is no objective measure of success. Nor is melatonin free of drawbacks: if it is given to people in certain unusual environments (such as people who live continuously in dim light), sleep can become fragmented (unpublished data).

Melatonin has been reported to have some antioxidant and immunostimulant effects at high concentrations—but pro-oxidant and immunosuppressant effects have also been described.[1 2 12-14] Melatonin has been claimed to inhibit the growth of cancer cells in vitro, but it can promote melanoma growth in hamsters.[15 16] Clinical trials of its use as an adjunct to chemotherapy and immunotherapy are still at too early a stage for the results to be evaluated.

Melatonin has been investigated as a contraceptive, given at huge doses (75-300 mg daily) combined with a progestin minipill, and curiously no effects on sleep have been reported in these trials.[17] Side effects included abnormal bleeding and headache. It can affect human reproductive hormones in lower doses.

Claims that melatonin slows aging are apparently based on research using strains of mice with a genetic deficiency in the ability to make melatonin—making the results of dubious applicability to humans.[18] There is no scientific evidence at all that melatonin will extend the normal human lifespan, improve cardiovascular and sexual function, or cure Alzheimer's disease or AIDS, as claimed in some popular texts.

Safety remains uncertain

Questions of safety have yet to be resolved and so are of great importance. No doses have yet been agreed for any condition, although dose-response studies suggest that for clock related problems 5 mg is more efficient than lower doses.[6] Pharmacokinetic studies of melatonin have given variable results, probably because of a large hepatic first pass effect.[3] Virtually no data are available to compare the efficacy of various formulations in different conditions. Acute studies on rodents have found low toxicity,[19] but no data exist on long term studies in humans. The effects of melatonin on human puberty, in lactation, in pregnancy on mother and fetus, and in combination with other medication are unknown.

Melatonin is available in Britain only on prescription on a named patient basis. If the American health food industry were to use some of its profits for evaluations of safety and efficacy, that would be a service to the millions of Americans reportedly taking melatonin. In the meantime the development of different formulations, agonists, and antagonists is awaited with interest.

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Primary HIV-1 infection: a new medical emergency?

Recognition of this initial illness may permit early diagnosis and treatment

Patients with HIV-1 infection are usually not diagnosed until they present with an opportunistic infection, often several years after their initial seroconversion. Increasingly, however, it is recognised that many people suffer an acute mononucleosis-like illness shortly after seroconversion. Despite the protean manifestations of this initial infection, primary HIV-1 infection is now recognisable as a distinct clinical entity. The clinical findings are associated with the immune response to the rapid dissemination of HIV throughout the body and may represent an important early opportunity for diagnosis and intervention.

Primary HIV-1 infection has been described as a "mononucleosis-like illness of acute onset occurring 2-6 weeks after HIV-1 infection, usually resolving after 1-2 weeks, though occasionally lasting considerably longer."[1 2] It has been estimated that 53-93% of gay men who have recently acquired HIV undergo an acute seroconversion illness and that most of them remain undiagnosed.[3] Those with a severe and long lasting illness have a poorer long term prognosis.[4]

The symptoms associated with primary HIV-1 infection are shown in the box. The most specific include a maculopapular rash affecting predominantly the upper part of the body and mucosal ulcers affecting the mouth and genital areas. Patients may also present with a predominantly gastrointestinal syndrome, which includes abdominal pain, nausea, vomiting, diarrhoea, hepatitis, and even gastrointestinal haemorrhage. Rarer presentations of encephalopathy, pneumonitis, and rhabdomyolysis associated with acute renal failure may also be encountered. As severe acute immunosuppression may occur during primary HIV-1 infection, AIDS defining illnesses may also develop and should arouse suspicion of seroconversion in patients with a recent negative result on HIV testing.

Differential diagnosis

Clinically the differential diagnosis of this acute retroviral syndrome includes mononucleosis caused by Epstein-Barr virus or cytomegalovirus, toxoplasmosis, rubella, syphilis, viral hepatitis, disseminated gonococcal infection, herpes simplex virus, typhus, acute Crohn's disease, and other viral and spirochaetal illnesses. Syphilis remains the main differential

Clinical features of primary HIV-1 infection

General	Neurological
Fever	Retro-orbital pain
Anorexia	Headache
Weight loss	Meningitis
Malaise	Encephalitis
Lethargy	Myelopathy
Arthralgias	Peripheral neuropathy
Myalgia	Guillain-Barré-like syndrome
Lymphadenopathy	
Pharyngitis	
Gastrointestinal	**Dermatological**
Odynophagia	Erythematous macular or
Abdominal pain	maculopapular rash
Nausea and vomiting	Orogenital ulcerations
Diarrhoea	Oral candidiasis
Oesophageal ulcers	
Hepatitis	
Gastrointestinal haemorrhage	

diagnosis in cases with a rash and mucocutaneous ulceration, a rare occurrence in Epstein-Barr virus (except the ampicillin rash), cytomegalovirus, and toxoplasmosis.

The laboratory investigations required to confirm a clinical suspicion of primary HIV-1 infection are measurement of p24 antigen, which becomes detectable early after infection with HIV in many but not all cases, together with western blotting and the enzyme linked immunosorbent assay (ELISA) antibody test. If suspicion is high and these tests give negative results they should be repeated a few days later together with direct viral identification using the polymerase chain reaction. Other less specific laboratory signs include a CD4 lymphopenia, a CD8 lymphocytosis, mild anaemia, thrombocytopenia, abnormalities on liver function tests, and atypical lymphocytes.[2]

Figure 1 shows the immunological consequences of the host-viral relation.[5] During primary HIV-1 infection the peak of viral replication is associated with the widespread seeding of a relatively homogeneous viral population throughout the body. This coincides with the acute illness and activation of the immune system, which eventually reduces viral load.

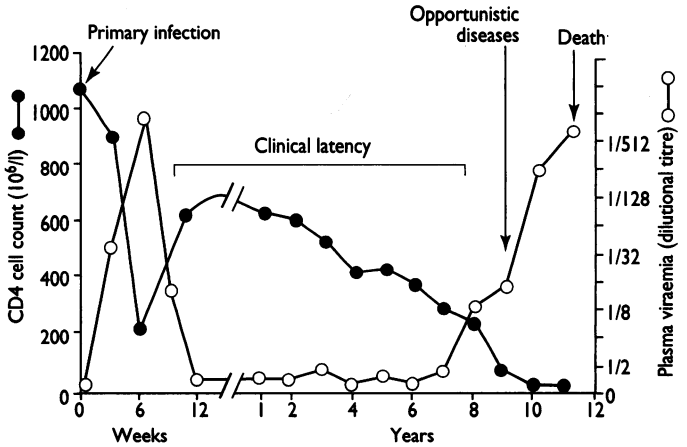

***Fig 1**—Changes in CD4 cell counts (●) and plasma viraemia (○) during HIV infection (modified from Fauci[5] with permission). During primary infection CD4 cell counts drop while plasma viraemia—measured by p24 antigen assay or polymerase chain reaction—is high, and in this early period HIV antibody levels can still be undetectable*

Recently, emphasis has been placed on early antiviral intervention, even as early as the "seroconversion illness," when it may be possible to limit the initial dramatic peak of viral dissemination and fall in CD4 cell counts. Without treatment the CD4 cell count bounces back to suboptimal levels after an initial drop (fig1), followed by an individually variable but relentless decline in CD4 numbers. Early antiretroviral treatment may alter this process, prevent the decline in CD4 cell count, and prolong a patient's disease free period and life expectancy. Preliminary data with zidovudine indicate that antiretroviral treatment is well tolerated, with a beneficial effect on both the CD4 cell count and the occurrence of minor opportunistic infections in the absence of new viral resistance.[6] It will be important to assess a "hit hard and early" approach using antiretroviral combination therapy from the rapidly growing number of drugs available.[7] Treatment should be started as soon as evidence of HIV infection is gathered and maintained for at least six months.[6]

Three challenges

Thus the challenges of primary HIV-1 infection are threefold. Firstly, it presents an opportunity to diagnose HIV infection early, before a patient presents with opportunistic infections and advanced collapse of the immune system. Secondly, it provides a chance to decrease transmission through early counselling and education. Thirdly, the recognition of primary HIV-1 infection as a clinical entity may allow us the opportunity to hit hard and early with the latest and most effective treatments. To meet these challenges will require effort from HIV referral centres to generate information about the clinical manifestations of primary HIV-1 infection. This in turn will facilitate its early recognition and permit referral of suspected cases for urgent p24 antigen and HIV serological testing as medical emergencies for early treatment.

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