Clinical review

Recent advances
HIV infection–I

Jonathan Allen Cohn

Impressive advances in the understanding of the virology and immunology of HIV infection have led to new treatments, new methods to monitor treatment, and new optimism regarding the treatment of early HIV infection. Although controversial, the possibility of curing HIV infection in selected patients by using existing technology was discussed at the 1996 international AIDS conference in Vancouver, Canada. However, the substantial expense, toxicity, and inconvenience of the new treatments make many clinicians and patients more cautious than are the investigators regarding the potential effectiveness of these new approaches. Further, 90% of the 22 million people with HIV infection worldwide live in societies without the financial resources to pay the current price for these treatments, and others in developed nations may lack access due to a lack of, or limitations on, health insurance. In industrialised nations, we can work with our patients to take advantage of the lessons learnt in the past year.

Recent advances

- Potent new antiretroviral combination therapies and new methods to monitor plasma concentrations of HIV have combined in the past year to provide new optimism and new opportunities for treating patients in developed nations
- Prospects for a cure remain uncertain
- Improved treatment is unaffordable for most people infected with HIV

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BMJ 1997;314:487–91

Can HIV infection be cured?

At the eleventh international AIDS conference in Vancouver, Canada, several investigators presented theory or data regarding the possibility of eradicating HIV infection by the aggressive use of combination antiretroviral treatment. David Ho discussed the steady state model of HIV infection derived from studies of viral replication and turnover in treated patients. Susceptible CD4 lymphocytes become infected with HIV and most develop productive infection, leading one and a half days later to a release of a large number of new virions and the death of the host cell (fig 1). These virions are cleared from plasma with a half life of about six hours and initiate a new round of infection in susceptible CD4 cells, predominantly within lymphoid tissue. Ho and colleagues estimate that 99% of the virus found in the plasma is derived from this cycle.[1] Using this model, Perelson *et al* have estimated that 10 billion or more new HIV virions may be produced in an infected individual daily, and up to two billion CD4 lymphocytes may be killed and replaced daily. When the body's ability to replace CD4 cells is exhausted, CD4 cell depletion and clinical immunodeficiency occur.

Disruption of the HIV replication cycle with potent antiretroviral treatment often leads to a decline over several weeks of up to 99% in the number of HIV RNA copies detected in the plasma. A slower decline in the remaining plasma HIV RNA may follow, which Ho and colleagues attribute to the more gradual reduction in the pool of longer lived cells chronically producing HIV virions (such as macrophages) or latently infected cells which are intermittently reactivated to become producers of virus. On the basis of the assumptions in this model, Perelson *et al* calculated that potent combination therapy for 60 to 120 weeks may lead to the eventual eradication of this pool of host cells that are either chronically or latently infected, or both.[2] Martin Markowitz is testing this concept in 12 men who were given antiretroviral treatment with zidovudine, lamivudine and ritonavir during their first weeks of HIV infection.[3] During the first months of treatment, plasma HIV RNA values (see below) decreased from a mean of

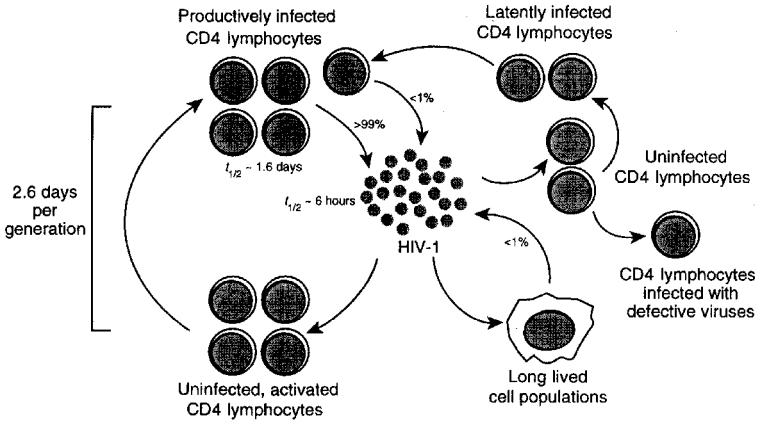
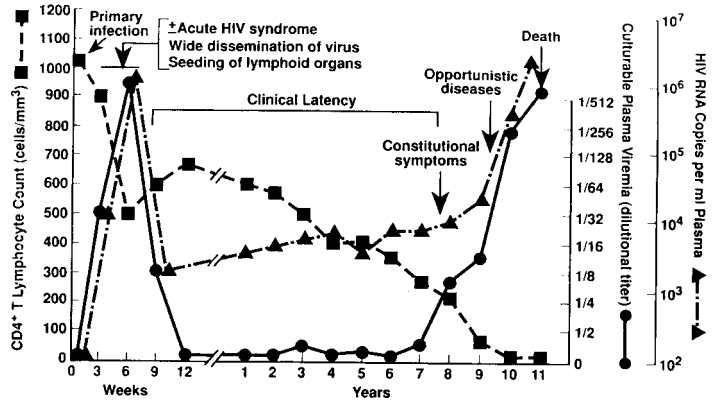


Fig 1 Schematic summary of the dynamics of HIV infection in vivo. Shown in the centre is the cell-free virion population that is sampled when the viral load in plasma is measured. Reprinted with permission from Perelson *et al*[1]; copyright 1996 American Association for the Advancement of Science

Box 1–Typical cause of HIV infection



The complex, multifactorial, multiphasic, and overlapping factors of the immunopathogenic mechanisms of HIV disease are shown. Throughout the course of HIV infection, virus replicates and immunodeficiency progresses steadily, despite the absense of observed disease during the so called clinical latency period. Immune activation and cytokine secretion vary among HIV infected persons, sometimes increasing dramatically as disease progresses. Immune activation and cytokine secretion play a major role in pathogenesis. Reprinted with permission from Fanci *et al*[5]

90 000 RNA copies/ml to fewer than 500 RNA copies/ml as measured by the bDNA assay; cultures of peripheral blood leucocytes have been negative for HIV; and HIV antibody values have decreased. Markowitz and Ho plan to sample lymphoid tissue in these patients after one year of treatment and to try to detect proviral DNA (latently infected cells). If no viral genomes are detected, they will consider withdrawing antiretroviral treatment to determine if HIV has been eradicated. This research into a possible cure of HIV with existing therapeutics is tremendously exciting, but it should not be misinterpreted to mean that a cure has been found, or even that a cure is likely.

Clinical course and surrogate markers

Between 30% and 60% of people infected with HIV experience a syndrome resembling infectious mononucleosis at the time of initial infection. This illness, termed the acute retroviral (or seroconversion) syndrome, includes fever, myalgia, a maculopapular rash, lymphadenopathy, and—less commonly—oral ulcers, neurological manifestations, and occasionally markers of immunosuppression such as oral candidiasis, accompanied by leucopenia and an acute reduction in CD4 lymphocytes.[4] Tests for HIV antibody give negative or indeterminate results, whereas measures of the viral p24 antigen in serum or HIV RNA in plasma are extraordinarily high. Without treatment, the clinical illness subsides, the values for virus in the plasma decrease to a plateau, and the CD4 lymphocyte count rebounds, although not back to the baseline before HIV infection (see box 1). Patients then enter a period of clinical latency, followed years later by progressive immunosuppression and symptomatic disease.[5] Recent data confirm that a longer duration of symptoms during this syndrome is associated with a more rapid decline of CD4 cells and progression to AIDS.[6] Further, a greater decline in CD4 cell number or percentage in the six months after seroconversion is associated with a more rapid progression to AIDS or death.[7]

John Mellors and his colleagues have shown that plasma HIV RNA values strongly predict progression to AIDS or death, even among patients with similar CD4 lymphocyte counts. The number of free virions in the circulation (each containing two strands of genomic RNA) can be estimated by using new quantitative assays of plasma HIV RNA. Good reproducibility is achieved by using quantitative reverse transcriptase polymerase chain reaction to amplify DNA copies of the target RNA (RT-PCR, available commercially as the Roche Monitor Assay) or branched chain DNA technology to amplify the signal of minute quantities of target RNA (bDNA assay by Chiron) or a variant of the polymerase chain reaction that directly amplifies target RNA (NASBA by Organon Technika).[8] Mellors and colleagues showed that a plasma level of 10 000 copies or more of HIV RNA within one year of seroconversion was significantly associated with the risk of progression to AIDS and that a level of 100 000 copies or more increased the risk of AIDS 11-fold.[9] The combination of CD4 lymphocyte counts with plasma HIV RNA values, and the use of serial measures of both markers, permitted even more accurate prediction. Mellors and colleagues also found that plasma HIV RNA measurements at other time points during the course of HIV infection provide similar prognostic information. Previously infected patients in the lowest quartile of viral load (an initial plasma HIV RNA level $\leq$4530 RNA copies/ml by bDNA) had an 8% probability of developing AIDS within five years, whereas those in the highest quartile ($>$36 270 RNA copies/ml) had a 62% probability of developing AIDS within five years (fig 3).[10] Whenever the quantitative assay is performed, a continuous gradient of risk with higher values of plasma HIV RNA has been observed.

Changes in laboratory tests and response to treatment

Improvements in CD4 lymphocyte counts accounted for only a small proportion of the clinical benefit associated with antiretroviral treatment.[11] Many studies have been conducted in the past year to determine if changes in plasma HIV RNA values during treatment predict the clinical response. Analyses of randomised trials of nucleoside analogue reverse transcriptase inhibitors support an association between treatment induced decreases in plasma HIV RNA values and either a delay in major opportunistic diseases or prolonged survival, or both.[12-15] Decreases in plasma HIV RNA of at least 70% (0.5 log copies/ml) were required for detecting an association with clinical benefit. Preliminary results of prospective studies have been presented for non-nucleoside reverse transcriptase inhibitors,[16] and studies are ongoing with protease inhibitors.

Guidelines for use of these new assays have been published.[8] However, the experience with these assays has been brief; there are few data on the correlation of HIV RNA in plasma and infection in lymphoid tissue; inconsistencies between virological, immunological, and clinical responses have been noted; and changes in CD4 cell counts and plasma HIV RNA values still do not account for all of the clinical benefit of antiretroviral treatment.[12] Therefore, it has been suggested that plasma HIV RNA assays need to be validated as predictors of a clinical response for each class of

antiretroviral drug and for patients in different stages of HIV infection.[17 18]

Newly licensed antiretroviral agents

Five drugs for treatment of HIV were licensed in the United States in the past 12 months, more than doubling the number of agents that have become available since zidovudine was licensed in 1987.

Nucleoside analogue reverse transcriptase inhibitors

Lamivudine (3TC or Epivir, Glaxo-Wellcome) is a nucleoside analogue reverse transcriptase inhibitor (as are all the previously licensed agents: zidovudine, didanosine, zalcitabine, and stavudine). When used as monotherapy it has modest antiviral activity, but resistant mutants appear within a few weeks or months. However, the mutation conferring resistance to lamivudine also reverses resistance to zidovudine, and it decreases the rate of other mutations in the reverse transcriptase gene.[19] Thus, the combination of zidovudine and lamivudine provides much greater sustained decreases in plasma HIV RNA than either drug alone.[20-22] Results from a recent meta-analysis suggest that a clinical benefit does occur with this combination.[23] The toxicity profile of the combination in adults is almost the same as with zidovudine alone, and this combination is now often prescribed.

HIV protease enzyme inhibitors

Three inhibitors of the HIV protease enzyme—saquinavir, ritonavir, and indinavir—were licensed during the first months of 1996. These potent drugs are often compared on the basis of the reduction in plasma HIV RNA values obtained in various studies, but direct randomised comparisons have never been done and variations among patients and assays make comparisons across studies unreliable.

Saquinavir (Invirase, Hoffman-LaRoche) is the least bioavailable. At currently approved doses saquinavir is the best tolerated protease inhibitor but it has the least antiretroviral activity. High dose saquinavir (36 capsules of 200 mg daily) had a more potent antiretroviral effect, but gastrointestinal side effects and raised serum aminotransferase occurred more frequently.[24] The combination of saquinavir, zidovudine, and zalcitabine produced greater decreases in plasma HIV RNA and greater increases in CD4 cell count than combinations of two of these drugs.[25]

Ritonavir (Norvir, Abbott) singly and in combination produces much greater reductions in plasma HIV RNA and rises in CD4 lymphocyte counts than does saquinavir, but it often causes gastrointestinal symptoms and paraesthesias which may be transient.[26-28] It also is a very potent inducer of the cytochrome P450 enzyme system, and thus it has a myriad of drug interactions. A preliminary trial of combined saquinavir and ritonavir assessed the safety of using such interactions to advantage, because ritonavir increases the bioavailability and serum concentrations of saquinavir.[29] A study comparing ritonavir with placebo, superimposed on baseline nucleoside antiretroviral treatment among patients with advanced AIDS, provided the first evidence of a clinical and survival benefit with any protease inhibitor.[30]

Indinavir (Crixivan, Merck) is as potent singly and in combination as is ritonavir and has fewer gastrointestinal and neurological effects, but it causes renal stones in 4% of patients and indirect hyperbilirubinaemia in 10%.[31 32] Indinavir, zidovudine, and lamivudine in combination led to the greatest sustained reductions in plasma HIV RNA concentrations of any protease inhibitor combination[33] and was associated with a decreased emergence of resistant mutants to any of the drugs.[34]

Non-nucleoside reverse transcriptase inhibitors

Nevirapine (Viramune, Roxane/Boerhinger Ingleheim) is the first of a new class of agents, non-nucleoside reverse transcriptase inhibitors, to be licensed. It is more active as a single drug than any nucleoside reverse transcriptase inhibitor, but as with lamivudine, resistant mutants emerge rapidly and plasma HIV RNA values return to near baseline in a matter of weeks or months. Impressive reductions in plasma HIV RNA values have been reported with the combination of zidovudine, didanosine, and nevirapine, but there was no clinical benefit over zidovudine with didanosine in a study with limited power to detect such differences.[35] Rash is the most frequent adverse event and was serious in 9% of patients taking nevirapine.

Drugs under trial

New protease inhibitors (nelfinavir, Agouron), and non-nucleoside reverse transcriptase inhibitors (delavirdine, Pharmacia-Upjohn) are progressing through

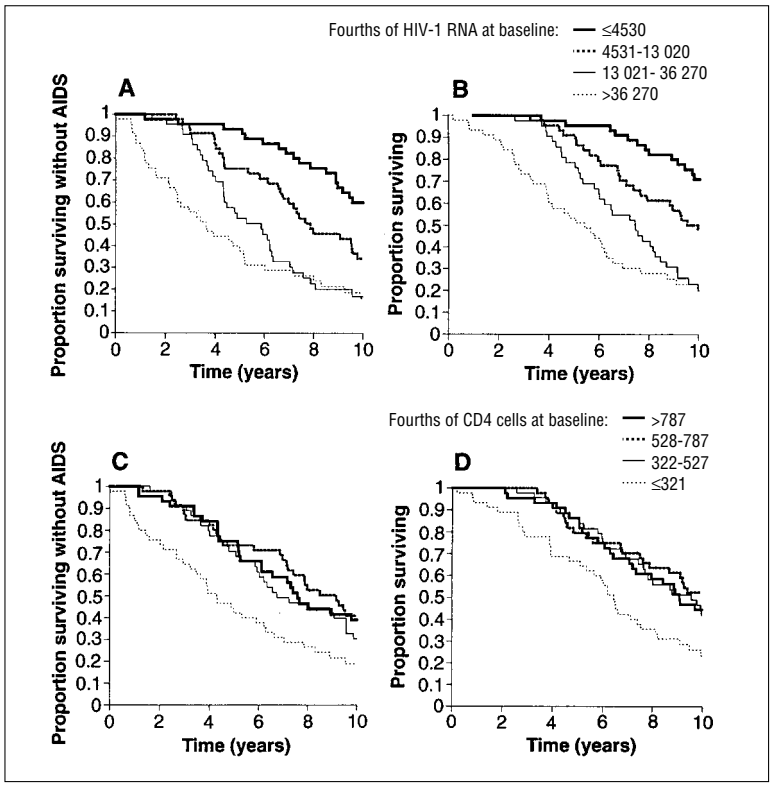


Fig 3 Relations between baseline markers (obtained in men without AIDS at a variable but unknown interval since seroconversion) and prognosis for AIDS. Kaplan-Meier curves for AIDS free survival and survival stratified by HIV-1 RNA and CD4 cell count. Reprinted with permission from Mellors *et al.*[10] Copyright 1996 American Association for the Advancement of Science

efficacy trials and are available through compassionate use mechanisms in the United States. New nucleoside and non-nucleoside reverse transcriptase inhibitors, new protease inhibitors, and new classes of antiretrovirals (nucleotide reverse transcriptase inhibitors and integrase inhibitors) are being developed.

Recommendations for antiretroviral treatment of adults

In the absence of long term clinical endpoint studies with the potent new therapies, current treatment is guided by data from shorter trials with clinical endpoints, trials with virological and immunological endpoints, and extrapolations from the new models of HIV pathogenesis. Three schools of thought regarding treatment have emerged. One is to use combination antiretroviral treatment aggressively and early in HIV infection so as to achieve maximal suppression of HIV replication before resistant mutants emerge and before the immune system sustains irreversible damage.[36] Another school is less aggressive in the absence of proof of efficacy of aggressive early treatment; it recognises limitations of inconvenience, toxicity, and cost of complex treatment.[37] Others view antiretroviral treatment as a partial intervention and anticipate that immunological manipulation must be combined with antiretroviral treatment to provide long term viral suppression, to restore waning immunological function, and to provide the possibility of cure.[17] Trials of interleukin-2 with antiretroviral treatment represent such a combined approach.[38 39]

For most practitioners, who rarely if ever diagnose acute retroviral syndrome and whose patients have limited access to drugs, the recently published recommendations of an international panel provide useful guidance.[37] Treatment is recommended when plasma HIV RNA values exceed 5000-30 000 copies/ml, or when the CD4 lymphocyte count is less than 500 cells$\times 10^6$/l, or with the onset of symptoms. The use of previously studied two drug combinations of nucleoside analogues or didanosine alone is suggested for patients with mild to moderate immunodeficiency, and three drug combinations including a protease inhibitor are recommended for patients with moderate to severe immunosuppression or high plasma HIV RNA values. A change in treatment should be considered when the plasma HIV RNA value returns to within 70% (0.5 log) of pretreatment values, or with a consistent fall in the CD4 cell count, or with the development of new symptoms. A new regimen should include one or more new drugs which the patient has not previously used and which are not cross resistant with drugs previously used, in an effort to overcome viral resistance. For example, ritonavir and indinavir share many resistance mutations and are thought to be cross resistant, so one should not be substituted for the other in cases of therapeutic failure. Further, it may be prudent to include a second new drug when a protease inhibitor is prescribed, in an effort to reduce the risk of emergence of resistance to these potent agents. The dosing schedules of three drug regimens are complex and difficult, especially when protease inhibitors may need to be taken with fatty food (ritonavir) or on an empty stomach (indinavir) to maximise absorption. Adverse events and potentially dangerous drug interactions may cause insurmountable obstacles to combining protease inhibitors for some patients. As nevirapine was not yet licensed when these guidelines were written, non-nucleoside reverse transcriptase inhibitors are not explicity included in the published recommendations. However, as pharmacokinetic and virological data on combinations including non-nucleoside agents accrue, these may be included in the two and three drug regimens by following the same basic strategy.

Prophylaxis after occupational exposure to HIV

An international case-control study of healthcare workers with percutaneous occupational exposure to HIV found that treatment after exposure with zidovudine (3-4 weeks of doses up to 1000 mg daily) reduced the probability of infection by approximately 80%, after adjustment for other risks.[40] Encouraged by these results, and by the potent antiretroviral therapies now available, the Centers for Disease Control and Prevention and the International AIDS Society—USA have each proposed guidelines for postexposure prophylaxis of healthcare workers.[37 41] The Centers for Disease Control recommend prophylaxis with three drugs (zidovudine-lamivudine-indinavir) for the highest risk exposures, with two drugs (zidovudine-lamivudine) for lower risk exposures, and no treatment for the lowest risk exposures. The International AIDS Society—USA recommendations are similar, but say that selection of the individual drugs in two and three drug combination regimens should be guided by knowledge of the index patient's previous treatment. Prophylaxis should be instituted within 24 hours, and preferably within one to two hours, after exposure; this requires healthcare facilities to have a system available to assist exposed healthcare workers and to start treatment 24 hours a day. Treatment for four weeks is recommended. The risk of toxicity in each case must be balanced against the relatively low rate of infection after the average percutaneous exposure (0.3%).

Conclusion

Even if rumour of a cure is premature, and the effectiveness of complicated and expensive treatments and monitoring assays are yet to be shown in clinical practice, discoveries made in the past year provide reason for optimism regarding HIV treatment in developed nations. The ability to identify people at greatest risk for progression, and combination antiretroviral therapies which can reduce plasma values of virus by 99% or more for at least one year, may provide the means of maintaining immunological function and substantially postponing disease progression and death. Application of these treatments may also improve results of prophylaxis for HIV transmission, reducing perinatal transmission and the risk of HIV infection for healthcare workers. Other approaches to prevention of HIV transmission, and treatment for people with advanced immunosuppression and AIDS, are discussed in the article to be published next week.[42]

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A MEMORABLE PATIENT
Protective pipe smoking

When I first started in general practice in 1946 a man of about 80 came to see me and, as it was my first contact with him, I asked a few leading questions about his health and his smoking habits. He replied—"I smokes a pipe and it's all the fault of you doctors." Sensing a story, I asked for an explanation. At the start of the century he was running a daily carrier service with a horse and cart between Tewkesbury and Gloucester, a distance of about 12 miles. Unfortunately in 1901 there was an outbreak of smallpox in Gloucester, and some of the inhabitants of Tewkesbury became worried about the possibility of this daily carrier service, which at the time was the only regular contact between the two towns, bringing the contagion back to Tewkesbury. As this service was his sole means of livelihood, my patient consulted the doctor who acted in the capacity of medical officer of health to the borough and put the problem to him. This learned doctor advised my patient to buy a large pipe, fill it to the brim, and light up as soon as he approached the toll gate on the outskirts of Gloucester. If he kept it going all the time he was in the city he "would be all right." He never did contract smallpox, and my patient continued with his carrier service and with his smoking. I was privileged to receive an invitation to his 100th birthday party, where I observed that he was still happily puffing away on his pipe.

Robert J House *is a retired general practitioner in Tewkesbury*

We welcome filler articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.