

Antiretroviral therapy for adults infected with HIV: Guidelines for health care professionals from the Quebec HIV care committee

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The appropriate use of antiretrovirals reduces morbidity and mortality caused by HIV infection. The present article provides health care professionals with a practical guide for the use of antiretrovirals. Therapy should be initiated based predominantly on clinical presentation and CD4 count, and should consist of three active drugs or at least two active drugs when this is not possible, as in cases of some treatment-experienced patients. This is the most effective way to achieve long-term suppression of viral replication. Selection of individual drugs in the regimen should consider the weight of the evidence supporting these choices, as well as their tolerability profiles and ease of use, the patients' comorbidities and treatment history. Treatment interruption is not recommended, either in aviremic patients or in those who have experienced virological failure. Instead, the therapeutic regimen should be adjusted to minimize side effects, promote adherence and suppress viral replication.

Key Words: Antiretrovirals; HAART; HIV; Practical guide

Antiretroviral therapy decreases mortality rates and improves quality of life by suppressing HIV replication. The availability of new generations of antiretrovirals opens additional therapeutic options for many patients, but also makes the task of optimizing treatment more complex. The present article provides health care professionals with a practical guide to antiretroviral therapy for HIV-infected adults. These recommendations also serve to support academic teaching and continuous medical education, as well as giving clinicians a voice in governmental decision-making processes.

The present guide was developed by a writing committee and approved by the Comité consultatif sur la prise en charge clinique des personnes vivant avec le VIH (Advisory Committee on the Clinical Management of Persons Living with HIV) – a Quebec-based panel of experts mandated by the Ministère de la Santé et des Services sociaux (Ministry of Health and Social Services) to establish clinical guidelines for the management and treatment of persons living with HIV. These recommendations were achieved by consensus and were based

L'antirétrovirothérapie pour les adultes infectés par le VIH : Lignes directrices pour les professionnels de la santé du comité québécois des soins du VIH

L'utilisation pertinente d'antirétroviraux réduit la morbidité et la mortalité attribuables à l'infection par le VIH. Le présent article fournit aux professionnels de la santé un guide pratique sur l'usage des antirétroviraux. Pour amorcer la thérapie, il faut se fier en grande partie à la présentation clinique et à la numération des lymphocytes CD4. Cette thérapie doit se composer de trois médicaments actifs ou, si c'est impossible, d'au moins deux médicaments actifs, comme c'est le cas chez certains patients déjà traités. C'est le moyen le plus efficace d'obtenir une suppression à long terme de la réplication virale. La sélection des médicaments de cette posologie doit tenir compte du poids de la preuve en appui à ces trois choix, de même que des profils de tolérabilité et de la facilité d'utilisation, des comorbidités du patient et de ses antécédents thérapeutiques. L'interruption du traitement n'est pas recommandée, que ce soit chez les patients avirémiques ou chez ceux qui ont subi un échec virologique. Il faut plutôt rajuster la posologie pour réduire les effets secondaires au minimum, promouvoir l'adhésion au traitement et supprimer la réplication virale.

on data from the published literature, or data presented at major scientific congresses up to June 2009 and the clinical expertise of the committee members.

Each recommendation is graded using a letter and a Roman numeral. As outlined in Table 1, the letter indicates the strength of the recommendation in the opinion of the committee members, while the numeral refers to the type of evidence on which the recommendation is based (1). Preferred regimens include strongly or moderately recommended medications for which efficacy data are conclusive. A moderate recommendation indicates that there are conflicting data on the efficacy, potential significant side effects or limited experience in a particular indication.

The present report is a condensed version of the document titled "La thérapie antirétrovirale pour les adultes infectés par le VIH. Guide à l'intention des professionnels de la santé du Québec", which will be available on the Ministère de la Santé et des Services sociaux website (<http://publications.msss.gouv.qc.ca/acrobat/f/documentation/>), as well

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TABLE 1
Explanation of recommendation grading system

Strength of recommendation	
A	The therapy is strongly recommended
B	The therapy is moderately recommended
C	Implementation of the recommendation is optional
D	The therapy is generally not recommended
E	The therapy is contraindicated
Type of evidence	
I	At least one randomized controlled clinical trial
II	Noncontrolled clinical studies, case studies or cohort studies
III	Expert opinion

Adapted from reference 1

as on the Programme national de mentorat sur le VIH/Sida (National HIV/AIDS Mentorship Program) website (www.pnmvs.org). The source article includes an extensive review of the studies on which the following recommendations are based, as well as a table summarizing the relevant drug-drug interactions.

THE PRINCIPLES OF ANTIRETROVIRAL THERAPY

The goals of antiretroviral therapy in HIV infection are multifold and often complementary. In addition to maintaining the health of persons living with HIV and reducing morbidity and mortality due to HIV infection, they include the following: long-term suppression of viral replication; improvement in immune function and enhancement of the quality of life in HIV-infected persons; prevention of viral resistance to medications; minimizing medication-related side effects; preserving future therapeutic options and preventing mother-to-child transmission of HIV. All persons infected with HIV, even those receiving antiretroviral therapy who have a plasma viral load below the threshold for detection, should be considered to be potentially infectious and should receive appropriate advice on the risks of HIV transmission. This position is different than that of the Commission fédérale suisse pour les problèmes liés au sida (Swiss Federal Commission for HIV/AIDS), which states that a seropositive person not harbouring any other sexually transmitted infection and undergoing antiretroviral treatment with completely suppressed viremia does not transmit HIV through sexual contact (2). The Swiss position is not endorsed by the international medical community because the currently available evidence does not prove that effective antiretroviral therapy prevents all transmission of HIV (3). Although no well-documented cases of transmission in the presence of a viral load of less than 50 copies/mL have been reported (4,5), cases of viral replication in sperm and female genital secretions have been documented in the absence of viral replication in plasma (6-8). Thus, insofar as low-level viral replication can occur even when the plasma viral load is below the threshold for detection, a theoretical risk of HIV transmission exists even in patients with an undetectable viral load (9) and this risk should be discussed with serodiscordant couples.

Long-term suppression of HIV replication is achieved through a combination of fully active antiretroviral drugs, determined based on the results of resistance testing and the patient's history of drug exposure.

INITIATION OF ANTIRETROVIRAL THERAPY

Antiretroviral therapy should be initiated for AIDS patients and individuals presenting with serious clinical symptoms related to HIV (such as fever, weight loss, diarrhea, severe *Candida* infection, etc), independent of CD4 count and viral load (AI) (Table 2).

In asymptomatic patients, the risk of progression to AIDS or recurrence of an opportunistic infection increases with the presence of one

TABLE 2
Initiation of antiretroviral therapy based on clinical presentation and CD4 count

Clinical presentation	CD4 count (cells/ μ L)	Treatment recommendation (strength of evidence)
Symptomatic	All counts	Initiate therapy (AI)
Opportunistic infection		
AIDS-associated neoplasia		
HIV-associated nephropathy		
Pregnancy		
HIV/HBV coinfection	All counts	Initiate regimen including two anti-HBV NRTIs (tenofovir plus either lamivudine or emtricitabine) when treatment of hepatitis is required (AII)
Asymptomatic	<350	Initiate therapy (AII)
Asymptomatic	\geq 350	Individualize decisions taking into consideration viral load, clinical context and comorbidities* (CIII)

**Factors that must be taken into account include the patient's motivation, viral load, rate of decline of CD4 count and coinfection with the hepatitis C virus, because early antiretroviral treatment can delay progression to fibrosis. Antiretroviral therapy should be considered for patients with a CD4 count of greater than 350 cells/ μ L, if the CD4 count is declining rapidly (decrease of more than 100 cells/ μ L/year) or if the HIV viral load is greater than 100,000 copies/mL (CII). HBV Hepatitis B virus; NRTIs Nucleoside and nucleotide reverse transcriptase inhibitors*

or more of the following factors: lower CD4 count, viral load of 100,000 copies/mL or greater, older than 50 years of age, injection drug use and previous diagnosis of AIDS (10-14).

Of these factors, CD4 count is paramount in establishing when to initiate treatment, although the viral load may predict the rapidity of progression (10-12). There is evidence from cohort studies (12,15-17) that antiretroviral treatment is associated with survival benefits in asymptomatic patients with a CD4 count below 200 cells/ μ L. However, there are no data from controlled studies confirming the optimal time to initiate antiretroviral therapy in asymptomatic patients with a CD4 count above 200 cells/ μ L. Observational cohort studies (18-20) evaluating survival as a function of CD4 count at the start of treatment have shown that there is a significant advantage to beginning treatment near the 350 cells/ μ L threshold. The benefits of initiating treatment above 350 cells/ μ L are less certain, although cohort studies have demonstrated that such therapy is associated with more frequent normalization of CD4 count (14,21), a decrease in mortality in one study (20) and a lower risk of conditions such as peripheral neuropathy, anemia and renal insufficiency (22) compared with starting treatment at a CD4 count of less than 350 cells/ μ L.

Treatment of asymptomatic HIV infection should be initiated when the CD4 count has been shown by repeated testing to have decreased to 350 cells/ μ L (AII) (Table 2). For patients with CD4 counts of greater than 350 cells/ μ L, antiretroviral treatment should be considered if the CD4 count declines rapidly (at a rate greater than 100 cells/ μ L/year) or if the plasma viral load is greater than 100,000 copies/mL (CII) (23,24). Other factors to consider when deciding whether to initiate therapy include the patient's willingness to start treatment (12) and whether the patient is coinfecting with the hepatitis C virus, because early antiretroviral treatment can delay progression to liver fibrosis in coinfecting patients (25,26). Other conditions, such as HIV-associated nephropathy, infection with hepatitis B virus (HBV) and pregnancy, may also influence the decision to initiate treatment (Table 2). For instance, pregnant women should be treated regardless of CD4 count to prevent maternofetal transmission of HIV (AI).

HIV-associated nephropathy, a condition observed more frequently in black people, is a cause of chronic kidney disease in persons living

TABLE 3
Antiretroviral agents available in Canada

NRTIs	NNRTIs	Protease inhibitors	Entry inhibitors	Integrase inhibitors
Nucleoside inhibitors	Delavirdine	Atazanavir	Fusion inhibitors	Raltegravir
Abacavir	Efavirenz	Fosamprenavir	Enfuvirtide [†]	Elvitegravir [†]
Didanosine	Nevirapine	Indinavir		
Emtricitabine*	Etravirine [†]	Lopinavir		
Lamivudine	Rilpivirine [‡]	Nelfinavir		
Stavudine	Lersivirine [‡]	Ritonavir		
Zidovudine		Saquinavir		
		Tipranavir [†]		
		Darunavir		
Nucleotide inhibitors			CCR5 antagonists	
Tenofovir			Maraviroc [†]	
			Vicriviroc [‡]	

*Only available in coformulation with tenofovir (Truvada [Gilead Sciences, USA]); †Only indicated in treatment-experienced patients in Canada; ‡Medications in development currently being used in research in Canada – other medications currently in development may not be listed. NNRTIs Non-nucleoside reverse transcriptase inhibitors; NRTIs Nucleotide and nucleoside reverse transcriptase inhibitors

with HIV. The pathogenesis of this condition involves replication of HIV in kidney tissue. Antiretroviral therapy has been shown to preserve renal function and improve survival prognosis in these patients regardless of the degree of immunosuppression (27,28). Treatment of HIV-associated nephropathy with antiretroviral therapy is thus recommended, regardless of CD4 count (AII).

When treatment of HBV infection is required in the context of HIV coinfection, initiating anti-HIV therapy that includes tenofovir with lamivudine or emtricitabine, which acts against both HIV and HBV, is recommended (BIII). This recommendation aims to avoid exposing HIV to suboptimal nucleoside or nucleotide analogue monotherapy when treatment for HBV is required and CD4 counts have not decreased below the 350 cells/ μ L threshold (29).

Finally, there is no conclusive evidence to suggest that the treatment of acute HIV infection should be based on different criteria than those used for chronic infection. However, treatment may be offered to persons presenting with recent HIV seroconversion (less than six months) in the context of a clinical trial, in consultation with an expert in this area (CIII) (30).

SELECTION OF FIRST-LINE ANTIRETROVIRAL TREATMENT

Antiretroviral agents available in Canada (Table 3), whether currently approved or available through compassionate access programs or research protocols, can be divided into six classes:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs);
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs);
- Protease inhibitors (PIs);
- Entry inhibitors, which include two classes:
 - Fusion inhibitors, and
 - Chemokine receptor antagonists such as CCR5 antagonists; and
- Integrase inhibitors.

First-line therapeutic regimens should include a backbone of two NRTIs (listed in column A of Table 4) and a third medication consisting of an NNRTI, a PI or an integrase inhibitor (listed in column B of Table 4). Combinations of three NRTIs should be only rarely used – for instance, when interactions and side effects exclude the use of other drug classes.

The NRTI backbone should consist of tenofovir with either emtricitabine (coformulated as Truvada [Gilead Sciences, USA]) or

lamivudine, or abacavir and lamivudine (coformulated as Kivexa [GlaxoSmithKline Inc, Canada]). However, both of these options may be associated with potential risks. For instance, the use of tenofovir has been associated with decreased glomerular filtration rate and tubular dysfunction, the so-called Fanconi syndrome. Although this renal toxicity has been rarely observed in published clinical trials, it has been well described in cohort studies and numerous case reports and case series. Additionally, conflicting data raise the possibility that abacavir is associated with an increased risk of myocardial infarction (31-33) or virological failure in patients with a viral load of greater than 100,000 copies/mL before initiating treatment (34). Nonetheless, randomized trials and other studies (35-38) have demonstrated no increased risk of myocardial infarction or virological failure in patients with high viral loads at inclusion with abacavir. Thus, abacavir remains a preferred option in treatment-naïve patients who are not carriers of the HLA-B*5701 allele. Caution is advised when prescribing abacavir to patients at high risk for cardiovascular events or for virological failure due to high viral loads. Backbones consisting of the older thymidine analogues, including zidovudine or stavudine, are not recommended as first-line options due to their lipodystrophic effects and increased risk of precipitating conditions such as peripheral neuropathy and lactic acidosis (39). Zidovudine is still recommended for use in pregnancy to prevent vertical transmission, unless contraindicated due to resistance, intolerance or significant anemia.

The third agent in a regimen should consist of efavirenz, raltegravir or a PI, such as atazanavir, lopinavir, fosamprenavir, saquinavir or darunavir, used in conjunction with low-dose ritonavir (ie, a boosted PI). Efavirenz has been proven effective and well tolerated when used in combination with an NRTI backbone (40,41). In addition, most studies comparing efavirenz with a PI have demonstrated a lower rate of treatment failure with efavirenz (42-44), as well as a lower risk of cardiovascular events (31,33). Clinical trials have shown that when boosted with ritonavir, fosamprenavir (45), saquinavir (46), atazanavir (47) and darunavir (48) were noninferior to boosted lopinavir, which is the standard comparator in PI studies due to its demonstrated benefit compared with an older unboosted PI (49), as well as its relatively large body of long-term clinical trial data. Raltegravir has been shown to be noninferior to efavirenz in two trials (50,51) conducted in treatment-naïve populations.

When selecting antiretroviral agents, consideration should first be given to easy-to-use combinations with proven efficacy, durability and acceptable tolerability profiles (listed as recommended combinations in Table 4). Treatment selection should also be based on the results of a genotypic resistance test, which should be conducted as early as possible in the course of HIV infection (AII). When combinations are contraindicated due to comorbidities, specific conditions or side effects, alternative combinations with poorer side effect profiles or less supporting evidence should be considered (listed as alternative combinations in Table 4). Other combinations (listed as nonrecommended combinations in Table 4) should be avoided, unless the potential benefit in a specific situation exceeds the risk. Certain antiretroviral drugs are mutually contraindicated. These combinations (listed as contraindicated combinations in Table 4) should never be used.

MODIFICATIONS TO INITIAL ANTIRETROVIRAL TREATMENT

An antiretroviral regimen may be changed to reduce or prevent side effects, facilitate adherence and in case of virological failure. Different strategies may be used depending on the desired result.

If the aim of the therapy modification is to manage side effects or improve adherence, the medication causing the problem may be replaced or the dosing regimen may be simplified.

In patients experiencing virological failure, the objective is to improve virological control. Intensification of therapy, consisting of adding only one active drug to a failing regimen, has not been shown to be effective in preventing subsequent treatment failure (52-54). Usually, the

TABLE 4
Guide to selecting agents for first-line antiretroviral therapy

	Column A: NRTI backbone	Column B: Third medication in regimen (PI, NNRTI, INI)
Recommended combinations	Tenofovir* [†] + lamivudine or tenofovir* [†] + emtricitabine (coformulated as Truvada) (AI) Abacavir + lamivudine (coformulated as Kivexa) ^{‡§} (BI)	Efavirenz qd ^{††} (tenofovir + emtricitabine + efavirenz is coformulated as Atripla) (AI) Atazanavir/ritonavir qd ^{††§§} (BI) Darunavir/ritonavir qd ^{††‡} (BI) Fosamprenavir/ritonavir bid ^{§**} (BI) Lopinavir/ritonavir qd or bid [§] (coformulated as Kaletra) (BI) Saquinavir/ritonavir bid (BI) Raltegravir bid [†] (BI)
Alternative combinations	Didanosine + lamivudine (CI) Zidovudine + lamivudine (CI)	Nevirapine bid ^{¶¶} (CI) Atazanavir qd ^{††‡***} (CI) Fosamprenavir/ritonavir qd ^{†§} (CI)
Nonrecommended combinations	Stavudine + didanosine (DI) Stavudine + lamivudine (DI) Zidovudine + lamivudine + abacavir (coformulated as Trizivir) (DI) [¶]	Delavirdine (DIII) Indinavir (DI) Indinavir/ritonavir (DII) Nelfinavir (DI) Ritonavir (DI) Saquinavir (DI)
Contraindicated combinations	Lamivudine + emtricitabine (EIII) Tenofovir + didanosine with an NNRTI** (EI) Tenofovir + abacavir + lamivudine (EI) [¶] Tenofovir + didanosine + lamivudine (EI) [¶] Zidovudine + stavudine (EIII)	

The strength of evidence is presented in parentheses. Medications in column B are presented according to class. *Tenofovir should be used with caution in patients with altered renal function or those taking concomitant nephrotoxic medications; [†]Insufficient data in pregnant women; [‡]This combination should be used when the results of the HLA-B*5701 test are negative, but it may be associated with lesser efficacy in patients with a viral load of 100,000 copies/mL or greater. The combination has not been studied in combination with darunavir/ritonavir once a day (qd), saquinavir/ritonavir or raltegravir in treatment-naïve patients; [§]May be associated with an increased risk of cardiovascular disease; [¶]Regimens based on three nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs); **The efficacy of a regimen consisting of tenofovir + didanosine + a protease inhibitor (PI) is unknown. The dose of didanosine should be reduced when used concomitantly with tenofovir; ^{††}Women of childbearing age should use effective contraception. The use of efavirenz should be avoided during pregnancy; ^{†††}The association between vascular diseases and atazanavir, atazanavir/ritonavir and darunavir/ritonavir has not yet been studied; ^{§§}Atazanavir should always be boosted with ritonavir if used with tenofovir; ^{¶¶}Nevirapine is considered to be an alternative solution for women with CD4 counts of lower than 250 cells/μL and for men with CD4 counts of lower than 400 cells/μL. Nevirapine should not be initiated in individuals with higher CD4 counts, unless the benefits clearly exceed the risk; ^{***}Unboosted atazanavir should not be used with didanosine + lamivudine (111). Atripla (Bristol-Myers Squibb, USA; and Gilead Sciences, USA); Kaletra (Abbott Laboratories, USA); Kivexa (GlaxoSmithKline Inc, Canada); Trizivir (GlaxoSmithKline Inc, Canada); Truvada (Gilead Sciences, USA). bid Twice a day; INI Integrase inhibitors; NNRTIs Non-nucleoside reverse transcriptase inhibitors

presence of resistance mutations in these patients requires that some or all of the current antiretrovirals in the therapeutic regimen be replaced by active drugs.

Treatment interruptions in aviremic patients

Evidence shows that persons living with HIV experience clinical disease progression when antiretroviral treatment is interrupted (55,56). For this reason, treatment interruptions are not recommended in clinical practice (DI).

However, if treatment must be stopped, it is safer to do so in asymptomatic patients with no history of syndromes indicative of AIDS and in patients with a nadir CD4 count of greater than 350 cells/μL (CII) (57-59). If the patient's regimen contains an NNRTI, the NNRTI may be replaced by a boosted active PI for a period of as long as four weeks before interrupting therapy to avoid functional monotherapy and prevent the emergence of resistance mutations to NNRTIs due to their long half-life and low genetic barrier to resistance (CIII) (55,56,60-62). Patients require careful follow-up involving clinical evaluation, CD4 cell count, measurement of HIV viral load and genotypic testing during the interruption period (BII). Patients should also be advised regarding the risks of occurrence of opportunistic infection, HIV primary infection syndrome, disease progression with rapid decrease in CD4 count and elevation of HIV viral load, transmission of HIV and development of viral resistance. Medication should be resumed at a CD4 count of higher than 250 cells/μL (BII), although the safe

threshold for resuming treatment has yet to be determined and is probably as high as 350 cells/μL (56,57).

Switching antiretroviral agents

Antiretroviral therapy may be associated with adverse effects in some patients; various alternative strategies have been shown to reduce certain side effects. Switching from one boosted PI to another may simplify the dosing regimen or reduce certain side effects (63-66). For example, switching from a PI other than darunavir to atazanavir, boosted atazanavir, nevirapine, abacavir or raltegravir may improve the lipid profile and reduce hyperlipidemia (67-74). However, the noninferiority of raltegravir has not yet been demonstrated with regard to switches from a PI to raltegravir, particularly in patients with previous therapeutic failures (74). For this reason, switching from a PI to raltegravir should be avoided in cases of previous failure, NRTI resistance acquired during primary infection or exposure to suboptimal monotherapy or dual therapy. Similarly, switching from a PI to abacavir should be avoided under the same circumstances because such switches have been shown to occasionally result in a resurgence of viremia (69,71,75). In the absence of more conclusive data, the same precautions are warranted for switching from a PI to an NNRTI or unboosted atazanavir. On the other hand, switching from enfuvirtide to raltegravir in treatment-experienced patients, whose current regimen fully suppresses viral activity, maintains viral suppression and improves patient quality of life (76).

TABLE 5
Therapies to consider based on the type of regimen failed

Type of regimen failed	Therapy for treatment-experienced patients
Three NRTIs	Two active NRTIs + one boosted PI Two NRTIs with residual activity, one boosted PI + one NNRTI
NRTIs + NNRTI	Two active NRTIs + one boosted PI
NRTIs + PI or boosted PI	Two NRTIs + one boosted PI to which the virus remains susceptible including, as necessary, boosted darunavir or boosted tipranavir for patients demonstrating extensive resistance to other PIs Two fully active NRTIs + one NNRTI Two NRTIs + one boosted PI + one NNRTI
NRTI + PI + NNRTI	Two active NRTIs + one boosted PI to which the virus remains susceptible including, as necessary, boosted darunavir or boosted tipranavir for patients demonstrating extensive resistance to other PIs Etravirine + NRTI + darunavir/ritonavir for patients demonstrating resistance to other PIs; lopinavir/ritonavir or saquinavir/ritonavir may be used as alternative boosted PIs Use maraviroc (in patients with R5-tropic virus) and raltegravir as necessary with NRTIs, new generation PIs and/or enfuvirtide to establish a therapeutic regimen including at least two and, if possible, three active medications There are no data on the relevance of maintaining NRTIs or PIs in the regimen in cases of extensive resistance to these agents Use investigational therapies as necessary to establish an active therapeutic regimen

NNRTI Non-nucleoside reverse transcriptase inhibitors; NRTI Nucleoside and nucleotide reverse transcriptase inhibitors; PI Protease inhibitor

Thymidine analogues, such as stavudine and zidovudine, are associated with an increased risk of lipodystrophy and lactic acidemia (77), and switching from these drugs to abacavir or tenofovir can partially reverse or prevent these conditions (78-84). However, switching from a thymidine analogue to abacavir may theoretically increase the risk of cardiovascular disease (31,33,85). Thus, when considering switching antiretroviral agents to improve adherence or quality of life, the risks and benefits of the proposed modifications should be carefully considered. It is also important to ensure that the new therapeutic regimen maintains the genetic barrier to resistance and does not entail drug interactions that could compromise an antiretroviral agent's effectiveness.

Regimen changes after virological failure

Since 2002, the incidence of virological treatment failure has decreased in the developed world, possibly because of access to simpler and better tolerated therapies and the greater emphasis placed on adherence (86,87). Despite this improvement, the emergence of drug-resistant viral strains remains an issue in the treatment of persons living with HIV.

In cases of suspected virological failure, it is important to confirm treatment failure by taking a second viral load measurement (AII). Virological failure is defined by many experts as a viral load of greater than 1000 copies/mL after 16 weeks of treatment, 400 copies/mL after 24 weeks of treatment or 50 copies/mL after 48 weeks of treatment. The cause of the failure should be determined by assessing the patient's adherence to therapy and, if necessary and possible, by measuring plasma levels of PIs and NNRTIs to evaluate whether pharmacokinetic factors are contributing to treatment failure. HIV genotypic testing should also be undertaken, and results should be interpreted taking into account both the patient's past therapies and the results of previous genotypic tests. When the use of a CCR5 antagonist is being considered, tropism testing is also required. The results of these tests, in conjunction with the patient's history of therapeutic regimens, comorbidities and adverse events, can then be used to determine viable therapeutic options to control viral replication.

As with first-line treatment, the goal of a second-line regimen is to achieve and maintain viral suppression, as indicated by a viral load of consistently less than 50 copies/mL. At least two active drugs should be included in any regimen (AI), and three active drugs should be used when possible (AI). When only partially active drugs are included in the regimen, more than three drugs might be required for complete viral suppression. New classes of antiretrovirals may be combined as required to achieve this goal. However, using a drug from a new class

as the only active medication in a regimen (DII) should be avoided, unless the patient's condition is seriously compromised in the short term (CIII).

The specific types of medications included in a second-line regimen will likely depend on the patient's previous regimen (Table 5). In patients failing a regimen including only NRTIs, studies (88) have demonstrated the effectiveness of regimens consisting of a PI and two new NRTIs with no cross-resistance to previously failed NRTIs or a boosted PI, one NNRTI and two NRTIs with residual activity. Studies (89,90) evaluating treatment options in patients failing first-line therapy consisting of NRTIs and an NNRTI suggest that a regimen of a boosted PI and active NRTIs is effective in this population. Regimens including two active NRTIs and an active boosted PI with or without an NNRTI may be considered for patients who failed a PI-based regimen (89-97).

Various therapeutic options are now available, even for patients who failed treatment using the three traditional classes of antiretroviral therapy (Table 5). Newer boosted PIs, such as darunavir and tipranavir, provide an alternative for some patients with extensive resistance to other PIs (98,99). Similarly, etravirine is a new NNRTI that, when used with a boosted active PI such as darunavir, lopinavir or saquinavir and other active drugs, has been shown to effectively suppress viral replication in patients resistant to first-generation NNRTIs and the two other traditional classes of drugs but with no significant resistance to etravirine (100,101). Other options shown to be effective in such treatment-experienced patients include antiretroviral agents from new classes, such as maraviroc (used in patients with R5-tropic virus) (102), raltegravir (103-105) and enfuvirtide (106,107). These new classes of antiretrovirals may be combined with NRTIs, PIs or new generation NNRTIs to establish a therapeutic regimen that includes at least two, and possibly three, active molecules (AI). When attempting to establish an active therapeutic regimen, it is recommended to consult an expert to explore access to new medications through clinical trials or compassionate access programs (CIII).

If it becomes necessary to select from drugs with compromised antiviral activity, well-tolerated antiretrovirals with residual antiviral activity or the ability to decrease viral replication (CIII) should be chosen. Interrupting treatment is not recommended in patients who have experienced virological failure. Clinical progression has been observed in studies evaluating this strategy (108,109). However, if a patient must take a drug holiday and is harbouring a virus with an M184V resistance mutation, retaining lamivudine as monotherapy is preferable to complete cessation of therapy, because this may have a beneficial effect on virological and immunological parameters (CI) (110).

CONCLUSIONS

By suppressing viral replication and maintaining adequate CD4 levels, antiretroviral therapy reduces morbidity and mortality. A therapeutic regimen consisting of three active antiretroviral agents is considered to be the most effective way to achieve this goal, and should be initiated in patients presenting with AIDS, serious clinical symptoms related to HIV, HIV-associated nephropathy, coinfection with HBV when treatment of hepatitis or HIV is required, pregnancy or a CD4 count of less than 350 cells/ μ L. Medications should be selected taking into consideration the medications' effectiveness and tolerability profiles, as well as the patient's concomitant conditions and treatment history. Treatment interruption is associated with clinical progression and should generally be avoided in both aviremic patients and those experiencing virological failure. Instead, the therapeutic regimen should be adjusted as necessary to minimize side effects, promote adherence and achieve a viral load of less than 50 copies/mL.

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