

III. SPECIAL CONSIDERATIONS FOR THE CARIBBEAN: MANAGEMENT OF THE PATIENT WITH HIV AND SICKLE CELL DISEASE, DENGUE FEVER, MALARIA, OR HTLV-1

TABLE OF CONTENTS

HIV AND SICKLE CELL DISEASE	III-1
Epidemiology	III-1
Clinical Manifestations	III-1
Management of the Patient with Co-Morbid SCD and HIV Infection.....	III-1
Paediatric Considerations.....	III-2
HIV AND DENGUE FEVER	III-2
Epidemiology	III-2
Management of the Patient with Dengue Fever and HIV Infection.....	III-2
Documentation	III-2
HIV AND MALARIA	III-2
Epidemiology	III-2
Clinical Manifestations	III-3
Diagnosis.....	III-3
Management of the Patient with Malaria and HIV Infection.....	III-3
Interactions between Malaria and HIV	III-3
Considerations for Pregnant Patients with Malaria and HIV or at Risk for Co-Infection.....	III-4
Other Treatment Considerations for Patients with Malaria and HIV.....	III-4
Prevention Considerations.....	III-5
Policy Recommendations.....	III-5
HIV AND HTLV-1	III-5
Epidemiology	III-5
Clinical Manifestations	III-5
Possible Interactions between HTLV-1 and HIV.....	III-6
Diagnosis.....	III-6
Treatment	III-6
Prevention	III-6
REFERENCES	III-7

HIV AND SICKLE CELL DISEASE

EPIDEMIOLOGY

Sickle cell disease (SCD) is a genetic disorder that is characterised by a chronic anaemia occurring almost exclusively in individuals of African descent. Individuals afflicted with SCD are homozygous for a key mutation in haemoglobin, whereas individuals who are heterozygous for this mutation are generally asymptomatic and are said to have *sickle cell trait*. SCD is relatively common throughout the Caribbean and could present some unique clinical management issues as a co-morbidity with chronic HIV infection.

CLINICAL MANIFESTATIONS

The clinical manifestations of SCD are due to both anaemia and vaso-occlusive events that result in tissue ischemia and infarction. SCD patients suffering from painful vaso-occlusive events are said to be in *sickle cell crisis*. Common causes of death for individuals with SCD are intercurrent infections, multiple pulmonary emboli, occlusion of a vessel supplying a major organ, and renal failure. The average life span of SCD patients is age forty to forty-five years.

Anaemia in SCD is usually stable but acute exacerbation of anaemia occurs in the setting of aplastic crisis, in which marrow red blood cell (RBC) production abruptly slows down. Aplastic crisis is usually the result of an acute infection; hence immunocompromised patients may be at higher risk for this complication. Individuals with sickle cell trait who are also HIV-infected are not expected to have significant worsening of any manifestations of their HIV disease or of their sickle cell trait.

MANAGEMENT OF THE PATIENT WITH CO-MORBID SCD AND HIV INFECTION

General Principles of Management

Infection with encapsulated organisms is more common in SCD patients with functional asplenia. HIV co-infection also appears to increase susceptibility to these infections, especially in children. Prophylactic antibiotics, pneumococcal vaccine, and early identification and treatment of serious bacterial infections are therefore critical.

The use of hydroxyurea (HU) in SCD is well established, and its use for treatment of HIV disease has been investigated. However, data from controlled clinical trials have revealed high rates of toxicity (e.g. pancreatitis, neuropathy, hepatotoxicity, and cytopenias) and blunted CD4+ T cell count responses in patients receiving HU with antiretroviral therapy (ART). Current guidelines therefore suggest that HU should generally not be offered as adjunctive therapy for HIV infection. Unfortunately, no data exist from controlled clinical trials involving patients with SCD who receive HU with ART. Clinicians considering the use of HU for HIV-infected patients with SCD should be aware of the potential additional toxicity of this agent when administered with nucleoside reverse transcriptase inhibitors (NRTIs).

Management of Anaemia

Anaemia is a common consequence of SCD, HIV disease, and some antiretroviral (ARV) agents, especially zidovudine (AZT). Therefore:

- √ Patients should be screened for anaemia prior to initiation of ART;
- √ The design of ARV regimens for patients at risk for anaemia should take into account the potential of individual agents to induce or exacerbate anaemia;
- √ Monitoring of haemoglobin levels is warranted after initiation of therapy, especially for patients with SCD or other risk factors for anaemia;
- √ ARV-induced anaemia typically improves once the offending agent is discontinued. Thus, appropriate modification of a patient's ARV regimen is advisable in the case of anaemia that is attributable to one or more of the prescribed ARV agents.

Management of Sickle Cell Crisis

Therapy is largely symptomatic for the sickle cell crisis. Standard interventions include rehydration, analgesics, and oxygen therapy. The presence of HIV infection in a patient suffering from a sickle cell crisis does not alter this general approach.

PAEDIATRIC CONSIDERATIONS

Splenic malfunction is common in both SCD and HIV infection. Therefore, several of the common infections seen in SCD also occur in HIV-infected children. However, while these two patient populations are not uncommon in the Caribbean, none of the publications on cohorts of children with HIV disease or sickle cell anaemia have described children afflicted with both disorders. Caribbean studies of pneumococcal and/or *Haemophilus influenzae* Type B infections have similarly failed to document outcomes involving children with both SCD and HIV infection.

HIV AND DENGUE FEVER

EPIDEMIOLOGY

Dengue is endemic in the Caribbean. Many dengue fever outbreaks have been documented in the region with all three types of viruses (type 1, 2 and recently type 3). However, not enough data exist to draw a firm conclusion regarding the relationship between dengue fever and HIV. The natural history and clinical manifestations of co-infection with HIV and dengue has not been established; CAREC therefore encourages Caribbean clinicians and researchers to investigate this issue.

MANAGEMENT OF THE PATIENT WITH DENGUE FEVER AND HIV INFECTION

Caribbean clinicians should be careful when using ARV drugs or agents to treat HIV-related conditions that may induce anaemia or haemorrhagic reactions since these two clinical manifestations are common among patients infected with dengue. Close monitoring is warranted for these complications among HIV-infected individuals who contract dengue fever.

DOCUMENTATION

Given the paucity of data on this topic, clinicians *must document* a history of dengue infection among HIV-infected patients, as well as any observed unusual or unexplained clinical manifestations or adverse effects of medications used to treat HIV and HIV-related conditions among persons co-infected with HIV and dengue.

HIV AND MALARIA

EPIDEMIOLOGY

Malaria is endemic in Belize, the Dominican Republic, French Guiana, Guyana, Haiti, and Suriname. Other countries may also see sporadic cases of malaria infection due to migration and tourism. In endemic countries, the intensity and periodicity of malaria transmission and the predominant *Plasmodium* species vary broadly. For example, in Haiti and the Dominican Republic, nearly all malaria is caused by *P. falciparum*, and the annual parasitic index (API, or number of confirmed malaria cases per 1,000 population at risk) is 2.1. In contrast, in Suriname, where malaria transmission is more intense than anywhere else in the Americas, the API is 370.8, with cases contributed by three different species of malaria: *P. falciparum* (approximately 80% of cases), *P. vivax* (10%), and *P. malariae* (10%).¹

Drug resistance patterns also vary within the region. Although chloroquine-susceptible malaria, particularly *P. vivax*, still occurs, resistance to both chloroquine and sulfadoxine-pyrimethamine (SP) has become widespread particularly in the Amazon River basin, where some degree of *P. falciparum*

resistance to mefloquine and *P. vivax* resistance to primaquine have also been observed.² Because antimalarial drug resistance is evolving rapidly in many sites, the Pan American Health Organization (PAHO), in conjunction with the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID), has recently established a network for ongoing evaluation of antimalarial drug resistance, for the purpose of guiding antimalarial drug policy.³ Some countries with particularly high burdens of antimalarial drug resistance are now introducing artemisinin-based combination therapies, such as artemether/lumefantrine, as recommended by recent World Health Organisation (WHO) guidelines.^{4,5}

CLINICAL MANIFESTATIONS

In both HIV-infected and -uninfected persons, clinical syndromes caused by malaria infection vary depending on transmission patterns (stable vs. unstable), *Plasmodium* species (*P. falciparum* vs. others), and host immunity (related to age, transmission intensity, nutritional status, and HIV infection). At its most symptomatic, malaria causes acute febrile syndromes that may be complicated by seizures, coma, renal failure, and/or death. The clinical spectrum of malaria also includes chronic, often severe, anaemia in the otherwise asymptomatic person.⁶ Although often undiagnosed until its later stages, malaria-related anaemia is associated with more fatalities than any other malaria-related syndrome.⁷ Because of the great variation in malaria species and transmission patterns in the Caribbean region, predominant clinical syndromes will vary by site. Increased vigilance for anaemia is warranted in HIV-infected patients at risk for malaria (especially in those who have other risk factors for anaemia, such as AZT use), and clinical suspicion of malaria is warranted in the HIV-infected patient with unexplained anaemia or fever.

DIAGNOSIS

Although rapid tests for detection of *Plasmodium* species are currently being developed and evaluated, inspection of stained blood smears for the presence of malaria is still the standard means of diagnosis. Where multiple *Plasmodium* species are endemic, laboratory diagnosis should seek both to detect malaria and to classify the infecting species. Creation of new laboratory capacity may be required in some sites.

MANAGEMENT OF THE PATIENT WITH MALARIA AND HIV INFECTION

Malaria infection can be rapidly fatal, especially in non-immune patients. Therefore, prompt diagnosis and rapid administration of effective treatment must be easily available to patients where malaria is endemic. Appropriate treatment for malaria infection depends on several factors: the severity of infection; the responsible *Plasmodium* species (bearing in mind that mixed infections may occur); the pregnancy status of the patient; local antimalarial drug-resistance patterns; national drug policy and availability; and the likelihood of interactions or overlapping toxicities involving antimalarials and other medications the patient may be taking, including ARV agents and other medications used in the management of AIDS and its complications. Clear treatment guidelines devised to respond to varying local conditions should be created at national (or regional) levels and should be updated frequently in response to changing drug-resistance and transmission patterns.

The differential diagnoses of fever and anaemia are broad in the HIV-infected patient. In order to avoid the unnecessary prescription (with resultant risks of toxicity and resistance) of antimalarials, it is important to encourage laboratory confirmation of malaria infection prior to treatment (other than prophylaxis in pregnancy) and to discourage patients from self-treatment with antimalarials where these agents are available without prescription.

INTERACTIONS BETWEEN MALARIA AND HIV

HIV infection appears to increase both the susceptibility to and the severity of malaria infection. Most of our understanding of the interaction between malaria and HIV comes from studies performed in Africa, primarily involving infection with *P. falciparum*.

International literature suggests that HIV-infected patients appear to be more susceptible to acquiring malaria infection,⁸ particularly if they are pregnant. Both the prevalence of malaria parasitaemia and the incidence of clinical attacks of malaria are greater in patients with HIV-induced immunosuppression. Furthermore, the risks of severe malaria and malaria-related death appear to be increased significantly in HIV-infected patients of all ages who live in regions where malaria transmission is unstable.⁹

The influence of malaria on HIV infection is not as well characterised, but malaria infection appears to increase the HIV viral load, which could result in an increased rate of HIV disease progression as well as an increased risk of HIV transmission to others.¹⁰

CONSIDERATIONS FOR PREGNANT PATIENTS WITH MALARIA AND HIV OR AT RISK FOR CO-INFECTION

Malaria infection is more common in pregnancy, especially in primigravidae and in the HIV-infected of any gravidity.¹¹ Although malaria in pregnancy is commonly asymptomatic, its consequences may include severe maternal anaemia, maternal death, and low infant birth weight, regardless of maternal HIV status. Infants born to HIV-infected mothers with malaria are more likely to die¹² and are approximately twice as likely to be infected perinatally with HIV if a high placental burden of malaria exists in the mother.¹³ Intermittent preventive treatment (IPT) with antimalarial agents (usually SP) during pregnancy improves pregnancy outcomes in regions of intense transmission of *P. falciparum*, probably by reducing maternal malaria parasitaemia and placental malaria burden. The WHO now recommends IPT for malaria in pregnancy in countries with high burdens of *P. falciparum* malaria.¹⁴

IPT regimens are not yet well-defined in regions where *P. falciparum* is not the predominant strain of malaria, where transmission is infrequent, or where there are high levels of resistance to SP and chloroquine. Where the risk of malaria is low, WHO recommends aggressive management of symptomatic malaria cases and regular use of insecticide-treated bednets (ITNs), rather than IPT. The safety of many newer antimalarials has not yet been well-established for use in pregnancy.¹⁵ Therefore, guidelines for treatment of symptomatic malaria in pregnancy may require frequent revision as new data become available.

Prophylactic co-trimoxazole (TMP-SMX) has been shown to reduce the prevalence of malaria parasitaemia and the incidence of symptomatic malaria in non-pregnant adults in some settings.¹⁶ Therefore, the WHO now recommends that preventive SP not be given to HIV-infected pregnant women who take daily TMP-SMX.¹⁷ However, no studies have yet demonstrated the effectiveness of daily TMP-SMX prophylaxis for prevention of malaria complications in pregnancy, and the eventual development of malaria resistance to TMP-SMX could limit the durability of this drug's usefulness for malaria prevention.

OTHER TREATMENT CONSIDERATIONS FOR PATIENTS WITH MALARIA AND HIV

SP Treatment in Patients Taking Daily TMP-SMX

As noted above, TMP-SMX has antimalarial activity with an efficacy similar to that of chloroquine or SP in some studies.¹⁸ Unfortunately, TMP-SMX and SP are chemically similar enough that clinically significant cross-resistance between the two agents is common. Hence, patients on prophylactic TMP-SMX probably should not be treated with SP for symptomatic malaria where better options exist. Some fear that cross-resistance could hasten the loss of SP as an effective antimalarial agent in regions where TMP-SMX use becomes widespread.^{19,20} However, as artemisinin-containing combination regimens supplant chloroquine and SP as first-line antimalarial agents, this issue may become less important.

Management of Fever in Children

Current WHO Integrated Management of Childhood Illness (IMCI) guidelines for malaria-endemic regions recommend presumptive treatment of fever in children age five years or younger. TMP-SMX is endorsed because of its effectiveness for treatment of both pneumonia and malaria.²¹ Where TMP-SMX is being used prophylactically in large populations over a long period of time, it may lose its efficacy in

treating pneumonia, otitis, and malaria due to the development of drug resistance.^{22,23} The introduction of new paediatric AIDS treatment initiatives may require revision of local IMCI algorithms.

Drug-Drug Interactions and Overlapping Toxicities

Some ARVs and antimalarials are known to have overlapping side effect profiles. For example, both nevirapine (NVP) and SP have been associated with Stevens-Johnson syndrome and hepatic necrosis.^{24,25,26} SP and AZT have both been associated with bone marrow suppression, and the manufacturers of pyrimethamine (PZA) note that severe anaemia may result from co-administration of PZA and AZT.²⁷ There is little published or anecdotal information on drug interactions between newer antimalarials and ARVs, although concerns about potential drug-drug interactions have been raised regarding the co-administration of lumefantrine or halofantrine with many protease inhibitors (PIs). Similar concerns exist regarding the co-administration of quinine or atovaquone with various PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).²⁸ Increased vigilance for adverse drug reactions is advisable when treating malaria in the patient who is also taking ARVs.

PREVENTION CONSIDERATIONS

Use of ITNs prevents malaria-related morbidity and mortality.²⁹ ITN use is strongly recommended by the WHO and others for children age five years or younger and pregnant women in areas where malaria is endemic.³⁰ In malaria-endemic regions, ITN use should also be recommended to all HIV-infected persons. Where feasible, indoor residual spraying of insecticides should also be considered to prevent malaria transmission.

POLICY RECOMMENDATIONS

In malaria-endemic regions, management guidelines and policies must be based upon regional incidence, prevalence, and transmission patterns, as well as patterns of antimalarial drug resistance. Where these data do not exist, efforts should be made to collect them. Close collaboration between national and regional malaria and HIV control programs is essential for effective, evidence-based policy making. This collaboration will be especially critical in developing diagnostic and management guidelines for HIV-infected persons who develop febrile syndromes and/or anaemia, and for HIV-infected pregnant women who are simultaneously eligible for prophylactic antimalarial regimens and long-term ART. Because of the paucity of available information on drug interactions involving newer antimalarial drugs, ARVs, and other medications involved in management of AIDS, pharmacovigilance directed toward detection of drug interactions involving these agents is also strongly advised.

HIV AND HTLV-I

EPIDEMIOLOGY

HTLV-1 seroprevalence rates in the Caribbean vary from 0.3% to 7% in the general population, to 2% to 7% in pregnant women, and 5% in HIV-infected persons.³¹ Although HTLV-1 and HIV have similar routes of transmission (perinatal, parenteral, and sexual), transmission of HTLV-1 is less efficient.³² Sexual transmission is more frequent from male-to-female than *vice versa*.³³ Perinatal transmission of HTLV-1 occurs primarily via breastfeeding, and although breastfeeding for more than six months is a significant risk factor for perinatal transmission, periods less than six months may, in fact, protect against transmission.³⁴

CLINICAL MANIFESTATIONS

HTLV-1 is associated with adult T-cell leukaemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), but 95% of those infected with HTLV-1 never develop symptoms.³⁵ Infective dermatitis is a common HTLV-1-associated condition in the Caribbean characterised by persistent refractory coetaneous infections with saprophytic staphylococcal and

streptococcal bacteria.³⁶ A variety of other clinical conditions, including uveitis, arthritis, and Sjogren's syndrome, have been anecdotally associated with HTLV-1 infection.³⁷

POSSIBLE INTERACTIONS BETWEEN HTLV-1 AND HIV

Co-infection of the same cell by HTLV-1 and HIV is possible.³⁸ Some studies suggest a more severe clinical course with shortened survival for AIDS patients co-infected with HTLV-1, whereas others demonstrated no detrimental effect of HTLV-1 upon progression of HIV infection.³⁹

DIAGNOSIS

Diagnosis of HTLV-1 infection requires positive serum HTLV-1 ELISA with confirmatory Western blot assay. PCR is more sensitive and specific than serologic testing, and could be considered for patients seronegative by conventional testing.

TREATMENT

Although there is no curative treatment for HAM/TSP, mild to moderate beneficial effects have been reported with corticosteroids, immunosuppressants, gamma-globulin, and vitamin C.⁴⁰ The HTLV-1 protease enzyme is distinct from the HIV protease enzyme, suggesting that some medications used for HIV infection may not be effective for HTLV-1 infection.⁴¹ *In vitro* studies of the PIs indinavir (IDV), saquinavir (SQV), ritonavir (RTV), and nelfinavir (NFV), have demonstrated no effect of these medications upon HTLV-1.⁴² Two nucleoside analogues, AZT and zalcitabine (ddC), inhibit the production of proviral HTLV-1 DNA *in vitro*.⁴³ In people with HAM/TSP, use of AZT was associated with improvement in neurologic function, but no improvement was noted in non-ambulatory patients.⁴⁴ Chemotherapy can be curative for ATL, but is less successful for acute and lymphoma-type ATL.

PREVENTION

Guidelines published by the CDC and the U.S. Public Health Service (USPHS) recommend that an HTLV-1-infected person should: not donate blood, semen, body organs, or other tissues; not share needles or syringes; not breastfeed infants; and consider using latex condoms to prevent sexual transmission.⁴⁵ In resource poor settings, or in areas where clean water is not available for baby formula, breastfeeding for six months may be necessary. In HIV-infected persons, condom use would likely prevent acquisition or transmission of HTLV-1.

REFERENCES

- ¹Pan American Health Organisation. Status report on malaria programs in the Americas (based on 2001 data). Washington, DC: Pan American Health Organisation; 2002 Report No. CSP26/INF/3 (Eng.).
- ²Carter K. Avances de la Red Amazónica de Vigilancia de la Resistencia a las Drogas Antimaláricas (Ravreda). *Biomédica (Bogotá)* 2003;23(Suppl 1):75-6.
- ³Pan American Health Organisation. Pan American Health Organisation's proposed contribution to the United States Agency for International Development (USAID)/Latin America and Caribbean Bureau's *Amazon Malaria Initiative (AMI)*: project proposal and workplans for years 2 & 3. Mar 2003. Last accessed 9 November 2004, <http://www.paho.org/english/hcp/hct/mal/Mar03-paho-ami-2.htm>.
- ⁴Suriname to get new malaria drug. PAHO Today [serial on the Internet] 18 Mar 2004 [cited 9 November 2004]:[about 1 pg]. Available from: http://www.paho.org/English/DD/PIN/ptoday18_mar04.htm.
- ⁵World Health Organisation. Position of WHO's *Roll Back Malaria* Department on Malaria Treatment Policy. Last accessed 9 November 2004 <http://www.paho.org/English/AD/DPC/CD/mal-who-position-paper.htm>.
- ⁶Ekvall H. Malaria and anemia. *Curr Opin Hematol* 2003;10:108-14.
- ⁷Breman J, Alilio M, Mills A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. *Am J Trop Med Hyg* 2004;71(Suppl 2):1-15.
- ⁸Grimwade K, French N, et al. HIV infection as a cofactor for severe *falciparum* malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS* 2004;18:547-554.
- ⁹Grimwade K, French N, et al. Childhood malaria in a region of unstable transmission and high human immunodeficiency virus prevalence. *Ped Infect Dis J* 2003;22:1057-1063.
- ¹⁰Hoffman I, Jere C, et al. The effect of *Plasmodium falciparum* malaria on HIV-1 RNA blood plasma concentration. *AIDS* 1999;13:487-94.
- ¹¹Van Eijk A, Ayisi J, et al. HIV increases the risk of malaria in women of all gravidities in Kisumu, Kenya. *AIDS* 2003;17:595-603.
- ¹²Boland P, Wirima J, et al. Maternal HIV infection and infant mortality in Malawi: evidence for increased mortality due to placental malaria infection. *AIDS* 1995;9:721-726.
- ¹³Ayisi JG, van Eijk AM, et al. Maternal Malaria and Perinatal HIV Transmission, Western Kenya. *Em Infect Dis* 2004;10(4):643-53.
- ¹⁴World Health Organisation. Malaria and HIV/AIDS interactions and implications: conclusions of a technical consultation convened by WHO, 23-25 June, 2004. Last accessed 2004 <http://www.mosquito.who.int/malaria_HIV>.
- ¹⁵Newman RD, Parise ME, et al. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in *Plasmodium falciparum*-endemic sub-Saharan Africa. *Trop Med Int Health* 2003;8:488-506.
- ¹⁶Anglaret X, Chene G, et al. Early chemoprophylaxis with trimethoprim-sulfamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet* 1999;353(9163):1463-8.
- ¹⁷World Health Organisation. Malaria and HIV/AIDS interactions and implications: conclusions of a technical consultation convened by WHO, 23-25 June 2004. Last accessed 2004 <http://www.mosquito.who.int/malaria_HIV>.

-
- ¹⁸Omar SA, Bakari A, et al. Co-trimoxazole compared with sulfadoxine-pyrimethamine in the treatment of uncomplicated malaria in Kenyan children. *Trans R Soc Trop Med Hyg* 2001;95(6):657-60.
- ¹⁹Anglaret X. Trimethoprim-sulfamethoxazole prophylaxis in sub-Saharan Africa. *Lancet* 2001;358(9287):1027-8.
- ²⁰Iyer JK, Milhous WK, et al. *Plasmodium falciparum* cross-resistance between trimethoprim and pyrimethamine. *Lancet* 2001;358(9287):1066-7.
- ²¹World Health Organisation. Integrated management of childhood illness (IMCI) guidelines. 2001. Last accessed 9 November 2004 <<http://www.who.int/child-adolescent-health/integr.htm>>.
- ²²Madhi S, Petersen K, et al. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. *Pediatr Infect Dis J* 2000;19:1141-7.
- ²³Feikin DR, Dowell SF, et al. Increased carriage of trimethoprim-sulfamethoxazole-resistant *Streptococcus pneumoniae* in Malawian children after treatment for malaria with sulfadoxine/pyrimethamine. *J Infect Dis* 2001;181(4):1501-5.
- ²⁴Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985;9 November:1072-3.
- ²⁵Navin T, Miller K, et al. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet* 1985;8 June:1332.
- ²⁶2004 safety alerts for drugs, biologics, medical devices, and dietary supplements: Viramune[®] (nevirapine). Feb 2004. Last accessed 2004 <http://www.fda.gov/medwatch/SAFETY/2004/safety04.htm#viramune>.
- ²⁷PDR.net [homepage on the Internet]. Montvale (NJ): Thomson Healthcare; c2004-2005. [cited 9 November 2004] Available at: <http://www.pdr.net>.
- ²⁸HIV-druginteractions.org [homepage on the Internet]. Liverpool: Liverpool HIV Pharmacology Group, Department of Pharmacology & Therapeutics, University of Liverpool; c1999-2004. [cited 9 Nov 2004]. Available at: <<http://www.hiv-druginteractions.org>>.
- ²⁹Lengeler C. Insecticide-treated bednets and curtains for preventing malaria. *Cochrane Database Syst Rev* 2004;2:CD000363.
- ³⁰World Health Organisation. WHO Expert Committee on Malaria. Twentieth report. Geneva: World Health Organisation; 2000. WHO Technical Report Series No. 892 available at <http://mosquito.who.int/docs/ecr20_toc.htm>.
- ³¹Smikle MF, Heslop O, Vickers I, Dowe G, Deer D, Sue-Ho R, et al. A serosurvey of hepatitis B virus, hepatitis C virus, human T lymphotropic virus type-1 and syphilis in HIV-1-infected patients in Jamaica. *West Ind Med J* 2003;52:14-17 **and** de The G, Bomford R. An HTLV-I vaccine: why, how, for whom? *AIDS Res Hum Retroviruses* 1993;9:381-386 **and** Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, et al. HTLV-I associated myelopathy, a new clinical entity [letter]. *Lancet* 1986;1:1031-1032 **and** Blattner WA, Kalyanaraman VS, Robert-Guroff M, Lister TA, Galton DA, Sarin PS, et al. The human type-C retrovirus, HTLV, in blacks from the Caribbean region, and relationship to adult T-cell leukemia/lymphoma. *Int J Cancer* 1982;30:257-264 **and** Virus diseases. Public health implications of HTLV-I in the Caribbean. *Wkly Epidemiol Rec* 1990;65:63-65.
- ³²Pierik LT, Murphy EL. The clinical significance of HTLV-I and HTLV-II infection in the AIDS epidemic. *AIDS Clin Rev* 1991:39-57.
- ³³Tajima K, Kamura S, Ito S, Ito M, Nagatomo M, Kinoshita K, et al. Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL-endemic island: a report of the community-based

-
- co-operative study in Tsushima, Japan. *Int J Cancer* 1987;40:741-746 **and** Mueller N. The epidemiology of HTLV-I infection. *Cancer Causes Control* 1991;2:37-52 **and** Kajiyama W, Kashiwagi S, Ikematsu H, Hayashi J, Nomura H, Okochi K. Intrafamilial transmission of adult T cell leukemia virus. *J Infect Dis* 1986;154:851-857.
- ³⁴Hino S, Yamaguchi K, Katamine S, Sugiyama H, Amagasaki T, Kinoshita K, et al. Mother-to-child transmission of human T-cell leukemia virus type-I. *Jpn J Cancer Res* 1985;76:474-480 **and** Takezaki T, Tajima K, Ito M, Ito S, Kinoshita K, Tachibana K, et al. Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. The Tsushima ATL Study Group. *Leukemia* 1997;11 Suppl 3:60-62 **and** Takahashi K, Takezaki T, Oki T, Kawakami K, Yashiki S, Fujiyoshi T, et al. Inhibitory effect of maternal antibody on mother-to-child transmission of human T-lymphotropic virus type I. The Mother-to-Child Transmission Study Group. *Int J Cancer* 1991;49:673-677.
- ³⁵Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, et al. HTLV-I associated myelopathy, a new clinical entity [letter]. *Lancet* 1986;1:1031-1032 **and** Bartholomew C, Cleghorn F, Charles W, Ratan P, Roberts L, Maharaj K, et al. HTLV-I and tropical spastic paraparesis [letter]. *Lancet* 1986;2:99-100 **and** Robert-Guroff M, Gallo RC. Establishment of an etiologic relationship between the human T-cell leukemia/lymphoma virus (HTLV) and adult T-cell leukemia. *Blut* 1983;47:1-12 **and** Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, et al. Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. *Int J Cancer* 1982;29:631-635 **and** Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, Miyoshi I, Golde D, Gallo RC. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. *Science* 1982;218:571-573 **and** Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* 1985;2:407-410 **and** Roman GC, Roman LN, Spencer PS, Schoenberg BS. Tropical spastic paraparesis: a neuroepidemiological study in Colombia. *Ann Neurol* 1985;17:361-365 **and** Osame M et al., 1986 **and** Bartholomew C, et al., 1986 **and** Robert-Guroff M et al., 1983 **and** Hinuma Y, et al., 1982 **and** Kalyanaraman VS, et al., 1982 **and** Gessain A, et al., 1985 **and** Roman GC, et al., 1985.
- ³⁶LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W. Infective dermatitis of Jamaican children: a marker for HTLV-I infection [see comments]. *Lancet* 1990;336:1345-1347.
- ³⁷Hanada S, Uematsu T, Iwahashi M, Nomura K, Utsunomiya A, Kodama M, et al. The prevalence of human T-cell leukemia virus type I infection in patients with hematologic and nonhematologic diseases in an adult T-cell leukemia-endemic area of Japan. *Cancer* 1989;64:1290-1295 **and** Ijichi S, Matsuda T, Maruyama I, Izumihara T, Kojima K, Niimura T, et al. Arthritis in a human T lymphotropic virus type I (HTLV-I) carrier. *Ann Rheum Dis* 1990;49:718-721 **and** Lee SY, Mastushita K, Machida J, Tajiri M, Yamaguchi K, Takatsuki K. Human T-cell leukemia virus type I infection in hemodialysis patients. *Cancer* 1987;60:1474-1478 **and** Mann DL, DeSantis P, Mark G, Pfeifer A, Newman M, Gibbs N, et al. HTLV-I-associated B-cell CLL: indirect role for retrovirus in leukemogenesis. *Science* 1987;236:1103-1106 **and** Morgan OS, Rodgers-Johnson P, Mora C, Char G. HTLV-I and polymyositis in Jamaica. *Lancet* 1989;2:1184-1187 **and** Nishioka K, Maruyama I, Sato K, Kitajima I, Nakajima Y, Osame M. Chronic inflammatory arthropathy associated with HTLV-I [letter]. *Lancet* 1989;1:441 **and** Sugimoto M, Nakashima H, Watanabe S, Uyama E, Tanaka F, Ando M, et al. T-lymphocyte alveolitis in HTLV-I-associated myelopathy [letter]. *Lancet* 1987;2:1220.
- ³⁸De Rossi A, Saggiaro D, Calabro ML, Cenzato R, Chieco-Bianchi L. Reciprocal activation of human T-lymphotropic viruses in HTLV-I-transformed cells superinfected with HIV-1. *J Acquir Immune Defic Syndr* 1991;4:380-385.
- ³⁹Okubo S, Yasunaga K. Significance of viral co-infections by HIV, HTLV-1, Epstein-Barr virus and cytomegalovirus for immunological conditions in Japanese hemophiliacs [letter]. *AIDS* 1988;2:318-

-
- 319 **and** Page JB, Lai SH, Chitwood DD, Klimas NG, Smith PC, Fletcher MA. HTLV-I/II seropositivity and death from AIDS among HIV-1 seropositive intravenous drug users [see comments]. *Lancet* 1990;335:1439-1441 **and** Gotuzzo E, Escamilla J, Phillips IA, Sanchez J, Wignall FS, Antigoni J. The impact of human T-lymphotropic virus type I/II infection on the prognosis of sexually acquired cases of acquired immunodeficiency syndrome [see comments]. *Arch Intern Med* 1992;152:1429-1432 **and** Brites C, Pedroso C, Netto E, Harrington W, Jr., Galvao-Castro B, Couto-Fernandez JC, et al. Co-Infection by HTLV-I/II is associated with increased viral load in PBMC of HIV-1 infected patients in Bahia, Brazil. *Braz J Infect Dis* 1998;2:70-77 **and** Cleghorn FR, Blattner WA. Does human T-cell lymphotropic virus type I and human immunodeficiency virus type 1 coinfection accelerate acquired immunodeficiency syndrome? The jury is still out [editorial; comment]. *Arch Intern Med* 1992;152:1372-1373.
- ⁴⁰Osame M, Igata A, Matsumoto M, Kohka M, Usuku K, Izumo S. HTLV-I-associated myelopathy (HAM), treatment trials, retrospective survey and clinical and laboratory findings. *Hematol Rev* 1990;3:271-284 **and** Matsuo H, Nakamura T, Shibayama K, Nagasato K, Tsujihata M, Nagataki S. Long-term follow-up of immunomodulation in treatment of HTLV-I-associated myelopathy [letter]. *Lancet* 1989;1:790 **and** Kuroda Y, Takashima H, Endo C, Neshige R, Kakigi R. [Treatment of HTLV-I-associated myelopathy with alpha-interferon and high-dose of gamma-globulin]. *Rinsho Shinkeigaku* 1990;30:594-598; Kataoka A, Imai H, Inayoshi S, Tsuda T. Intermittent high-dose vitamin C therapy in patients with HTLV-I associated myelopathy. *J Neurol Neurosurg Psych* 1993;56:1213-1216.
- ⁴¹Hruskova-Heidingsfeldova O, Blaha I, Urban J, Strop P, Pichova I. Substrates and inhibitors of human T-cell leukemia virus type 1 (HTLV-1) proteinase. *Leukemia* 1997;11 Suppl 3:45-46.
- ⁴²Pettit SC, Sanchez R, Smith T, Wehbie R, Derse D, Swanstrom R. HIV type 1 protease inhibitors fail to inhibit HTLV-I Gag processing in infected cells. *AIDS Res Hum Retroviruses* 1998;14:1007-1014.
- ⁴³Mitsuya H, Jarrett RF, Matsukura M, Di Marzo Veronese F, DeVico AL, Sarngadharan MG, et al. Long-term inhibition of human T-lymphotropic virus type III/lymphadenopathy-associated virus (human immunodeficiency virus) DNA synthesis and RNA expression in T cells protected by 2',3'-dideoxynucleosides in vitro. *Proc Natl Acad Sci U S A* 1987;84:2033-2037.
- ⁴⁴Macchi B, Faraoni I, Zhang J, Grelli S, Favalli C, Mastino A, et al. AZT inhibits the transmission of human T cell leukaemia/lymphoma virus type I to adult peripheral blood mononuclear cells in vitro. *J Gen Virol* 1997;78 (Pt 5):1007-1016 **and** Sheremata WA, Benedict D, Squillacote DC, Sazant A, DeFreitas E. High-dose zidovudine induction in HTLV-I-associated myelopathy: safety and possible efficacy. *Neurology* 1993;43:2125-2129.
- ⁴⁵CDC. Guidelines for counseling persons infected with human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II). *Ann Intern Med* 1993;118:448-454.