels the rate of HIV disease progression.

Although it is now accepted that the consequences of continued activation and proliferation of immune system cells contribute to the loss of CD4 cells and the development of disease, the precise way it does so is not yet known, although there are a number of different mechanisms that could account for it. The associated inflammation also has adverse effects beyond the immune system. For more detailed information on these mechanisms there are references to two reviews at the end of this article^{iv}.

Sustained immune activation is therefore at the heart of HIV/AIDS pathogenesis. It is the sustained nature of the activated state that is critical. Short lived states of immune activation are of course beneficial allowing us to recover from infections. But in progressive HIV disease the process continues at variable rates. Understanding what causes continued immune activation is central to an understanding of the pathogenesis of HIV disease.

What causes Immune activation?

While infection with HIV may start the process, other causes of immune activation are almost certainly also necessary to keep it going.

The following all contribute:

1: The immune response to HIV itself. This includes both innate and adaptive immune responses. As noted above, adaptive responses are the familiar specific antibody and cell mediated responses that provide generally lifelong immunity to specific infectious agents. Innate responses depend on recognition of molecular patterns common to several organisms.

Some suggest that HIV contributes directly to immune activation through binding of some of its proteins to immune system cells.

2: Microbial products that can penetrate into the intestinal wall as a result of damage caused by HIV. These microbial products then activate immune system cells.

3: Other infections.

Some like active herpesvirus infections or the more traditional opportunistic infections can be seen as indirect effects of HIV infection.

Others are infections that can cause disease in people with intact immune systems like the endemic infections in developing nations. Some of these can be more severe in the setting of HIV infection.

Infections that can accelerate HIV replication include those caused by bacteria, viruses, protozoa and helminths.

Those that promote HIV disease progression can usefully be described in three categories.

A: Herpes virus infections. These are probably the most important worldwide. Virtually 100% of adults are infected with some of them. They represent infections that are more often latent, but are readily activated in HIV infected individuals.

B: Endemic infections caused by a variety of different microorganisms than promote HIV disease progression and HIV replication. These are important in developing nations.

C: Other infections. These include the opportunistic infections, as well as those that can affect people with intact immune systems. TB may be the most important. HIV infected individuals are much more susceptible to active TB infections than those who are HIV uninfected. HIV transcriptional activity and viral load have been noted to be higher in people with active TB.

Here is a little more detail about these three classes of infection:

A: Herpesviruses.

There are eight members of the herpesvirus family that can infect humans. Herpes simplex virus types 1 and 2 (HSV-1, HSV-2) are perhaps the most familiar. Cytomegalovirus (CMV) and the Epstein-Barr virus (EBV) infect close to 100% of adults. Varicella-Zoster virus (VZV) causes chicken pox on initial infection and shingles when reactivated. Of the three remaining human herpes viruses HHV-6, HHV-7, and HHV-8, the last is associated with Kaposi's sarcoma.

With all of the herpes viruses, once infected, individuals carry them for the rest of their lives, usually in a dormant or inactive state. All can be periodically reactivated with or without symptoms.

Humans and herpes viruses have co-existed for evolutionary periods and are well adapted to each other. The immune system generally maintains these viruses in a latent state so that they cause no harm. Reactivation does occur periodically but is generally limited. Virtually 100% of adults will carry some viruses of the herpesvirus family, usually in a dormant or latent state.

The impaired immunity characteristic of HIV disease however results in reactivation of herpes virus infections. In progressive HIV disease these viruses become active and through a variety of mechanisms, including their contribution to immune activation, promote the replication of HIV. Cytomegalovirus (CMV) may be the most important of the herpesviruses that promote HIV disease progression. It can be part of a positive feedback system in its interactions with HIV.

HIV → latent herpes infections → active herpes infections → HIV

It is not only through their contributions to immune activation that herpes viruses promote HIV replication. In addition to the pro-inflammatory cytokines that have this effect, herpes virus gene products can directly activate HIV if a cell is infected with both viruses. This process, called transactivation works both ways; HIV can also activate herpes viruses.

In addition herpes infections cause a receptor (Fc) to appear on cell surfaces that allows HIV to enter it. In this way cells that do not possess CD4 molecules can become infected with HIV. Active CMV infections can also exert a mildly immunosuppressive effect.

Herpesviruses, particularly CMV are singled out because they probably play a significant role in the pathogenesis of HIV disease. CMV infections are so common that it is hard to find HIV infected individuals who are free from it so that they can be compared to those who are not. But as early as 1991 this was done with HIV infected haemophiliac patients, when it was noted that those also infected with CMV had a much more rapid progression of their HIV disease^v.

That CMV may play a role was suggested by many very early in the epidemic. A multifactorial model for the development of this disease published in 1983 before HIV was discovered suggested a major role for CMV and EBV^{vi}. The considerable evidence for a role for herpesviruses, particularly for CMV, did not disappear with the discovery of HIV. The interactions of CMV and other herpes viruses with HIV that have been discovered may now explain their role.

Large studies on the effects of acyclovir on the course of HIV infection have provided compelling evidence that active infection with these viruses can be regarded as part of the disease process for most HIV infected individuals. Investigators focussed on HSV-2 undoubtedly because it is the most common cause of genital ulcers. The dose of acyclovir used would also have suppressed HSV-1, which is even more prevalent than HSV-2 and may be more sensitive to acyclovir. HIV viral loads and the rate of HIV disease progression were reduced in individuals receiving acyclovir compared to those receiving placebo. Although genital ulcer recurrences were suppressed by acyclovir, the drug had no effect on the transmission of HIV.

The effects of acyclovir on HIV probably resulted from suppression of active herpes infection. This is entirely consistent with a model that places HIV and herpesviruses in a positive feedback relationship.

EBV and CMV are much more resistant to acyclovir than HSV-1 and 2. But it cannot be excluded that this drug did not have some effect in also diminishing reactivations of CMV and EBV. If samples from the trial have been stored appropriately, this can be looked at. EBV reactivation patterns are easily recognized, CMV virus isolation is possible and even detection and quantification of activated T lymphocytes would tell us something.

B: Endemic infections:

These are singled out because of their high prevalence in some parts of the developing world.

These infections affect significant proportions of the population, they tend to be chronic and persist in the absence of treatment. The specific infections will depend on geography and many are transmitted by insects. Many of these can also accelerate HIV disease progression, and some also progress more rapidly in the setting of HIV infection^{vii}.

C: Other infections:

On an individual level, some episodic infections can promote HIV replication. An acute febrile illness may increase HIV viral loads, but this is a transient effect lasting for the duration of the infection.

Most of the serious opportunistic infections occur late in the course of HIV disease, and may promote even further disease progression.

TB deserves special consideration because of its high prevalence in HIV infection. Susceptibility to TB is increased even at higher CD4 levels. Active TB can then promote further HIV replication thus becoming a partner with HIV in a positive feedback interaction^{viii}.

A role for immune activation in a positive feedback system:

One way to look at the process of disease acquisition in HIV infection assigns a central role to immune activation.

Immune activation not only results from HIV infection, it can also promote further replication of HIV.

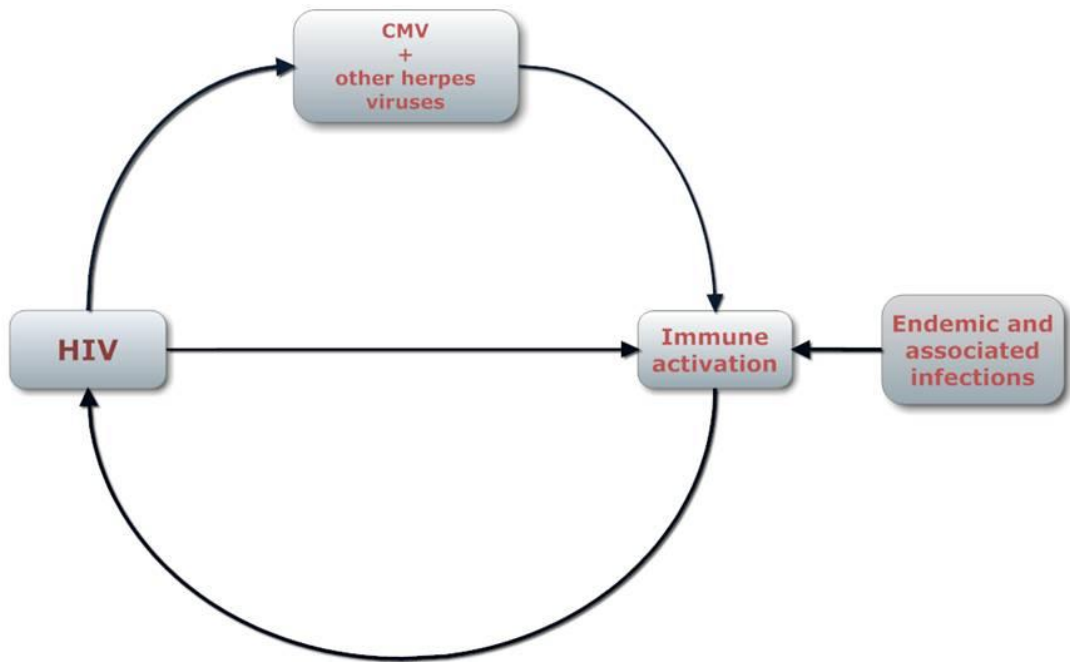
HIV replicates more efficiently in activated immune system cells. Secondly, the pro-inflammatory cytokines that are associated with an activated immune system can directly stimulate HIV replication. Progressive HIV disease and immune activation are therefore components of a positive feedback system in this way.

HIV disease → Immune activation → HIV disease → Immune activation

The process starts with HIV infection, and is promoted by other infections, some of which are activated by HIV infection.

Whatever is driving immune activation is driving HIV disease.

The following diagram illustrates this.

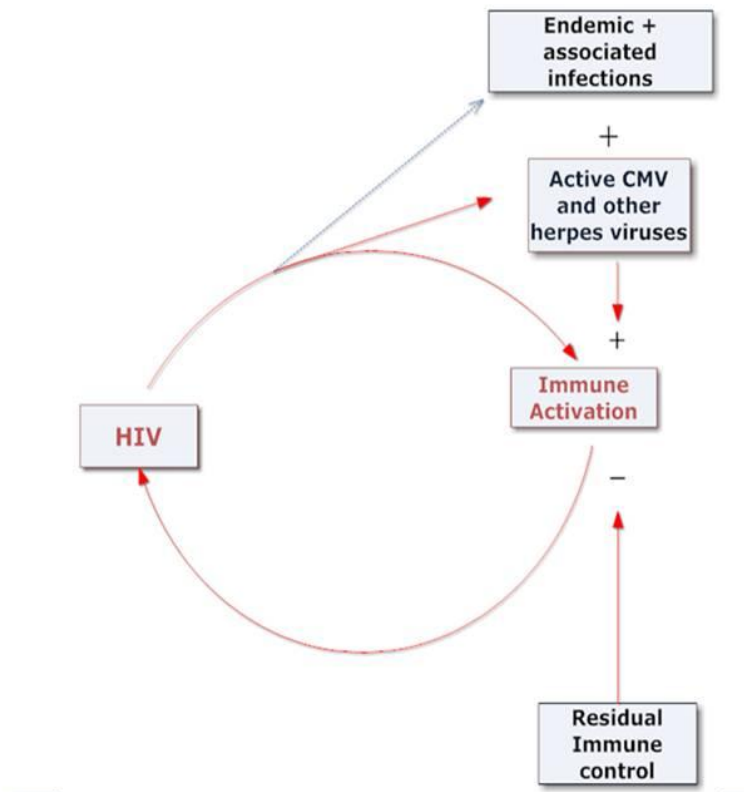


Looking at the course of HIV infection in this way has a number of implications.

Pathogenesis.

In the above diagram the course of HIV disease is represented by a self-perpetuating cycle proceeding in a clockwise direction. In addition to the elements that have positive effects in driving the process, there will also be those that retard the cycle. This is illustrated in the next diagram which focuses for simplicity on the immunological control of HIV infection and of those infections that add to immune activation. Of course there are other mitigating factors, for example, genetic factors conferring varying degrees of resistance resulting from receptor polymorphism.

In the diagram, the connection of HIV with CMV and other herpes viruses is probably constant and indicated by a red arrow. The connection of HIV with endemic and associated infections is indicated by a blue dotted line, because HIV infection does not increase susceptibility to all of them, nor does it accelerate the progression of all.



The positive feedback cycle starts with HIV infection. At least some of the determinants of the rate of disease progression may be found in the conditions that exist at the time of initial infection that promote or retard the cycle.

There is evidence that the degree of immune activation at the time of seroconversion predicts future disease progression.^{ix x} It may also be an important determinant of what is called the set point. This is the point following initial infection with HIV, from which CD4 numbers decline.

The degree of immune activation at seroconversion thus influences the starting CD4 level; the rate of subsequent decline is influenced by the degree of immune activation in a system where once started, conditions can exist where immune activation increases with falling CD4 numbers, in a self-perpetuating and accelerating fashion. Whatever the outcome, it will be the balance of positive and negative influences.

In the earliest years there were reports of EBV reactivation preceding HIV seroconversion^{xi}.

I have not seen any follow-up of this interesting report. It at least suggests that there might even be situations in which active herpes infections could sometimes promote seroconversion. They certainly produce signals that can activate HIV transcription from proviral DNA.

Treatment and prevention.

The role of immune activation in driving HIV disease is generally accepted now. There are sources of immune activation other than HIV and some of these can be controlled.

Attempts to identify and control additional sources of immune activation may be critical in the fight against HIV/AIDS.

Perhaps the most significant benefit in this respect concerns the developing world, where there are so many additional sources of immune activation. Even ascariasis, infestation with the common intestinal round worm is associated with significant immune activation. Worldwide prevalence is estimated to be about one billion, with 173 million in sub-Saharan Africa.

Many highly prevalent endemic infections can promote HIV replication. Controlling these are perfectly appropriate targets in the fight against HIV/AIDS, and of course this would independently improve the lives of millions of individuals.

Measures to control endemic infections include traditional public health interventions, such as the provision of sanitation and clean water and the control of insect vectors. Effective drugs are sometimes inexpensive. Peter Hotez has written an article entitled "Africa's 32 cent solution to AIDS".^{xii} This refers to the price of Praziquantel, effective in treating schistosomiasis as a single dose.

The lives of impoverished populations are ravaged and shortened by these infections. Many of these infections also interact with HIV to compound the devastation they cause. Poverty, multiple endemic infections and HIV are intimately intertwined and in many instances reciprocally affect each other.

Recent and ongoing studies will probably lead to the routine use of drugs that are effective against herpes virus infections. Trials of valacyclovir to reduce HIV viral loads are in progress. Given the ubiquitous nature of herpes infections, the use of acyclovir as adjunctive therapy might be warranted even in the absence of recurrent herpetic ulcers. Valacyclovir unfortunately is not yet available as a generic medication.

Unfortunately EBV and CMV are much more resistant to these drugs. The development of agents less toxic than valgancyclovir is important. Valgancyclovir has already been shown to reduce immune activation in HIV infected individuals as measured by a reduction in activated CD8 lymphocytes.

In summary it is useful to explicitly recognize the positive feedback interactions between HIV and other infections that can promote its replication, some of which are in turn promoted by HIV. Control of the AIDS epidemic in Africa must include measures to prevent and treat multiple endemic infections that affect hundreds of millions of individuals.

ⁱ This is of particular interest to me as I was involved in the discovery of large amounts of interferon in the circulation of people with HIV/AIDS in 1981, the year the disease was first described.

http://aidsperspective.net/articles/Interferon_Vilcek.pdf

<http://aidsperspective.net/blog/?p=118>

ⁱⁱ <http://aidsperspective.net/articles/Interferon-AZT-1991.pdf> Fig 1 shows CD4 counts in relation to serum interferon . Presented 1986 at the 2nd international aids conference in Paris.

ⁱⁱⁱ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2491901/>

^{iv} **Immune activation and inflammation in HIV-1 infection: causes and consequences.**

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^v <http://www3.interscience.wiley.com/journal/119316871/abstract?CRETRY=1&SRETRY=0>

^{vi} <http://aidsperspective.net/articles/NYAS.pdf>

^{vii} Endemic infections in Africa have everything to do with HIV/AIDS:

<http://aidsperspective.net/blog/?p=403>

^{viii}

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1905977/>

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