Education

Éducation

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Guidelines for antiretroviral therapy for HIV infection

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Abstract

Objective: To develop guidelines for health care providers and their HIV-positive patients on the clinical use of antiretroviral agents for HIV infection.

Options: Recommendations published in 1996 by an international panel.

Outcomes: Improvement in clinical outcomes or in surrogate markers of disease activity.

Evidence and values: The Canadian HIV Trials Network held a workshop on Oct. 19–20, 1996, to develop Canadian guidelines that incorporate information from recent basic and clinical research.

Recommendations: Recommendations for the use of antiretroviral drugs in HIV infection are provided for initial therapy, continuing therapy, primary infection, vertical transmission, pediatric therapy and postexposure prophylaxis.

Validation: The guidelines are based on consensus of the participants attending the workshop: Canadian investigators, clinicians and invited representatives from the community, government and the pharmaceutical industry. They are subject to review and updating as new information on clinical benefits is published.

Sponsors: The workshop was organized by the National Centre of the Canadian HIV Trials Network. Unrestricted educational grants were provided by 8 pharmaceutical companies. Additional support was provided from the National AIDS Strategy of Health Canada.

Résumé

Objectif : Créer, pour les fournisseurs de soins de santé et leurs patients infectés par le VIH, des lignes directrices sur l'utilisation clinique des agents antirétroviraux contre l'infection par le VIH.

Options : Recommandations publiées en 1996 par un groupe international.

Résultats : Amélioration des résultats cliniques ou des marqueurs substituts de l'activité morbide.

Preuves et valeurs : Le Réseau canadien pour les essais VIH a organisé, les 19 et 20 octobre 1996, un atelier afin d'établir des lignes directrices canadiennes qui comprennent l'information tirée de recherches fondamentales et cliniques récentes.

Recommandations : Les recommandations sur l'utilisation des agents antirétroviraux dans la lutte contre l'infection par le VIH portent sur le traitement initial, le traitement continu, l'infection primitive, la transmission verticale, la thérapie pédiatrique et la prophylaxie après l'exposition.

Validation : Les lignes directrices sont fondées sur le consensus dégagé chez les participants à l'atelier : chercheurs et cliniciens canadiens et représentants invités de la communauté, des gouvernements et de l'industrie pharmaceutique du Canada. Ces lignes directrices pourront être révisées et mises à jour à mesure que l'on publiera de nouveaux renseignements sur les avantages cliniques.

Commanditaires : L'atelier a été organisé par le Centre national du Réseau canadien pour les essais VIH. Huit sociétés pharmaceutiques ont versé des subventions d'éducation sans restriction. La Stratégie nationale sur le SIDA de Santé Canada a fourni de l'aide supplémentaire.

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Abbreviations

AZT	zidovudine
ddC	zalcitabine
ddI	didanosine
d4T	stavudine
NRTI	nucleoside analogue reverse transcriptase inhibitor
NVP	nevirapine
PCP	*Pneumocystis carinii* pneumonia
3TC	lamivudine

Recent scientific discoveries and the availability of new antiretroviral drugs are changing the approach to the treatment of HIV infection. New techniques that quantify HIV-1 RNA in the blood have shown close links between the baseline plasma viral load and disease progression[1,2] and between drug-induced changes in viral load and clinical benefits of treatment.[3] Use of viral genome measurements have also improved our understanding of the dynamic equilibrium between viral replication, lymphocyte regeneration, the plasma viral load and the CD4 count.[4,5] The speed at which new information and drugs have appeared has left many physicians confused about the optimal treatment of HIV infection in various groups of patients.

In order to develop Canadian guidelines that incorporate information from recent basic and clinical research, the Canadian HIV Trials Network held a workshop in Toronto on Oct. 19–20, 1996. The objectives were (a) to examine the current recommendations for the use of antiretroviral agents in the management of HIV infection[6] and (b) to develop national guidelines for clinical use of antiretroviral agents. Participants included Canadian investigators, clinicians and invited representatives from the community, government and the pharmaceutical industry. Recently published guidelines and supporting published material were circulated to all invitees before the workshop. Following a series of presentations, attendees chose or were assigned to 1 of 5 working groups. Each session was chaired by a facilitator, and another individual was asked to present a summary of the group's recommendations at a plenary session. The speakers, facilitators and rapporteurs shared in the manuscript preparation.

The recommendations that emerged were enriched by data from clinical trials, including presentations at scientific meetings held in Birmingham, England, later in 1996 and in Washington early in 1997. These data were incorporated into the guidelines under the leadership of the senior author (A.R.R.) following teleconferences and circulation of drafts of the manuscript to all authors. The revised recommendations were circulated for comment to each of the original participants, who were asked to report suggestions for major changes to one of the principal authors (A.R.R. or D.P.Z.). This article thus represents the current consensus in Canada on the approach to antiretroviral therapy for HIV infection. It focuses on 6 main areas: initial therapy, continuing therapy, primary infection, vertical transmission, pediatric therapy and postexposure prophylaxis.

Background

Viral load

Until recently, clinicians made treatment decisions about the initiation or alteration of antiretroviral therapy for HIV infection and the introduction of chemoprophylaxis for opportunistic infections on the basis of clinical parameters and CD4 counts. Implicit in this approach was a belief that a period of latency followed infection. New data have shown that HIV replicates actively throughout the course of infection, with about 10 billion new viral particles produced and cleared daily. When replication is blocked, 99% of the virus is cleared from the circulation in 2.6 days.[4,5] Adequate evidence exists to support the use of plasma viral load (number of HIV-1 RNA copies per millilitre) as a surrogate marker and predictor of clinical outcomes, including progression to AIDS and death.[1–3] The CD4 count alone is not as predictive of clinical outcome.[4] A positive correlation has been shown between a decrease in viral load as a result of antiretroviral therapy and clinical outcome.[3,7,8]

Three commercial assays are available that can measure viral load to a lower limit of quantitation of 200–500 HIV-1 RNA copies/mL. All 3 assays are comparable and are reproducible with a variability of about 0.3 $\log_{10}$ (i.e., 2- to 3-fold above and below the reported value). Thus, only reductions of 0.5 $\log_{10}$ (5-fold) or greater are considered to represent a response to treatment. Interpretation of changes in viral load must take into account other factors that may influence the plasma HIV-1 RNA, such as concurrent infections, nonadherence to the treatment regimen and vaccinations.[9,10] A more sensitive assay is being developed to detect viral loads to a lower limit of quantitation of 20–50 HIV-1 RNA copies/mL.

Clinical studies have not yet clearly defined a precise value or threshold of HIV-1 RNA at which treatment should be started. There is consensus that the lower the viral load, the better the prognosis. The goal of therapy at present is to prolong life and delay disease progression by reducing the viral load to below the level of quantitation of the assay being used. Clinical benefit can still be achieved at levels below 5000 HIV-1 RNA copies/mL or with a decrease of 1 $\log_{10}$ in the viral load regardless of the initial level.[8] The CD4 count remains important, particularly as it decreases toward 0.3×10^9/L or lower. Because it reflects damage to the immune system, the CD4 count predicts the risk of opportunistic infection and the timing of chemoprophylaxis.

Viral resistance in clinical practice

The development of resistance by HIV to antiretroviral drugs depends on several factors: the inherent propensity of HIV to introduce mutations as it replicates, the rate of viral replication, the viral burden, the immunologic response of the host, selective pressure exerted by specific antiretroviral drugs, dosing and pharmacokinetics of drugs (especially

penetration of drugs into specific body compartments) and patient adherence to the therapeutic regimen.

The ability of HIV to develop mutations that confer drug resistance has been documented.[5,11–14] The frequency of mutation is directly related to the rate of viral replication. Thus, the current goal of therapy should be to reduce the viral burden to such low levels that viral replication is virtually eliminated. Viruses that cannot replicate will not have the opportunity to mutate into drug-resistant forms. Monotherapy with the currently available antiretroviral agents does not suppress viral replication sufficiently and is associated with rapid emergence of drug-resistant mutants. It is recommended that monotherapy be avoided and that combination therapy be used instead to treat HIV infection, with emphasis on patient compliance.[15]

Studies involving patients not previously given antiretroviral therapy

The baseline viral load may be extremely high in newly infected patients, 50% of whom present with over 100 000 HIV-1 RNA copies/mL.[1] After initial infection and seroconversion, patients achieve a "set point" of viral load that is predictive of the course of illness.[2] If aggressive treatment were to be initiated early, the potential exists to maintain the viral load as low as possible and to prolong the disease-free interval.[16] Evaluation of triple combination therapy — for example, zidovudine (AZT or ZDV), lamivudine (3TC) and ritonavir, or AZT, didanosine (ddI) and 3TC — in this setting is under way.[17,18]

Several studies involving patients with established HIV infection who have not previously received antiretroviral therapy[19–21] have shown that combination nucleoside analogue reverse transcriptase inhibitor (NRTI) therapy with AZT and ddI or zalcitabine (ddC) delayed progression to AIDS or death compared with AZT alone. Further studies have shown that AZT combined with 3TC is more effective than AZT alone.[22,23] A triple combination of AZT, ddI and nevirapine (NVP), a non-NRTI, provided significant reduction in viral load compared with dual combination therapy, but clinical outcomes were not assessed.[24] Because triple combination therapy with 2 NRTIs and a protease inhibitor has been found to result in significant and sustained reductions in viral load and increases in CD4 counts, improved clinical outcomes are anticipated.[25]

Studies involving patients previously given antiretroviral therapy

The addition of another NRTI (ddI or 3TC) in patients previously prescribed AZT or AZT-containing regimens has been found to delay clinical progression.[19–23,26] The benefit of non-NRTIs in patients previously prescribed antiretroviral therapy is limited.[27,28] In such patients, the addition of a protease inhibitor (saquinavir, indinavir or ritonavir) to 2 NRTIs, or even the use of 2 protease inhibitors alone, can result in a decrease in the viral load by more than 2 $\log_{10}$ (99%).[25,29–31] Several studies have shown clinical benefit from adding a protease inhibitor in patients with more advanced disease previously given NRTIs.[32–34]

Guidelines

Initial therapy

Based on current knowledge of HIV pathogenesis and clinical trial results, patients should be fully informed of the available data and risks with respect to long-term side effects of antiretroviral therapy and durability of response. Treatment must be decided on an individual basis so that quality of life is not adversely affected. There are no data to support withholding treatment at any stage of HIV infection.

When should antiretroviral therapy be started?

Antiretroviral therapy should be offered to all patients who are symptomatic (US Centers for Disease Control and Prevention [CDC] classification B or C).[35] In asymptomatic patients, initiation of therapy is based on laboratory criteria, primarily the viral load and secondarily the CD4 count. A plasma viral load above 5000–10 000 HIV-1 RNA copies/mL, regardless of the CD4 count, is considered an indication for treatment. A CD4 count of less than 0.3×10^9/L is an indication for treatment regardless of the plasma viral load, to prevent further damage to the immune system. For treatment decisions physicians may need to consider viral load, immune function (CD4 count) and clinical status.

Which agents should be used?

Monotherapy with currently available agents (Table 1) is not indicated. The choice of drugs for combination therapy depends on the anticipated viral load reduction, differential side effects, drug interactions, patient tolerance and dosing schedules. The inclusion of AZT, stavudine (d4T), 3TC or NVP in combination regimens may have therapeutic advantage because these agents penetrate into cerebrospinal fluid reasonably well.[36,37]

When choosing a protease inhibitor one must consider effectiveness, bioavailability, adverse effects and drug interactions. Although saquinavir is highly potent in vitro and well tolerated, poor bioavailability of the current for-

mulation limits clinical efficacy. A new, soft gelatin capsule with greater bioavailability has been developed. Ritonavir, indinavir and nelfinavir have similar clinical efficacy, but choice depends on considerations for individual patients such as absorption related to food intake, drug interactions and differing toxic effects. Combinations of ritonavir

Table 1: Antiretroviral agents used in the treatment of HIV infection

Drug	Dose	Side effects	Interactions
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)			
Zidovudine (AZT) Retrovir®	200 mg tid or 300 mg bid	Anemia, neutropenia, myopathy, nausea, insomnia, headache, fatty liver, lactic acidosis	Myelosuppressive agents (ganciclovir, chemotherapy); probenecid
Didanosine (ddI) Videx®	≥ 50 kg: 200 mg bid < 50 kg: 125 mg bid On empty stomach	Pancreatitis, peripheral neuropathy, diarrhea	Interference with absorption (antacids, ketoconazole, quinolones, tetracyclines); other drugs associated with peripheral neuropathy; other drugs associated with pancreatitis (e.g., pentamidine)
Zalcitabine (ddC) Hivid®	0.75 mg tid	Aphthous stomatitis, pancreatitis, peripheral neuropathy, rash	Other drugs associated with peripheral neuropathy; other drugs associated with pancreatitis (e.g., pentamidine)
Stavudine (d4T) Zerit®	≥ 60 kg: 20 or 40 mg bid < 60 kg: 15 or 30 mg bid	Peripheral neuropathy, pancreatitis (rare)	Other drugs associated with peripheral neuropathy
Lamivudine (3TC) Epivir®	150 mg bid	Neutropenia, gastrointestinal intolerance	
Non-NRTIs*			
Delavirdine Rescriptor®	400 mg tid	Rash, elevated liver enzyme levels	Amiodarone, astemizole, benzodiazepines, carbamazepine, cimetidine, cisapride, clarithromycin, ddI, ergot alkaloids, fluoxetine, indinavir, ketoconazole, omeprazole, phenobarbital, phenytoin, ranitidine, rifabutin, rifampin, ritonavir, saquinavir, terfenadine, warfarin
Nevirapine Viramune®	200 mg once daily for 14 d, then 200 mg bid	Rash, elevated liver enzyme levels	Carbamazepine, clarithromycin, corticosteroids, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nelfinavir, oral contraceptives, phenytoin, rifabutin, rifampin, ritonavir, saquinavir
Protease inhibitors			
Saquinavir Invirase®	600 mg tid With high-fat meal	Rash, gastrointestinal intolerance	Astemizole, cisapride, clarithromycin, delavirdine, dexamethasone, erythromycin, ketoconazole, itraconazole, nevirapine, phenytoin, rifabutin, rifampin, terfenadine, triazolam
Ritonavir Norvir®	300 mg bid × 3 d 400 mg bid × 4 d 500 mg bid × 5 d then 600 mg bid With food	Elevated liver enzyme levels, circumoral/peripheral paresthesia, gastrointestinal intolerance, altered taste, elevated lipid levels	Alprazolam, amiodarone, astemizole, bepridil, bupropion, carbamazepine, cisapride, clozapine, desipramine, diazepam, disulfiram, encainide, ergot alkaloids, ethinyl estradiol, flecainide, flurazepam, meperidine, midazolam, phenobarbital, phenytoin, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, rifampin, saquinavir, terfenadine, theophylline, triazolam
Indinavir Crixivan®	800 mg q8h On empty stomach or with light meal	Elevated indirect bilirubin level, renal calculi	Amiodarone, astemizole, cisapride, delavirdine, ergot alkaloids, itraconazole, ketoconazole, midazolam, nevirapine, quinidine, rifabutin, rifampin, terfenadine, triazolam
Nelfinavir* Viracept®	750 mg tid With food	Diarrhea	Amiodarone, astemizole, carbamazepine, cisapride, delavirdine, ergot alkaloids, ethinyl estradiol, midazolam, norethindrone, phenobarbital, phenytoin, quinidine, rifabutin, rifampin, saquinavir, terfenadine, triazolam

*Not currently approved for use in Canada.
Drugs are not listed in order of preference but, rather, chronologically in order of development.

and saquinavir have been found to be effective in reducing viral load, but data on long-term use and clinical outcomes are not yet available.[31] Nelfinavir and saquinavir are being studied as another potential protease inhibitor combination.[38] Cross-resistance between protease inhibitors can limit sequential therapy and requires further clarification. Drug interactions must be considered before combining the non-NRTIs delavirdine and NVP with protease inhibitors.

The expected antiretroviral effect of combination therapy with 2 NRTIs is a decrease of 1.0 to 1.5 $\log_{10}$ HIV-1 RNA copies/mL. A decrease of more than 2.0 $\log_{10}$ HIV-1 RNA copies/mL can be achieved with a triple drug combination of 2 NRTIs and a protease inhibitor. The combinations listed in Table 2 are recommended on the basis of clinical outcome or surrogate marker data. There are no comparative studies indicating preferred initial regimens. Choice of a regimen should take into consideration patient factors related to drug adherence, other medical conditions and medications as well as possible future treatment options.

Combinations that should be avoided include a single NRTI plus a non-NRTI because of the rapid emergence of resistance, and d4T plus AZT because of possible antagonism. Therapy with d4T plus ddC or ddI plus ddC, if used, should be monitored closely because of overlapping toxic effects. Combination therapy with d4T and ddI has been administered without significant toxic effects in the short term.[39]

What is optimal monitoring of therapy?

The clinical parameters that should be monitored include adherence, adverse effects and symptoms of progression (opportunistic infection, weight loss, fever, diarrhea and fatigue). The plasma viral load should be measured 4 to 8 weeks after initiation or change of therapy. An effective regimen should provide a decrease of at least 1 $\log_{10}$ HIV-1 RNA copies/mL at this time. However, maximal viral load reduction may not occur for 16 to 20 weeks. Viral load should be measured every 3 to 4 months thereafter to ensure that viral suppression is maintained. The CD4 count should be determined every 3 to 4 months, because decisions on appropriate chemoprophylaxis for opportunistic infections continue to be based on this measurement.

Table 2: Recommended antiretroviral drug combinations

NRTI combination	Possible third drug
AZT + 3TC	*Protease inhibitor*
d4T + 3TC	Indinavir
d4T + ddI*	Ritonavir
AZT + ddI	Nelfinavir†
AZT + ddC	Saquinavir‡
	or
	Non-NRTI§
	Nevirapine†
	Delavirdine†

*Data on long-term safety are limited.
†Not approved for sale in Canada but may be available through expanded access programs.
‡Given the poor absorption of the currently available formulation, saquinavir is not recommended unless used in combination with ritonavir or nelfinavir. Data on the long-term safety of these combinations are limited.
§Non-NRTIs are not approved for sale in Canada but may be considered as a third drug in combination with 2 NRTIs. Drug interactions must be considered when non-NRTIs are used in combination with protease inhibitors.

Continuing therapy

When should therapy be changed?

The most important determinant is viral load. Ideally, viral load should be below the limits of quantitation of clinically available assays (generally less than 500 HIV-1 RNA copies/mL). If after 4–6 months the viral load has not decreased below 500 copies/mL, therapy may be continued if other therapeutic options are not available or the initial viral load was high enough that it limited an optimal response. These patients should be monitored closely. An increase in viral load after an initial decline to undetectable levels warrants close observation and consideration of treatment alteration. A viral load greater than 5000–10 000 HIV-1 RNA copies/mL indicates treatment failure and the need to change therapy. Therapy should be altered if there is evidence of intolerance to the medication or of major toxic effects. Immunologic (decrease in CD4 count), clinical or virologic progression should prompt consideration of a change in therapy.

What is the antiretroviral therapy of choice if a change is required?

Ideally, 3 new drugs with no overlapping toxic effects and no cross-resistance with previous agents should be considered. If this is not possible, it may be acceptable to offer 2 new drugs as part of a 3-drug regimen. The addition of a single drug to an existing failing regimen is strongly discouraged.

How can the impact of a change in therapy be evaluated?

In addition to clinical improvement, one can expect the CD4 count to stabilize or increase and the viral load to decrease by at least 1 $\log_{10}$, ideally to the desired target of below 500 HIV-1 RNA copies/mL. In patients previously given antiretroviral therapy the latter may not always be achieved, but the goal is to aim for the lowest viral load possible, given individual circumstances.

Can antiretroviral therapy be stopped?

Patients continue to benefit from antiretroviral therapy at all stages of HIV infection. However, quality-of-life issues, including drug intolerances or toxic effects, must be considered throughout the course of disease.

Can prophylaxis be stopped if the CD4 count increases in response to therapy?

Secondary prophylaxis or suppressive therapy against *Pneumocystis carinii* pneumonia (PCP), cerebral toxoplasmosis or cryptococcal meningitis should be continued. It is unknown whether the increased CD4 count in response to antiretroviral therapy is accompanied by restoration of the immune system to the extent that primary prophylaxis can be stopped.

Primary infection

What is primary HIV infection?

The clinical criteria for the diagnosis of primary HIV infection are heterogeneous, and symptoms may or may not develop. The most common acute clinical syndrome associated with primary infection is a mononucleosis-like illness, with fever, lethargy, rash, myalgia, lymphadenopathy and occasionally certain organ-specific symptoms.

Laboratory confirmation occurs when a previously HIV-seronegative person is found to be HIV seropositive. Although seroconversion may take as long as 6 months, it typically occurs in 2–3 months. The presence of p24 antigen in plasma also confirms infection, even if the HIV antibody test result is negative. Patients without p24 antigen but with indeterminate HIV antibody test results on Western Blot testing should be identified for serial testing over the subsequent 6 months because this pattern may represent early seroconversion. Measurement of the plasma HIV-1 RNA level, if available, may aid in early diagnosis.

What are the criteria for starting antiretroviral therapy?

Patients presenting with a compatible clinical syndrome and in whom there is laboratory evidence of confirmed or presumed HIV infection should be offered antiretroviral therapy. All patients, including those who decline treatment, should be offered appropriate counselling as well as clinical and laboratory evaluation and monitoring.

What is the antiretroviral therapy of choice?

The treatment of choice in primary HIV infection consists of triple combination therapy, with 2 NRTIs plus 1 protease inhibitor (Table 2). Other combinations have not been evaluated in this context, and monotherapy is not indicated. The importance of compliance with drug dosage regimens must be emphasized. The long-term benefits of effective combination therapy for primary infection are unknown; therefore, patients should be encouraged to enrol in clinical trials.

What criteria are used to evaluate therapy?

Primarily the plasma viral load and secondarily the CD4 count should be used to evaluate the efficacy of antiretroviral therapy. The goal of therapy should be to reduce the viral load to levels below the limits of quantitation of the currently available assays. Treatment is considered to have failed if the viral load is above 5000–10 000 HIV-1 RNA copies/mL; a change in antiretroviral therapy would thus be indicated to achieve further reduction in viral load, if possible, to less than 500 HIV-1 RNA copies/mL.

When can antiretroviral therapy be stopped?

Clinical criteria for stopping antiretroviral therapy in primary HIV infection include drug intolerance or major toxic effects. Regardless of the stage of infection, patients receiving antiretroviral therapy must be counselled to consult with their physician before stopping any of their drugs, to minimize the development of drug resistance while on a less than fully suppressive drug regimen.

There are as yet no laboratory or virologic criteria for determining the duration of therapy. More sensitive assays of the viral load in plasma and lymphoid tissue and tests for the presence of HIV DNA in the circulation, lymphoid tissue and other sites will be required to determine whether viral eradication can be achieved. At this time, antiretroviral therapy is considered to be a lifelong commitment.

Vertical transmission

Is antiretroviral therapy indicated for all HIV-positive pregnant women?

Without antiretroviral therapy about 25% of infants born to HIV-positive women will be infected.[40] In a randomized controlled trial (AIDS Clinical Trials Group [ACTG] protocol 076) Connor and associates[40] evaluated the use of AZT monotherapy, administered to the mother during the antepartum and intrapartum periods and to the newborn for 6 weeks after birth. The incidence of maternal–fetal transmission was reduced by about two-thirds. The results of this trial strongly support the role of antiretroviral therapy during pregnancy. However, combination therapy,

given its improved therapeutic effects, may be more effective than monotherapy with AZT in preventing vertical transmission, especially if there is increasing AZT resistance.

Women should be counselled at the onset of pregnancy and offered HIV antibody testing early in pregnancy. Treatment decisions must take into account the well-being of both the mother and the infant. Women must be advised concerning the risks to the fetus of exposure to antiretroviral agents, singly or in combination, in both the short and long term. Patients should be followed by or in collaboration with physicians having expertise in this area.

HIV-positive women who become pregnant while being successfully treated with antiretroviral therapy should consider continuing the therapy.

What treatment regimens are available?

The goal of antiretroviral therapy in this setting is to decrease viral load while minimizing fetal drug exposure. Only AZT is licensed in Canada for use during pregnancy, but other antiretroviral agents should be considered after weighing the maternal and fetal benefits and risks. There are few data regarding safety in pregnancy except for AZT use in the ACTG 076 study.[40] Small studies of the combination of AZT and 3TC or NVP suggest that these combinations may be safe to the newborn.[41] Data on other NRTIs are limited. Potential toxic effects in the fetus related to protease inhibitors are unknown.

When should antiretroviral therapy be started in pregnancy?

If the pregnant HIV-positive woman has not previously been given antiretroviral therapy and is asymptomatic, therapy may be started at 14 weeks' gestation. If she is symptomatic, antiretroviral therapy should be chosen using agents that optimize maternal and fetal health, taking into consideration the recommendations for nonpregnant adults and the limited data on toxic effects in the fetus.

How long should newborns be treated?

The results of the ACTG 076 trial suggest that 6 weeks of AZT therapy after birth may be sufficient.[40] Newborns that are possibly HIV positive at 6 weeks may then be given further antiretroviral therapy (see the next section).

Pediatric therapy

Who should receive antiretroviral therapy?

Prophylactic antiretroviral therapy is recommended at birth for all newborns of HIV-positive women. Current practice is to use AZT monotherapy for prophylaxis until the newborn is 6 weeks old. The newborn should be evaluated for HIV infection during the first weeks of life. If at 6 weeks the infant is asymptomatic but the HIV status is still uncertain, prophylaxis against PCP should be started until a definitive diagnosis can be established. If the infant is confirmed to be HIV positive, combination antiretroviral therapy should be considered and PCP prophylaxis continued. Choice of therapy depends on the clinical stage of HIV infection and the degree of immune suppression. The role of viral load in deciding on therapy in newborns has not yet been determined.

Infants and children found to be HIV positive after birth should be offered combination therapy if they are symptomatic or have moderate to severe immune suppression, as defined in the 1994 CDC classification.[35]

What drug regimens are available for pediatric use?

Some pharmacokinetic data are available for the use of the following drugs in children: AZT, ddI, ddC, d4T, 3TC, NVP, ritonavir, indinavir and nelfinavir. A number of combinations have been evaluated in children: AZT plus ddI (ACTG protocol 152),[42] AZT plus NVP (ACTG protocol 180), AZT plus ddC (ACTG 190), ddI plus AZT plus NVP (ACTG 245), and ddI plus d4T (ACTG 327). (Final reports of the preceding trials, except ACTG 152, have not been published yet.) Studies under way include ones evaluating AZT plus ddI (ACTG 232) and AZT plus 3TC (ACTG 300). Because HIV-related encephalopathy is a major problem in children with HIV infection, the ability of an agent to cross the blood–brain barrier is particularly important when choosing antiretroviral agents for pediatric use. For infants and young children, therapeutic choices are limited by the lack of availability of drug suspensions. The only antiretroviral agents with licensed suspensions in Canada are AZT and 3TC. For some of the other agents, suspensions are available through compassionate access programs.

What are the criteria for changing antiretroviral regimens in pediatric cases?

Current criteria for changing therapy in adults are treatment failure, indicated by deterioration of clinical or immune function, or drug intolerance. There is no reason to believe that plasma viral load measurement cannot be used in children to monitor therapy in a fashion similar to that described for adults. However, the algorithm for infants and children probably differs from that for adults. There is insufficient information to make recommendations for this algorithm. Similarly, the clinical application of viral resistance testing has not been established.

Postexposure prophylaxis

Postexposure prophylaxis is recommended if there is a high risk of transmission. The risk is estimated to be about 0.3% for percutaneous exposure to HIV-infected blood.[43,44] The risk after exposure of mucous membrane and skin to HIV-infected blood is significantly lower, about 0.1% and less than 0.1% respectively. Guidelines are available for chemoprophylaxis after occupational exposure to HIV.[45] They are based on data from a retrospective case–control study[46] in which risk was shown to be increased if exposure involved a deep injury to the recipient, visible blood on the device causing the injury, a device previously placed intravascularly, or a source patient who died from AIDS within 60 days after exposure. Treatment recommendations for situations other than those described for health care workers (i.e., possible exposure of law enforcement personnel, cases of sexual assault, condom failure),[47] can be made only on the basis of estimating the degree of risk after consideration of the above factors. The risk of toxic effects must be considered in the recommendation for chemoprophylaxis.

When is postexposure prophylaxis indicated?

The CDC recommendations provide a classification of the site and method of exposure and the risk as evaluated in relation to source material (Table 3).[45,48,49]

Postexposure prophylaxis should be recommended when there is increased risk or if the exposure involves HIV-infected blood. In other situations, the decision to provide postexposure prophylaxis must be made on an individual basis. In all instances appropriate counselling is mandatory.

What antiretroviral regimens should be used?

In a retrospective case–control study postexposure prophylaxis with AZT was associated with a 79% reduction in risk of HIV transmission.[46] Current knowledge would favour the use of combination therapy in this situation, which may have increased efficacy for potentially drug-resistant strains.

Triple combination therapy, as indicated for the treatment of HIV infection in adults, is advised for cases of high-risk exposure. Drug administration should be started as soon as possible after exposure (preferably within 1–2 hours) and continued for 4 weeks. However, starting therapy after a longer interval, such as 1–2 weeks, may be considered for the highest risk exposures. Immediate access to postexposure prophylaxis should be made available, with an initial supply of drugs adequate to allow people time to obtain the remainder of the prescribed therapy. Prescribing physicians should have access to information regarding antiretroviral therapy through appropriate guidelines and through consultation with experts, and patients should have access to counselling services.

What criteria are used to evaluate treatment?

HIV antibody testing should be repeated after baseline at 6, 12 and 36 weeks. If acute seroconversion is suspected or confirmed, the patient should be evaluated and treatment considered (see Primary infection [page 501]). Failure of postexposure prophylaxis is considered if seroconversion occurs within 6 months after exposure. It is critical that surveillance data be collected for epidemiologic evaluation.

Conclusion

The treatment of HIV infection is at a new crossroads with the presence of highly active antiretroviral therapy and the ability to suppress the viral load to levels below the limit of quantitation of current assays. The usefulness of viral load measurement in conjunction with determina-

Table 3: Summary of CDC recommendations for HIV postexposure prophylaxis

Type of exposure	Action
Massive percutaneous exposure (e.g., deep injury with large-bore needle previously in source patient's vein or artery) **or** exposure to lesser amount of blood with high HIV titre	Recommend: AZT (200 mg tid) and 3TC (150 mg bid) with or without IDV*
Massive percutaneous exposure (as above) to blood with high HIV titre	Recommend: AZT (200 mg tid) and 3TC (150 mg bid) and IDV (800 mg tid)†
Percutaneous exposure to lesser amount of blood with low titre, to fluid containing visible blood or to other potentially infectious fluid (semen; vaginal, cerebrospinal, synovial, pleural, peritoneal, pericardial or amniotic fluid) or tissue	Offer: AZT (200 mg tid) and 3TC (150 mg bid)
Mucous membrane or high-risk skin exposure‡ to blood	Offer: AZT (200 mg tid) and 3TC (150 mg bid) with or without IDV*
Mucous membrane or high-risk skin exposure to fluid containing visible blood or other potentially infectious fluid or tissue	Offer: AZT (200 mg tid) with or without 3TC
Percutaneous, mucous membrane or skin exposure to other body fluid (e.g., urine)	Do not offer prophylaxis

Note: CDC = US Centers for Disease Control and Prevention, IDV = indinavir.
*Possible toxic effects of other drug may outweigh benefit.
†If IDV is unavailable, saquinavir (600 mg tid) may be subsituted.
‡High-risk skin exposure = high HIV titre in source patient; prolonged contact; extensive area involved; skin integrity compromised.
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tion of the CD4 count is now well established, and these measurements should be routine in the care of HIV-positive patients. The guidelines in this article are intended to help physicians inform and treat their HIV-positive patients according to current knowledge. Because new information is constantly emerging, these guidelines will be updated periodically. When possible, consultation[50] with an expert in antiretroviral therapy is recommended, and programs to facilitate this are available in Canada.

Addendum

Following the workshop, during the preparation of this article, additional sets of antiretroviral therapy guidelines were published.[51–55] The Canadian HIV Trials Network Antiretroviral Working Group will review them in the near future and subsequently update our guidelines. For example, since preparation of this article, expert opinion has moved toward the initiation of antiretroviral therapy in adolescents and adults using 3 drugs (e.g., a protease inhibitor plus 2 NRTIs). Although we are confident that our guidelines will be useful in most situations, we recognize that there have been recent advances and revised recommendations in the area of pediatric therapy. For the time being, we point readers to the revised pediatric guidelines[54] for further information.

Since preparation of this article, new antiretroviral drugs are now in clinical development, some of which may be available through expanded access programs: one NRTI — 1592U89 (abacavir); a nucleotide RTI — GS840 (adefovir dipivoxil [Preveon]); a non-NRTI — DMP-266 (efavirenz [Sustiva]); a nonpeptidic protease inhibitor — 141 W94, VX-470 (amprenavir); and Combivir (a new fixed combination of 300 mg of AZT plus 150 mg of 3TC).

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