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ANTI-RETROVIRAL TREATMENT: SIDE EFFECT MANAGEMENT

Report Prepared by
Dr. Anita Rachlis, MD, FRCPC
University of Toronto, Toronto, Ontario

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Contributors

Dr. A. MacLeod, Vancouver

Dr. J. Montaner, Vancouver

Dr. J. Gill, Calgary

Dr. K. Logue, Toronto

Ms. M. Bonner, Toronto

Dr. R. Beaulieu, Montreal

Dr. W. Schlech, Halifax

Dr. F. Lebel, Montreal

Ms. L. Houle, Burroughs Wellcome, Montreal

Pharmaceutical Group, Bristol-Myers Squibb, Montreal

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1. INTRODUCTION

The progression of infection with the human immunodeficiency virus (HIV) varies with the individual patient. The median time from initial infection with HIV to development of AIDS is now approximately ten to twelve years. Symptoms associated with HIV infection can be related directly to the viral infection or indirectly to infections or malignancies that occur as a result of the immune suppression (depletion of CD4 cells) induced by the virus. Management of HIV infection involves the treatment and prophylaxis of associated infections, treatment of malignancies, and anti-retroviral treatment.

This report provides information on how to monitor patients on anti-retroviral therapy, specifically the two nucleoside analogues, zidovudine (azidothymidine, AZT, Retrovir®) and didanosine (dideoxyinosine, ddI, Videx®). It also discusses the management of the adverse reactions associated with these agents.

It is important to recognize that knowledge about HIV infection is rapidly changing and that new clinical information may alter this publication.

2. ZIDOVUDINE (AZT, RETROVIR®)

Therapeutic Activity

Zidovudine is a thymidine analogue that inhibits virus replication. The drug interferes with a virus-specific enzyme, reverse transcriptase, which is an RNA-dependent DNA polymerase and which acts as a chain terminator of viral DNA synthesis.

Benefits Seen in Clinical Studies

Studies of zidovudine in patients with advanced HIV infection (CD4 cell count of less than 200/mm^3) have demonstrated prolonged survival, decreased severity and frequency of opportunistic infections, weight gain, and improved performance status. In patients with mildly symptomatic infection-for example, those with oral candidiasis; oral hairy leukoplakia; single dermatomal Herpes zoster; chronic seborrheic dermatitis or folliculitis; mild weight loss, intermittent diarrhea, significant fatigue, and CD4 cell count of between 200/mm^3 and 500/mm^3; or asymptomatic infection and CD4 cell count of less than 500/mm^3-progression to more advanced disease (i.e., AIDS-Related Complex-ARC) or AIDS has been delayed. Improved neurologic function has also been demonstrated. Furthermore, zidovudine has been beneficial in the treatment of HIV-associated immune thrombocytopenia.

Indications

Zidovudine is indicated for the treatment of HIV-infected persons with evidence of impaired immunity as defined by a CD4 cell count of about 500/mm^3 or less.

Dosage Forms

Zidovudine is supplied by Burroughs Wellcome in 100 mg capsules or as a strawberry-flavoured syrup in a concentration of 50 mg per 5 mL. An intravenous formulation is available for patients unable to take oral medication.

Dosage Regimen

Adults

Symptomatic patients: 600 mg daily (100 mg Q4h).

Asymptomatic patients: 500 mg daily (100 mg Q4h while awake).

The value of initiating symptomatic patients with a four-week course of 1200 mg daily (200 mg Q4h) is not clear and is probably not necessary.

For patients with HIV-related neurologic disease, doses of 1200 to 1500 mg daily may be considered so that higher levels of zidovudine can be achieved in the cerebrospinal fluid (CSF).

Longer dosing intervals (every six or eight hours) are likely to have similar clinical efficacy.

The minimal effective dose of zidovudine is not known, but patients receiving a lower dose (300 mg/d) had a reduction in viral replication.

Children

All patients: 180 mg/m^2 Q6h (not to exceed 200 mg Q6h).

Monitoring the Patient on Zidovudine

When two CD4 cell counts, at least one week apart, register less than 500/mm^3, the physician should order a series of baseline laboratory tests before initiating the patient on zidovudine. This series should include: hemoglobin, white blood cell count, neutrophil count, platelet count, reticulocyte count, urea, creatinine, CK, AST, (ALT), ALP, bilirubin, serum B_{12} level, and red blood cell folate level.

Two weeks after the zidovudine has been initiated, the physician should order hemoglobin, white blood cell count, differential count, and platelet count (CBC). Thereafter, the patient should have CBC and liver function tests each month. A CD4 cell count should be performed every three months. Six months after the zidovudine has been initiated and every three months thereafter, the physician should order a creatine kinase (CK).

Vitamin B_{12} or folic acid replacement need be given only if baseline levels of these vitamins are below normal.

After an initial rise, CD4 cell counts often decline despite evidence of continued clinical benefit. No current laboratory test reliably indicates the patient's response to zidovudine. Clinical parameters should be used. However, the physician should continue to monitor the patient's CD4 cell counts every three months and should institute primary prophylaxis for *Pneumocystis carinii* pneumonia when the CD4 cell count falls below 200/mm^3 or the CD4 percentage falls below 20.

Clinically indicated follow-up should be undertaken when new symptoms or toxicity develop.

Adverse Effects

A number of adverse effects have been directly linked to zidovudine therapy. Some of these may, however, be a consequence of HIV infection or of the disease's progression.

The incidence of toxicity appears to be related both to the dose of zidovudine and to the stage of the disease. Side effects from zidovudine are less frequent and milder at a dose of 500 mg daily and at an earlier stage of HIV infection.

Early Adverse Reactions

Within the first several weeks of zidovudine treatment, patients may complain of headaches, confusion, nausea and vomiting, malaise and fatigue, or abdominal discomfort. These symptoms usually resolve with continued therapy and should be treated symptomatically if necessary.

Early adverse hypersensitivity reactions, which include fever and rash, occur rarely. If this hypersensitivity occurs, it may be necessary to discontinue zidovudine as a treatment.

Desensitization has been successfully used as a treatment in some patients experiencing rash.

Hematologic Adverse Reactions

The most significant adverse effect of zidovudine is bone-marrow toxicity, which affects erythropoiesis and granulopoiesis. Marrow aplasia is rare.

Patients receiving zidovudine may experience significant elevations in platelet count. Zidovudine is indicated for the treatment of HIV-related immune thrombocytopenia.

Anemia

Anemia, if it occurs, usually manifests within the first three months of treatment. The incidence of anemia is less than five percent in patients with asymptomatic infection. The incidence in patients with more advanced HIV infection is higher.

Macrocytosis (elevation in MCV) occurs within six months in 75 percent of zidovudine-treated patients. Additional vitamin B_{12} or folate neither alters macrocytosis nor prevents anemia. However, when anemia occurs in association with macrocytosis, the anemia is usually mild.

A significant anemia that is normocytic and normochromic may develop, although macrocytosis may be seen. Reticulocyte counts will be low, indicating suppression of erythropoiesis. Where the fail in hemoglobin is less significant and the reticulocyte count is normal, a reduction in the zidovudine dose may be sufficient to alleviate the anemia. Where the reduction in hemoglobin is more significant and the reticulocyte count is low, it may be necessary to temporarily interrupt the zidovudine so that the hemoglobin may recover.

It may be possible to reinstitute the zidovudine at lower doses and to slowly increase the dose without recurrence of the anemia.

Transfusion may be required in symptomatic patients or in those whose hemoglobin levels are less than 80 g/L.

In patients with anemia and EPO levels less than 500 IU/L, recombinant human erythropoietin (EPO) has been found to decrease the requirement for transfusion or significant zidovudine dose reductions.

The development of anemia, particularly in patients who have been on zidovudine for some time, warrants investigation of the patient for direct bone-marrow involvement resulting from an opportunistic infection (e.g., mycobacteria) or malignancy.

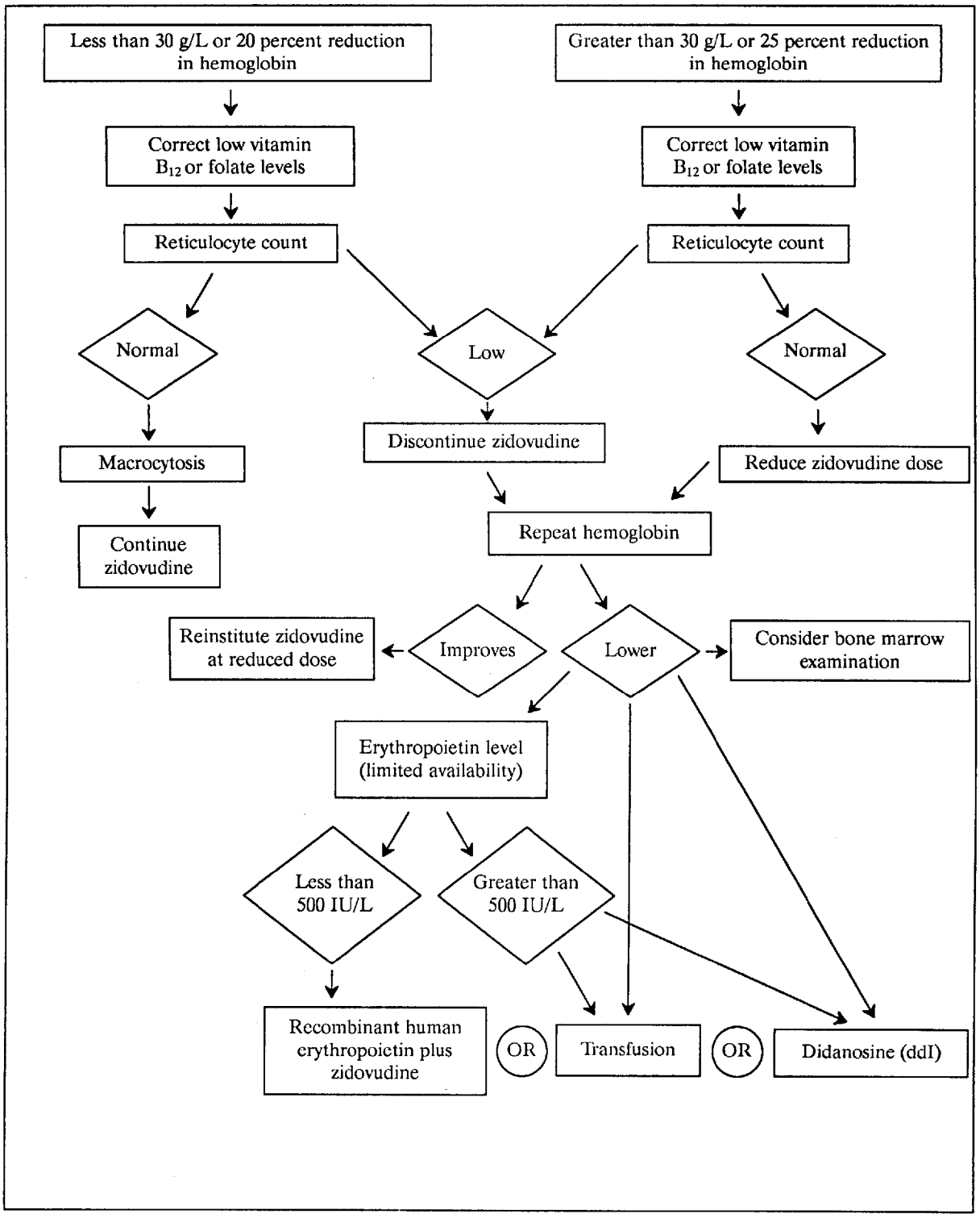

Figure 1: Approach to Management of Anemia

Neutropenia

Neutropenia usually occurs within three months of the stan of therapy but may also be a late complication.

When the neutrophil count is less than 0.75 x 10^9/L, the dose of zidovudine should be reduced to 300 mg daily.

Discontinue any concomitant myelosuppressive agents. The combined use of zidovudine and ganciclovir (Cytovene®) may be associated with profound neutropenia and is therefore strongly discouraged.

Zidovudine should be temporarily discontinued if the neutrophil count falls to less than 0.5 x 10^9/L. When the neutrophil count recovers, zidovudine can be reinstituted at a reduced dose.

Granulocyte-macrophage colony-stimulating factor (GM-CSF), an investigational cytokine, is currently undergoing clinical study for the treatment of zidovudine-induced neutropenia.

Neurologic Adverse Reactions

Confusion, agitation, and insomnia have been attributed to zidovudine. If the symptoms do not improve with continued therapy, dose reduction may be beneficial. Discontinuation of zidovudine may be necessary.

Seizures have been associated with zidovudine both alone and in combination with other agents such as acyclovir.

An acute encephalopathy has been described in patients who have had their dosage reduced rapidly or their medication stopped. It appeared to be self-limited.

HIV infection is itself associated with neurologic complications, including opportunistic infection. It is therefore appropriate to investigate patients exhibiting neurologic symptoms or signs to exclude other causes of neurologic dysfunction before attributing those symptoms or signs to zidovudine, particularly as zidovudine may be beneficial in treating neurologic disease owing to HIV.

Late Adverse Reactions

Myopathy

Proximal muscle weakness, myalgia, and muscle wasting have been described in patients given zidovudine for more than six months. CK levels may also be elevated in patients given zidovudine.

Electron microscopy has revealed mitochondrial abnormalities in the muscle cells of patients given zidovudine. However, there is an HIV-associated myopathy that may appear clinically similar.

Zidovudine treatment should be discontinued in patients whose symptoms are compatible with myopathy and who exhibit elevations in CK. Improvement should occur within two weeks. Zidovudine may then be reinstituted at reduced doses and, in some patients, will not be associated with the recurrence of symptoms. If a patient develops a recurrence at a dose of 100 mg Q8h or less, zidovudine should be discontinued and alternative anti-retroviral therapy should be considered.

Nonsteroidal anti-inflammatory agents may be helpful in the treatment of symptomatic patients.

Hepatotoxicity

An elevation in transaminases has been noted in patients given zidovudine over a long period. Appropriate investigations, which may include liver biopsy, should be undertaken, as the problem may be a complication arising from the HIV infection rather than from the zidovudine treatment.

Nail Discolouration

A bluish pigmentation of the nail beds has been described, although infrequently, in some zidovudine-treated patients.

Carcinogenicity

Rodent carcinogenicity studies have revealed the development of vaginal neoplasms, but the significance of this finding to female patients receiving zidovudine is not known.

Drug Resistance

Isolates of HIV from patients taking zidovudine for more than six months have been found to be resistant to the drug. The development of zidovudine resistance appears to be less in patients with less-symptomatic or asymptomatic disease.

The clinical significance of the development of drug resistance remains controversial. However, isolates of HIV that are resistant to zidovudine remain sensitive to didanosine (ddI).

Concomitant Medications

Because patients with HIV infection and AIDS are often taking a number of other medications, drug interactions can potentiate toxicity. Hematologic toxicity is a particular problem.

Zidovudine is metabolized by hepatic glucuronidation. The drug's pharmacokinetics may be altered in the presence of other agents metabolized by this route.

Early clinical studies suggested that anemia appeared more frequently in patients who were taking acetaminophen in addition to zidovudine. Patients receiving zidovudine have therefore been advised to avoid acetaminophen. However, subsequent studies have not confirmed significant alterations in zidovudine pharmacokinetics when zidovudine is taken concurrently with acetaminophen. Zidovudine use should not be considered a contraindication to the coadministration of acetaminophen but, rather, an indication for closer attention to possible toxicity.

Toxicity may occur if zidovudine is coadministered with the following drugs:

- Acetaminophen
- Morphine
- Probenecid*
- Nonsteroidal anti-inflammatory agents (including ASA)

* Drugs that are contraindicated in combination with zidovudine.

The following myelosuppressive agents coadministered with zidovudine enhance hematologic toxicity:

- Cancer chemotherapy
- Pyrimethamine
- Trimethoprim/sulphamethoxazole
- Ganciclovir*
- Interferon
- Dapsone

The following nephrotoxic agents coadministered with zidovudine may impair renal excretion:

- Intravenous pentamidine
- Amphotericin B
- Foscarnet

Caution and more frequent monitoring are advised whenever the medications mentioned above are used in conjunction with zidovudine.

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* Drugs that are contraindicated in combination with zidovudine.

3. DIDANOSINE (DIDEOXYINOSINE, ddI, VIDEX®)

Therapeutic Activity

Didanosine (ddI) is a purine nucleoside analogue that inhibits virus replication. The drug interferes with a virus-specific enzyme, reverse transcriptase, which is an RNA-dependent DNA polymerase and which acts as a chain terminator of viral DNA synthesis. *In vitro,* didanosine is less myelotoxic than zidovudine to human hematopoietic progenitor cells.

Benefits Seen in Clinical Studies

A number of phase I studies have been carried out on patients with advanced ARC or AIDS. These studies have shown beneficial changes in weight, clinical signs or symptoms, CD4 counts, and serum levels of HIV p24 antigen. Clinical efficacy studies are ongoing.

Indications

Didanosine is available through a compassionate-use open study. Regional co-ordinators can provide the drug for

- symptomatic HIV-positive patients whose CD4 count is less than 200/mm^3 and who have been diagnosed with AIDS, or for
- patients who have become intolerant to zidovudine despite a dose reduction to 500 mg or less daily, or who have shown disease progression despite a daily dose of at least 500 mg for at least six months.

Intolerance and resistance to zidovudine are defined by protocol criteria.

Dosage Forms

Didanosine is supplied as a powder. It is available in various doses. The didanosine powder is reconstituted with four ounces of water and taken on an empty stomach at least two hours after the last meal and not less than one-half hour before the next meal. The drug is prescribed according to the patient's weight, as shown in the following table:

Weight	Dose
35 kg - 49 kg	167 mg bid
50 kg - 74 kg	250 mg bid
Greater than 74 kg	375 mg bid

Monitoring

Before initiating didanosine, the physician should order a series of baseline laboratory tests. This series should include hemoglobin, white blood cell count, neutrophil count, platelet count, urea, creatinine, electrolytes, AST,(ALT), ALP, bilirubin, LDH, uric acid, amylase, and triglycerides. Two weeks after initiation and monthly thereafter, the laboratory tests should be repeated, and a clinical evaluation for toxicity performed.

More frequent follow-up is required if new symptoms or toxic effects are noted.

Adverse Effects

A number of adverse reactions have been reported by patients receiving didanosine. The true incidence of these reactions and their relation to didanosine are currently unknown. The long-term effects of didanosine are also currently unknown.

Neurologic Adverse Effects

Peripheral Neuropathy

Peripheral neuropathy appears to be dose-related, based on observations in the phase I dose-escalating studies.

Early clinical symptoms include dysesthesias (numbness, tingling) and pain in the lower extremities, especially the soles of the feet.

Physical signs may be absent or may include diminished vibratory sensation and loss of ankle reflexes.

Standard electrophysiologic tests (nerve conduction) may not be helpful in providing objective evidence for the neuropathy, as the tests may be normal or reveal slightly decreased amplitude.

Careful clinical evaluation for pre-existing peripheral neuropathy should be carried out before didanosine is started.

The following drugs have been associated with peripheral neuropathy:

- Isoniazid
- Ethionamide
- Dilantin
- Dapsone
- Metronidazole
- Disulfiram
- Vincristine
- Hydralazine
- Thalidomide

Use of these drugs concomitantly with didanosine should be avoided. If avoidance is not possible, the didanosine should be temporarily or permanently discontinued, or the patient should be monitored more closely.

Didanosine may be reinstituted at a lower dose when symptoms resolve. If the neuropathy recurs, didanosine should be permanently discontinued.

Central Nervous System Symptoms

Seizures have been reported, but they may be related directly to the HIV infection, as no relationship to didanosine has been established.

Confusion, headache, insomnia, irritability, and restlessness have also been attributed to didanosine. Dose reduction or dose discontinuation may be necessary if significant symptoms occur.

Gastrointestinal Adverse Effects

Pancreatitis

The incidence of pancreatitis associated with didanosine appears to be about two percent.

Pancreatitis may be life-threatening. Its occurrence strongly correlates with a prior history of pancreatitis. Didanosine should not be used in patients with such a history.

Patients being treated with didanosine should avoid concomitant consumption of alcohol, as such consumption may predispose the patient to pancreatitis.

Pancreatitis may be exacerbated when the following drugs are taken concomitantly with didanosine:

- Metronidazole
- Acetaminophen
- Cimetidine
- Ranitidine
- Corticosteroids
- Thiazide diuretics
- Sulphonamides
- Methyldopa
- Nitrofurantoin
- Tetracycline
- Procainamide
- Valproic acid
- Ethambutol

If it is deemed necessary to use didanosine and one of the above drugs concomitantly, caution should be exercised. The patient should be monitored more frequently. If adverse effects occur, serious consideration should given to alternative agents or to the discontinuation of the didanosine.

Didanosine should be temporarily discontinued when intravenous pentamidine or high-dose sulphonamides are being used. The didanosine should not be reinstituted until one week after completion of such therapy.

The risk of pancreatitis is greater for patients with more advanced HIV infection and for those with cytomegalovirus (CMV) and mycobacterial infection. The greater risk is likely due to pancreatic involvement.

If the patient exhibits symptoms such as abdominal pain, fever, nausea, and vomiting, the didanosine should be discontinued until a diagnosis of pancreatitis is excluded. If pancreatitis is confirmed, didanosine must be permanently discontinued.

Asymptomatic rises in amylase have been noted in patients treated with didanosine. If a rise in amylase should occur, the amylase test should be monitored more frequently, and the patient should be evaluated for clinical evidence of pancreatitis. Didanosine should be withheld until the amylase level returns to normal. The drug can then be reinstituted at a lower dose, often without recurrence of the abnormal amylase. Fractionation of amylase may be helpful in distinguishing between pancreatic and salivary enzyme levels.

The occurrence of pancreatitis may be predicted if an elevation in triglyceride levels is observed in patients on didanosine. Caution should be exercised for patients who have pre-existing hypertriglyceridemia. Didanosine therapy should be interrupted if triglycerides rise. The drug should be discontinued when triglyceride levels rise above 8.5 mmol/L.

Diarrhea

Diarrhea can be treated symptomatically because it is largely attributed to the citrate-phosphate buffer in which the didanosine is administered.

Dry Mouth

Dry mouth has been reported but is usually of no clinical significance.

Hepatotoxicity

Elevations in hepatic transaminases have been reported in patients on didanosine. The elevations are without other apparent etiology. Discontinuation of the drug may result in a reversal of the abnormalities.

Hyperuricemia

Elevations in uric acid are probably a consequence of didanosine metabolism via purine catabolic pathways. Significant elevations are unlikely with current doses, and no clinical symptoms of hyperuricemia were observed even at high doses.

Cardiac Arrythmias

Several deaths attributed to cardiac arrythmias and several episodes of asymptomatic arrythmias were reported in patients receiving didanosine concomitantly with clofazimine and rifabutin for treatment of mycobacterial infection. Some of these patients also had electrolyte abnormalities that may have contributed to the etiology. Caution and close monitoring are recommended when these drugs are used in combination with didanosine.

Other Adverse Effects

Other adverse effects reported to be associated with didanosine are electrolyte abnormalities, hypokalemia, hypomagnesemia, hypocalcemia, thrombocytopenia, fever, and rash.

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REGIONAL RESOURCE PHYSICIANS

WEST COAST

Julio S. G. Montaner MD, FRCPC
St. Paul's Hospital C-371
1081 Burrard St.
Vancouver, B.C.
V6Z 1Y6
Tel: (604) 631-5036
Fax: (604) 631-5210

W. Alastair McLeod MD, MSc, FRCPC
Suite 302
1160 Burrard St.
Vancouver, B.C.
V6Z 2E8
Tel: (604) 688-1388
Fax: (604) 682-8656

PRAIRIES

M. John Gill MD, FRCPC
University of Calgary
Health Science Centre
3330 Hospital Dr. NW
Calgary, Alta.
T2N 4N1
Tel: (403) 220-6032
Fax: (403) 283-4740

ONTARIO

Anita R. Rachlis MD, FRCPC
A226
Sunnybrook Health Science Centre
2075 Bayview Ave.
Toronto, Ont.
M4N 3M5
Tel: (416) 480-4689
Fax: (416) 480-5808

...continued

QUEBEC

Raymond Beaulieu MD, FRCPC
Hôtel-Dieu de Montréal
3840 rue Saint-Urbain
Montreal, Qué:
H2W 1T8
Tel: (514) 843-2697
Fax: (514) 843-2708

MARITIMES

Walter F. Schlech MD, FRCPC
ACC-4089
Victoria General Hospital
1278 Tower Rd.
Halifax, N.S.
B3H 2Y9
Tel: (902) 428-3742
Fax: (902) 428-2023