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Journal review

Editorial Board

HIV / AIDS — crossing the barriers of specialisation

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In June 1981, a group of internists reported an unusual cluster of *Pneumocystis carinii* pneumonia (now known as *Pneumocystis jirovecii*) among previously healthy young adult male patients in the *Morbidity and Mortality Weekly Report* (MMWR), which was the first glimpse of the HIV/AIDS pandemic. In the past twenty-five years, the health care model for HIV-infected patients gradually shifted from internal medicine to be put under the care of the infectious disease specialists, and lately HIV/AIDS specialists. In the 46th ICAAC Conference held in San Francisco this year, Dr. Anthony S. Fauci, Director of National Institute of Allergy and Infectious Diseases at the NIH however, made a comment in his keynote lecture suggesting that this trend of specialisation will be reversed in the coming decade. Internists in various medical sub-specialties will once again take up active roles in the care of the HIV-infected patients [1].

There are several reasons why the care of HIV-infected patients will increasingly involve specialties other than infectious diseases. Firstly, the global epidemic of HIV/AIDS is still progressing, especially in certain developing Asian and African countries. As of year 2005, around 40 million individuals worldwide are infected with the virus, of which 8.3 million are residing in Asia [2]. In year 2005 alone, globally, 4.9 million individuals acquired the infection; 3 million people died in the same year. In Asia, 1.1 million people became newly-infected in year 2005, and 0.5 million died. Up to mid-2006, Hong Kong has a cumulative number of HIV-infected persons over 3000, and AIDS cases over 800 [3]. Besides, HIV/AIDS is not limited to MSM (men-having-sex with men) as once widely perceived by the public; heterosexuals, injecting drug users and recipients/donors of commercial blood products in fact constitute a large part of the HIV-infected population, especially in Asian countries [4]. Also patients with pre-existing medical illnesses (e.g. diabetes, hypertension) may acquire HIV infection through these routes during their life time. With this growing number of patients and their diversified background, internists in every medical subspecialty will likely encounter more HIV-infected patients during their routine clinical practice. Doctors should therefore be prepared and get
familiar with the various clinical manifestations of HIV/AIDS, including “acute retroviral syndrome”, common opportunistic infections, and HIV/AIDS-associated malignancies. *Mycobacterium tuberculosis* infections, extensive candidiasis, recurrent pneumonia, invasive cervical cancer in female patients, lymphoma and dementia are some examples of the indicator conditions that can be easily overlooked. Detailed history taking and physical examination together with a high index of suspicion is mandatory for the early diagnosis of HIV/AIDS. Early diagnosis, which may mean a higher baseline CD4 cell count upon treatment initiation, is an important determinant for survival [5]. Normalising HIV testing in health care setting (“opt-out offer”) is now increasingly being advocated [6].

In the HAART (Highly Active Antiretroviral Therapy) era, AIDS-related mortality declined significantly [7]. With the advancement of more potent and durable antiretroviral therapies, patient’s outcome is expected to improve further. Patients can now live long enough to develop non-HIV related diseases as in the rest of the population e.g. diabetes, hypertension, smoking-related diseases, as well as long-term toxicities of HAART. In a recent study analysing the causes of death among AIDS patients in New York City [8], one-fourth of these

deaths are non-HIV related, which had increased by 33% in 5 years. Cardiovascular disease, non-AIDS-defining cancer, and substance abuse account for most (76%) non-HIV-related deaths. Therefore it was suggested that to reduce these deaths, a shift in the health care model for AIDS patients from a primary focus on managing HIV infection to providing care that addresses all aspects of physical and mental health is required. Similar observations are made in other cohorts. In another multi-centre study, it was observed that over 10 years the proportion of deaths attributable to non-AIDS diseases increased from 13% to 42%, and prominently included hepatic, cardiovascular, and pulmonary diseases, as well as non-AIDS malignancies. Longer time spent receiving HAART and higher CD4 cell counts at initiation of HAART were associated with death from non-AIDS causes. CD4 cell count at time of death increased over ten years from 60 to 280 cells/μl [9]. In Hong Kong, again only 25% of deaths among HIV-infected persons were AIDS related [10]. There is ample evidence that in the HAART era, HIV/AIDS patients may not only die from profound immunodeficiency, but also succumb to co-morbidities during stages of relative immunocompetence. Managing HIV/AIDS patients thus require multi-disciplinary approaches and joint care by various specialists [11]. Some examples of the interface areas will include: chronic obstructive airway disease, lung cancers (respirologists); HIV and HBV or HCV co-infections (hepatologists); dementia, stroke and neuropathies (neurologists); ischemic heart disease, congestive heart failure, systemic and pulmonary hypertension (cardiologists); diabetes, hyperlipidaemia and lipodystrophies (endocrinologists); as well as various forms of renal diseases (nephrologists).

Finally, long-term toxicities of HAART are common and often difficult to manage, which pose huge challenges for the HIV/AIDS specialists. Some nucleoside analogue reverse transcriptase inhibitors (NRTIs) may lead to mitochondrial toxicities, resulting in complications like lipoatrophy, insulin resistances, lactic acidosis and neuropathies; whereas protease inhibitors (PIs) may result in gross hypercholesterolemia, hypertriglyceridaemia, insulin resistance, diabetes, as well as various forms of lipodystrophies. The mechanism of drug toxicity is still poorly understood, but a disrupted metabolic pathway involving SREBP-1 and PPAR-γ is believed to be responsible [12]. These metabolic complications may translate to elevated cardiovascular risks, resulting in clinical diseases and mortality [13,14]. It has been shown that the risk of myocardial infarction increases with the duration of HAART exposure [13,14]. It is therefore recommended that treated AIDS patients should undergo regular cardiovascular risk and body composition assessments and managed accordingly [15,16]. Apart from antiretroviral drug switching which is sometimes difficult, initiation of insulin sensitising drugs e.g. metformin, rosiglitazone, insulin therapies, “statins” or “fibrates” to control hyperlipidaemia, and even antihypertensives are necessary in many cases. Issues of polypharmacy, adverse drug reactions and drug-drug interactions with HAART are now posing additional challenges in the care of HIV/AIDS patients.

In conclusion, care of HIV/AIDS patients is now crossing the barriers after 25 years of specialisation. With the growing number of patients from new diagnosis and improved survival, together with the changing pattern of complications from HIV disease, internists in every subspecialty in the coming decade will need to be involved increasingly to provide best care for these patients.

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Anaemia in HIV-infected patients

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Anaemia is recognised to be a significant clinical problem in patients with HIV infection and AIDS. The frequency and severity of anaemia increase with disease progression [1]. In an early series of AIDS patients, the prevalence of anaemia is 15-30% during the early stages, but rises to 70-95% in the late stages [2]. Another review shows that the yearly incidence of anaemia is 3% in asymptomatic HIV infection, 12% in asymptomatic patients with CD4 <200/μL and 37% in patients with clinical AIDS [3]. The presence of anaemia is associated with decreased survival, independent of CD4 count. Recovery from anaemia, however, is associated with improved survival and quality of life [3,4].

Aetiology

Anaemia in HIV-infected patients is usually multi-factorial. The factors can be divided into those with decreased erythropoiesis or increased destruction.

Decreased erythropoiesis

1. Direct effect of HIV

   HIV can cause anaemia by direct infection of the haematopoietic stem cells or indirectly as a consequence of infection of the stromal (e.g. endothelial cells) or accessory cells (e.g. monocytes). The infected stromal cells have abnormal cytokine secretion and an impaired capacity to support colony growth. Findings from 2 reviews [5,6] favours stromal or accessory cell dysfunction as the principal mechanism rather than viral infection of stem cells.

2. Opportunistic infections

   Patients with AIDS suffer from frequent bacterial, viral and fungal infections. Recurrent infections can lead to anaemia of chronic illness, which is a normochromic normocytic anaemia with low reticulocyte count, low serum iron and total iron binding capacity. The most common cause is mycobacterial infection, including atypical mycobacteria and *Mycobacterium tuberculosis* [1]. Disseminated penicilliosis is also relatively common as a cause of anaemia in this part of the world. Cytomegalovirus can cause anaemia together with neutropenia. Parvovirus B19, although rare, can cause chronic pure red cell aplasia, which is potentially life threatening [7]. It is characterised by a very low reticulocyte count, absence of erythroid precursors with giant pronormoblasts in the bone marrow. Diagnosis depends on detection of viral DNA in the serum or identification of viral antigens or viral DNA in bone marrow. The neutralising antibody levels against parvovirus are very low or absent.

3. Marrow infiltration by malignant cells

   Extranodal disease, including that of the bone marrow, is common with non-Hodgkin's disease in HIV infected patients. Most are of B-cell phenotype and belong to the high or intermediate grade. Hodgkin's disease and Kaposi's sarcoma are less common causes.

4 Iron deficiency

   Gastrointestinal bleeding may be a result of intestinal lymphoma, Kaposi's sarcoma, opportunistic infections like CMV. The anaemia is microcytic hypochromic. Reticulocyte count, serum iron and ferritin levels are low but the total iron binding capacity is elevated.

5. Nutritional deficiencies

   Vitamin B12 and folate deficiencies can be due to reduced dietary intake and intestinal

malabsorption. A decreased serum cobalamin level is also found in 10-30% of AIDS patients [8]. Typical macrocytic anaemia with hypersegmented neutrophils and frank megaloblastic changes in the bone marrow are not commonly seen.

6. Drugs

Drugs are responsible for 20% of anaemia in AIDS patients [3]. Nucleoside reverse transcriptase inhibitors, especially zidovudine, and less commonly stavudine can cause macrocytic anaemia. Macrocytosis is marked and almost invariable with zidovudine. Drugs used for treatment of opportunistic infections e.g. septrin, pyrimethamine, amphotericin B, rifabutin, isoniazid, and ganciclovir may also have myelosuppressive side effects.

Increased destruction

1. Autoimmune haemolytic anaemia

The presence of antibodies directed against red cell antigens is more common than overt haemolysis. A positive direct antiglobulin test has been found in 18% of patients with AIDS compared with <1% of non-infected blood donors [9]. It may be part of the polyclonal hypergammaglobulinaemia found in HIV-infected patients. The serum haptoglobin is low with microspherocytes on peripheral smear. Indirect bilirubin and serum LDH are elevated. Bone marrow shows erythroid hyperplasia. Reticulocytosis may be lacking if there is concomitant anaemia of chronic disease.

2. Drug-induced haemolysis

Ribavirin used for treatment of hepatitis C can lead to haemolysis. Primaquine and dapsone can provoke oxidative haemolysis in patients with G6PD deficiency. Hemolytic anaemia has been reported with indinavir but is rare in practice..

3. Microangiopathic haemolytic anaemia

HIV/AIDS is associated with an increased incidence of thrombotic thrombocytopenic purpura (TTP). It is responsible for as many as 3% of HIV-related deaths [12]. Patients will have haemolytic anaemia, thrombocytopenia, azotaemia and changes in mental status. The peripheral blood smear typically shows marked schistocytes, polychromasia and nucleated red blood cells. TTP is also associated with prolonged use of valacyclovir in patients with low CD4 count.

Diagnosis

Complete blood picture should be checked with particular attention to the mean corpuscular volume and any concomitant leukopenia and thrombocytopenia. Reticulocyte count and peripheral blood smear are often useful. Other tests e.g. serum iron, total iron binding capacity, stool occult blood, vitamin B12, folate, lactate dehydrogenase, direct and indirect bilirubin, haptoglobin, direct antiglobulin test, G6PD level and serum creatinine should be obtained according to the clinical suspicion. The stage of the patient's HIV infection should also be assessed with the drug history carefully reviewed.

Bone marrow aspiration can be used to assess the iron stores, infiltration by infection or neoplasm. It often shows characteristic but non-specific changes e.g. plasmacytosis and lymphoid aggregates which correlate to serum polyclonal hypergammaglobulinaemia [10]. More than 70% of patients will have a normocellular marrow [11], but myelodysplastic changes with increased cellularity are sometimes seen. Frank megaloblastic changes can be seen in patients treated with zidovudine, and less commonly in severe vitamin B12 or folate deficiencies. Poorly formed granulomas, serous atrophy, marrow necrosis, and haemophagocytosis are less commonly found.

Management

Treatment should begin with therapy of HIV infection and correction of reversible causes of anaemia. Any identified opportunistic infection or malignancy should be appropriately treated. Supportive care by blood transfusion and erythropoietin are important strategies if the underlying cause cannot be corrected.

In patients with anaemia of chronic disease due to advanced HIV infection, effective antiretroviral therapy may correct the anaemia and improve the quality of life [13]. Chronic pure red cell aplasia due to parvovirus B19 infection should be treated with intravenous immunoglobulin. Re-treatment may be required for relapse or as maintenance therapy [7,14]. Antiretroviral therapy is also helpful in achieving and maintaining remission.

Iron deficiency anaemia is treated by identification and correction of the source of blood loss and with iron supplementation. Patients with vitamin B12 or folate deficiencies should receive supplementation.

Treatment of autoimmune haemolytic anaemia is the same as in the non HIV-infected. It includes glucocorticoids, IVIG and splenectomy. Zidovudine therapy has also been shown to improve autoimmune haemolytic anaemia [15]. Thrombotic thrombocytopenic purpura is also treated similarly to that of the non HIV-infected, by intensive plasma exchange, fresh frozen plasma infusions, anti-platelet agents and corticosteroids.

When anaemia is due to adverse affect of a medication, the drug should be withdrawn as far as possible. If the medication is necessary and no acceptable alternatives are available, supportive care with growth factors or transfusion may be employed.

Recombinant erythropoietin is useful for anaemia caused by advanced HIV infection, zidovudine and cancer chemotherapeutic agents [16,17]. It has been shown to increase haemoglobin levels, decrease transfusion requirements and improve quality of life in AIDS patients [17]. It is also associated with reduced disease progression and mortality in HIV patients.

The need for blood transfusion should be based on the patient's symptoms and cardiopulmonary status but not solely on the level of haemoglobin. Appropriate use of blood transfusion improves symptoms but there are a number of special concerns in the HIV-infected patients.

Some studies show a decreased survival of AIDS patients who are given blood transfusion [18]. HIV viral loads increase several weeks after transfusion which may due to stimulation of lymphocytes after exposure to exogenous antigens in the packed cells. Another concern is transmission of blood borne viruses, especially CMV to CMV negative patients. Moreover, iron overload resulting from repeated transfusion may theoretically increase progression of HIV infection since increased iron level in macrophages leads to activation of the HIV [19], development of hepatic fibrosis and predilection for other infections [20].

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Neurological complications in HIV infection

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Epidemiology

Neurological manifestations most commonly occur as a result of opportunistic infections before the introduction of highly active anti-retroviral therapy (HAART). The incidence rates of these complications (including cryptococcal meningitis, toxoplasmosis and CMV encephalitis) and primary lymphoma of central nervous system (CNS) have declined since 1996. HIV, however, can also infect the nervous system directly, resulting in diseases like HIV encephalopathy, vacuolar myelopathy and peripheral neuropathy. These latter diseases also declined in incidence by up to 50% in the past decade. However, their incidence may rise in the future as a consequence of expected longer life expectancy. Disease manifestation may also be altered with HAART [1,2].

HIV encephalopathy

HIV encephalopathy usually occurs with significant immunosuppression at CD4 count below 200/μL, and is an important predictor of death in the HAART era. It classically produces a triad of cognitive, behavioural and motor dysfunction, often developing over a matter of weeks or months [3]. Focal neurological deficits and seizures are not typical of this disease. The HIV dementia scale can be used for earlier detection and rating of cognitive impairment in patients with HIV encephalopathy [4].

Non-specific cerebrospinal fluid (CSF) abnormalities, like raised protein level and increased IgG, can be present; but CSF examination is most useful to exclude opportunistic infections, including *Mycobacterium tuberculosis*, cryptococcus, cytomegalovirus and JC virus. CSF HIV viral load may correlate with severity of neurological deficits, but only in anti-retroviral treatment-naive patients [3]. MRI typically shows cortical and sub-cortical atrophy, and confluent, diffuse and relatively symmetrical deep white matter signal abnormalities. This contrasts with the more discrete, scattered and asymmetric white matter lesions in progressive multifocal leukoencephalopathy (PML).

The main goal of treatment is optimal suppression of viral replication in CNS. Choosing anti-retroviral therapy with better CSF penetration is important. Examples include zidovudine, lamivudine, nevirapine and indinavir [3]. Protease inhibitors attain low CSF concentrations due to the presence of multidrug-resistant proteins on endothelial cells, which act as active efflux pumps in the brain [5]. Poor control of CSF viral load despite good peripheral blood viral suppression was described in patients with progressive HIV dementia. Variable CSF penetration of different anti-retroviral drugs may result in ongoing viral replication in the CNS, resulting in drug selection pressure and drug resistant mutations in the CNS. Therefore, genotypic analysis in the CSF should be considered if CSF HIV RNA is detected despite anti-viral therapy [3].

Vacuolar myelopathy

Vacuolar myelopathy is characterised by painless progressive paraparesis, sensory ataxia and neurogenic bladder. It commonly occurs with the development of dementia. Its name was derived by the vacuolar changes in the spinal cord, particularly in the cervical and thoracic regions. Disturbance in cobalamin-dependent transmethylation contributes to its pathogenesis. Methionine supplement has been shown to improve electrophysiological parameters [3].

Peripheral nervous system diseases

A wide spectrum of diseases involving the peripheral nervous system (PNS) have been

described in HIV patients, including sensory neuropathy, inflammatory demyelinating polyneuropathy, mononeuritis multiplex, progressive polyradiculopathy, motor neuron disease and polymyositis. Among these entities, distal sensory polyneuropathy is the most common neurologic complication in HIV infection.

Distal sensory polyneuropathy has been described in 30-60% of HIV patients in various studies, mostly based on electrophysiological criteria, and is associated with lower CD4 count. Patients usually have symptoms of pain, with bilateral involvement and most severe on the soles. Axonal, length-dependent sensory polyneuropathy is demonstrated on nerve conduction test. Tricyclic antidepressants and anticonvulsants have been shown in clinical trials to be effective for improving neuropathic pain [3,6].

Neuropathy can also occur as a result of toxicity from specific anti-retroviral drugs, most notably dideoxynucleosides, such as stavudine, didanosine and zalcitabine. Mitochondrial toxicity is the presumed mechanism of axonal injury. Such adverse effects limit the use of these agents as first-line therapy for HIV infection in developed countries [3].

Impact of HAART on neurological complications of HIV infection

The clinical course of HIV encephalopathy has been altered after the introduction of HAART, resulting in various clinical subtypes. Patients with successful virological suppression may have reversible neurological deficits, or may live with a chronic inactive form of dementia with stable neurological status. On the other hand, patients with incomplete virological suppression continued to have slowly progressive chronic active dementia [3].

Although the incidence of HIV encephalopathy has declined, autopsy studies showed up to 30-45% of patients had evidence of HIV encephalopathy in the HAART era. Severe disease is uncommon, but mild and moderate HIV encephalopathy persists [1]. Long-term survival, which is expected in the HAART era, was shown to increase the risk of HIV encephalopathy. Production of early gene proteins, including Tat which induces various effects on brain cells, is not inhibited by any of the reverse transcriptase inhibitors or protease inhibitors, after the HIV genome is incorporated into the host chromosome [5]. This may explain the persistence of cognitive impairment in patients treated with HAART. A highly destructive form of leukoencephalopathy was also described in patients on anti-retroviral therapy but poor viral suppression, probably as a result of drug resistance [7].

Immune reconstitution inflammatory syndrome (IRIS) also occurs as a consequence of HAART. IRIS involving the CNS was reported following initiation of anti-retroviral therapy, in cases of cryptococcal meningitis, PML and HIV encephalitis. Although corticosteroid has been reported to improve outcomes in some cases, the management of IRIS is still controversial [8].

Impact of concurrent infections on neurological complications

Syphilis

HIV may alter the clinical course and management of syphilis. There is no consensus of when lumbar puncture should be performed. Most specialists perform lumbar puncture when patient presents with late latent syphilis, when neurological manifestations were present, or when a high titre on serological test is detected. Others perform the procedure in all patients with HIV infection [9,10].

Hepatitis C virus (HCV)

Increasing evidence shows that HIV-HCV co-infection increases neurological complications compared with infection by either virus. HCV infection is associated with neurocognitive

deficits, suggestive of frontal-subcortical dysfunction, and neuropsychiatric disorders. HCV exerts both direct and indirect effects on the brain, via neuroendocrine and neurotransmitter dysfunction. Confounding factors like substance abuse also play a role in the pathogenesis. A synergistic effect on viral replication of these two viruses may explain the higher prevalence of neurological symptoms with co-infection [11].

Conclusion

Neurological manifestations are common in HIV infection even in the HAART era. Increasing research is being performed in this area. Better understanding of the various effects of the virus on the nervous system will aid the development of new therapies in the control of the virus as well as its neurological consequences on the host.

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Journal review

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Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575-80.

The emergence of TB strains resistant to ≥3 classes of second-line drugs, termed "extensively drug resistant" TB (XDR-TB), is rapidly becoming a cause for great concern. Investigators recently assessed the prevalence and outcome of XDR-TB at a South African rural hospital (40% of inpatients being HIV-infected). Three groups of patients were included: patients with smear-positive or recurrent TB for whom cultures were done between January and May 2005; all inpatients on the TB wards on a single day in February 2005; and inpatients and outpatients with suspected TB who presented between June 2005 and March 2006. Sputum samples were obtained for culture and susceptibility testing. Among 1539 patients, 542 were found to be culture-positive. Multidrug-resistant (MDR, defined as resistance to isoniazid and rifampin) TB was identified in 221 patients (41%), including 53 (10%) with XDR-TB (defined as resistant also to ethambutol, streptomycin, aminoglycosides, and fluoroquinolones). The median age of patients infected with XDR-TB was 35 years. Over half (55%) of the patients had never received treatment for TB before; 67% had been admitted to the same rural hospital within last 2 years. All 44 tested were HIV-infected. There was apparently no between-patient contact except for healthcare at the same hospital. Majority (98%) of the patients (including two healthcare workers at the hospital) died. Based on genotypic analysis performed on 46 of the isolates, 85% were found to be genetically related.

Points to note: XDR-TB has emerged because of inadequate TB-control programs. Its full extent is currently unknown due to inadequate mycobacterial cultures and drug-sensitivity testing in many resource-limited areas. The results of the study clearly show that XDR-TB can spread nosocomially and is extremely lethal, especially in areas with high HIV prevalence and inadequate infection control. Urgent global interventions to address this problem are now urgently required. It is of note that CDC, in collaboration with WHO, has recently updated their case definition of XDR-TB. It is now defined as isolates resistant to isoniazid and rifampin, as well as to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naive and treatment-experienced patients. J Acquir Immune Defic Syndr 2006; 43: 1-5.

HIV resistance to currently available classes of antiretroviral therapy necessitates the continuous development of new drugs aiming at novel viral targets, and the HIV integrase is one such target. Investigators recently conducted a double-blind study of GS-9137, a new integrase inhibitor manufactured by Gilead. Forty treatment-naive and experienced HIV-infected patients were randomised to receive 10 days of monotherapy with GS-9137 or placebo at 200, 400, or 800 mg twice daily; 800 mg once daily; or 50 mg once daily co-administered with 100 mg of ritonavir, which is capable of boosting the levels of the experimental drug to above the estimated therapeutic level for an extended period of time. Antiviral activity was significantly better with GS-9137 than with placebo at all of the doses studied. Participants receiving 400 or 800 mg twice daily or 50 mg with ritonavir once daily had viral load declines of more than 1.9 log10 copies/mL. No integrase inhibitor resistance

was detected.

Points to note: HIV integrase is a promising new target for new antiretroviral drugs. Another drug company, Merck, is testing an integrase inhibitor in phase 3 studies, and the drug will soon become available for clinical use. GS-9137 is also progressing well through clinical trials. It is hoped that integrase inhibitors will provide a new class of medications for HIV-infected patients whose virus is resistant to currently available therapies.

Laufer MK, Thesing PC, Eddington ND, et al. Return of chloroquine antimalarial efficacy in Malawi. N Engl J Med. 2006; 355: 1959-66.

It is well-known that malarial parasites have become increasingly drug-resistant, and resistance has also spread geographically. In 1993, when the efficacy of chloroquine (CQ) against falciparum malaria dropped to below 50%, Malawi decided to replace this agent countrywide with sulfadoxine-pyrimethamine (SP) for first-line treatment of uncomplicated malaria. In one Malawian city, researchers measured the on-going prevalence of a molecular marker associated with CQ resistance. Because the marker became less prevalent and then disappeared from this area in 2001, they decided to reassess the efficacy of CQ. In a trial conducted in 2005, they randomised over 200 children aged 6 months to 12 years with uncomplicated falciparum malaria to receive directly observed CQ or SP and followed them for 28 days. Non-responders were treated with halofantrine. Among study completers, treatment failure occurred in 1 of 80 in the CQ group and 71 of 87 in the SP group, corresponding to efficacies of 99% and 21%, respectively. Assays on blood collected at enrolment found that all specimens had the wild-type genotype associated with susceptibility to CQ.

Points to note: Although these findings suggest that SP is no longer effective in Malawi and that parasites in this population have become susceptible to CQ, experts caution against returning to CQ as first-line monotherapy. Although CQ is safe, inexpensive, rapid-acting, and well tolerated, it no longer works in most malarious areas, including those countries neighbouring Malawi. Thus, wide-spread use of CQ would favour the emergence of resistance. Artemisinin-based combination therapy is now the preferred treatment for falciparum malaria, but these drugs are expensive and are not yet available for routine use in Africa. It is postulated that if CQ were withdrawn throughout Africa, it might become useful again in some settings in the future.