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European guidelines for the clinical management and treatment of HIV-infected adults in Europe

Editors: Robert L Murphy
Brian Gazzard

LIPPINCOTT WILLIAMS & WILKINS

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Editorial

Robert Murphy[a] and Brian Gazzard[b]

Antiretroviral treatment guidelines have a number of important functions. In a field that changes as rapidly as HIV therapeutics, periodic review of the best quality and most up-to-date evidence from randomized and controlled clinical trials is of critical importance for all clinicians especially those with limited experience in retroviral therapy. Of more importance is providing treatment consensus in therapeutic areas where evidence to guide clinicians is less secure. Such guidelines also help to reassure third party payers and public health authorities that their actions are appropriate and defensible.

Some years ago, guidelines in Europe and the United States were widely disparate. The strength of the "Hit Early, Hit Hard" editorial in 1995 [1] which accompanied early results with protease inhibitors, was that it formed a testable hypothesis, albeit a wrong one. Observational cohorts, such as the Multicenter AIDS Cohort Study, have provided supporting evidence that deferral of therapy is actually a reasonable option for a significant proportion of patients [2,3]. Strategic studies have still not been developed to address the "when to treat" question, although the SMART study organized by the CPCRA may do so for a naïve-treatment population. Guidelines in 2002 have converging views about the optimum timing of therapy initiation based upon the pragmatic issues related to the inability to eradicate HIV infection with prolonged treatment, long term toxicities and difficulties with adherence over many years.

With regard to potency, it appears that many regimens in present use today have very similar potency and therefore, the main differentiating factors are adherence and toxicity. Although strenuous efforts have been made to improve adherence with a variety of physical and psychological aids, these have had little impact [4–7]. The developing paradigm is of simplifying regimens and thus making drugs easier to adhere to rather than expect a treated individual to change his or her lifestyle.

Guidelines are very influential but it is important that they are not given a status that stifles innovative research to improve patient treatment. It is also important to recognize that they may be appropriate for only a small percentage of the world's HIV-infected population. Such guidelines should not be perceived to be the standard of care in resource limited countries and regions. One of the ethical principles that we all espouse is that the cost of treatment should not disadvantage other individuals in need and thus it behooves all of us, particularly those in resource limited settings, to obtain best value for money. It would be wrong to translate European guidelines unchanged into different settings without a frank assessment of the cost implications.

The influential nature of these guidelines also means that we have to be scrupulously careful that they are free of commercial influence. By and large, the synergism between the treating community and pharmaceutical and diagnostics companies works to everyone's advantage, but as with the European guidelines published here, it is essential that there is complete transparency about potential conflicts of interest.

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European guidelines for the clinical management and treatment of HIV-infected adults in Europe

The EACS Euroguidelines Group

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Introduction

Many clinical guidelines for the treatment and management of patients with HIV infection have been published. None addresses the care of the patient from a European perspective.

Patient management in Europe benefits from numerous particularities, the most obvious being the access to care that is almost universal and is related to the social security systems existing in most western European countries. In addition, the European Union has a centralized process of drug registration, through the European Agency for the Evaluation of Medicinal Products, which aims to homogenize access to new drugs throughout Europe.

However, there still exist important differences in the treatment and management of patients with HIV infection within different regions of Europe, making it appropriate to define common guidelines.

Therefore, the European AIDS Clinical Society (EACS) convened a meeting in Brussels in May 2001 bringing together a group of specialists, including clinicians, virologists and immunologists from major HIV clinical centres in Europe. A consensus guidelines document was drawn up that includes comprehensive clinical recommendations on the initiation of therapy, patient follow-up and the management of toxicities and treatment failures. These guidelines were updated in December 2002.

Considerations of resistance testing are only briefly discussed in these guidelines, as these have been extensively covered in the European Guidelines on resistance.

Specific topics, such as treatment during pregnancy, management of the HIV-2-infected patient, as well as that of hepatitis C virus (HCV) or hepatitis B virus (HBV) co-infected patients have been included. Information on anti-HIV drugs, together with recommendations on the prevention of opportunistic infections (OI), are presented in the appendices.

These guidelines attempt to summarize the current state of knowledge of HIV disease management and treatment, which is a rapidly evolving medical field and will therefore require regular change and update in the coming years. They are not intended to be an exhaustive document, but rather a useful and practical guide for practitioners.

Follow-up of HIV-infected adult patients in Europe

The recommendations made here include: the lists of tests that should be performed in a patient recently diagnosed with HIV infection; the follow-up of untreated patients; and the follow-up of treated patients (see Table 1).

These recommendations refer to the standard follow-up of a patient. Additional investigations should be performed as appropriate to the individual condition or clinical history of the patient. For considerations of resistance testing, refer to the resistance guidelines [1].

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Table 1. Recommendations for follow-up of HIV-infected adult patients in Europe.

Tests	Newly diagnosed patient	Untreated patient	Treated patient
HIV viral load	✓ (consider controlling viral load if acute infection is suspected)	2–4/year	After treatment initiation, months 1 and 3 and 4/year thereafter
CD4 cell count	✓	2–4/year	4/year
Complete blood cell count	✓	2–4/year	4/year
Liver		If clinically indicated	4/year
ASAT, ALAT, alkaline phosphatase, LDH, bilirubin	✓		
Kidney		If clinically indicated	4/year
Urea, creatinine	✓		
Pancreas		If clinically indicated	4/year
Amylase, lipase	✓		
Lipids[a]		If clinically indicated	4/year
Cholesterol, (HDL-cholesterol), triglycerides	✓		
Glucose[a]	✓	If clinically indicated	4/year
CPK, lactate		If clinically indicated	If clinically indicated
Serology			
Anti-HAV IgG[b]	✓	Re-check annually[d]	Re-check annually[d]
HbsAg	✓	If clinically indicated	If clinically indicated
Anti-HBc IgG, anti-HBs[b]	✓	Re-check annually[d]	Re-check annually[d]
Anti-HCV IgG[c]	✓	Re-check annually[d]	Re-check annually[d]
VDRL, TPHA (syphilis), IgG if available, toxoplasmosis (IgG), CMV (IgG)	✓	Re-check annually[d]	Re-check annually[d]
Chest X-ray	If clinically indicated	If clinically indicated	If clinically indicated
PPD test (tuberculin) or Mantoux test	Optional[e]	If clinically indicated Re-check annually[d]	If clinically indicated Re-check annually[d]
Fundoscopy	If CD4 cell count < 100	2–4/year if CD4 cell count < 100	2–4/year if CD4 cell count < 100
Gynaecological examination	✓	1/year	1–2/year
Optional: thyroid function, testosterone (in men)	✓	1/year	1/year

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; HAV, hepatitis A virus; HBc, hepatitis B core; HBs hepatitis B serum; HBsAg, hepatitis B serum antigen; HCV, hepatitis C virus; PPD, purified protein derivative; TPHA, *Treponema pallidum* haemogglutination antibody; VDRL, Venereal Disease Research Laboratory.
[a]Fasting preferred.
[b]For considerations on vaccination refer to Appendix 2.
[c]If HCV is negative, but abnormal liver tests perform HCV-RNA polymerase chain reaction.
[d]To be re-checked annually if negative at start.
[e]Optional, depending on CD4 cell level and tuberculosis prevalence in a particular geographical area.

Primary HIV infection

Primary HIV-1 infection (PHI) is often missed or misdiagnosed in clinical practice, and represents only 1–3% of patient presentations in most European centres. Early treatment with antiretroviral drugs may delay disease progression and preserve or expand the cellular immune effector T cells against HIV as well as anti-HIV humoral immune responses [2–7].

Life-long anti-HIV therapy is hampered by long-term toxicity and the potential for the emergence of resistant strains of HIV. Preliminary data of supervised treatment interruptions in patients treated for PHI showed that a significant number (20–40%) could be off therapy for prolonged periods. However, in the remainder, the viral load rebounded and the CD4 cell count declined and treatment had to be restarted [8].

New options are currently being investigated, including adjunctive immune therapy such as cytokines to increase or maintain CD4 cell levels, or vaccines that could reduce viral rebounds by increasing HIV-specific cellular responses or immune suppressors in order to reduce cell activation, and subsequently the viral reservoir (see section on Future approaches).

Diagnosis of primary HIV infection

The early diagnosis of PHI should be considered a priority, and for this purpose educational campaigns directed at the general population and physician community should be reinforced.

The diagnosis of PHI includes both clinical and laboratory evidence. A recent history of possible exposure to HIV together with clinical signs and symptoms, including fever, malaise, fatigue, neurological symptoms and signs, headaches, myalgia, pharyngitis, diarrhoea, skin rash, enlarged lymph nodes, meningoencephalitis and hepatitis are suggestive of recent contamination with HIV. Blood tests can reveal liver abnormalities, leukopenia or thrombocytopenia, whereas HIV-1 serology will remain negative during the first weeks after exposure and infection. Table 2 summarizes the clinical signs and symptoms of PHI [9].

Table 2. Symptoms and signs of primary HIV infection.

Symptoms and signs	%
Fever (≥ 38°C)	77.1
Lethargy	65.6
Skin rash	56.4
Myalgia	54.6
Headache	50.9
Pharyngitis or sore throat	44.0
Cervical adenopathy	39.0
Arthralgia	30.7
Oral ulcers	28.9
Axillary adenopathy	24.3
Weight loss	23.9
Nausea	23.9
Diarrhoea	22.9
Night sweats	22.0
Cough	22.0
Anorexia	21.1
Inguinal adenopathy	20.2
Abdominal pain	19.3
Oral candidiasis	17.0
Vomiting	12.4
Photophobia	11.9
Sore eyes	11.5
Meningismus	9.2

Adapted from Vanhems *et al.* [9], with permission.

Patients with PHI are at risk of infection by viral strains already containing key drug resistance mutations against one or more classes of antiretroviral therapy. Multi-resistant viruses have been documented in patients diagnosed with PHI [10–13]. Plasma storage and resistance testing should be considered, or performed, in accordance with the Euroguidelines on resistance [1].

Two categories of PHI have been defined:

Patients with acute primary HIV infection
These patients have had a high risk of exposure within the previous 2–8 weeks, and three or fewer bands are present on the Western blot or Immunoblot. The determination of p24 antigen is recommended and an HIV-1 plasma viral load should be performed as a priority to confirm the diagnosis as quickly as possible.

Patients with early HIV infection
These patients have more than three bands on the Western blot, and history of exposure to infection within the previous 6 months or a documented negative HIV test within the previous 6 months.

Treatment of primary HIV infection

The rationale for treating patients with PHI is to preserve and improve the immune response against HIV (including the T-cell repertoires) and to reduce virus spreading and viral heterogeneity. At this time the amount, type and duration of therapy is not defined. The enrolment of patients with PHI in clinical trials to investigate the potential benefits of supervised treatment interruption or adjunctive immune-based approaches should be favoured.

Treatment for acute primary HIV infection
Because of the high replication rate of HIV and the rapid spread into lymphoid tissues when the plasma viral load is high, initial treatment should include a combination of protease inhibitors (PI) and nucleoside analogue reverse transcriptase inhibitors (NRTI). Treatment may be adapted depending on the characteristics of the source patient (if known), and whether resistance testing is available and indicates the presence of key resistance mutations.

Other options combining antiretroviral therapy with immunological approaches (IL-2, vaccines or blockers of cell activation) are under evaluation.

Treatment of early HIV infection
This should be considered for all patients, if possible in clinical trials exploring the current physiopathological hypothesis. Treatment is recommended if the criteria for treating chronically infected individuals are fulfilled (see section on Chronic HIV-1 infection). PI-containing regimens should be considered for patients with plasma viral loads greater than 100 000 copies/ml.

It is particularly important to carefully assess the willingness of the patient to initiate treatment and to stress the importance of full adherence to treatment.

Chronic HIV-1 infection

In the natural history of HIV-1 infection, a patient is considered to be chronically infected when infection is diagnosed more than 6 months after risk exposure or is of unknown or undefined duration. Viral load and CD4 cell levels are the best prognostic markers for progression to AIDS or death. With the treatments currently available, viral eradication is unachievable. In the case of treatment interruption, a rebound of the plasma viral load generally occurs [14–16].

Because of the need for life-long treatment with the present state of our knowledge, a risk–benefit balance should be established on a case by case basis, between the need to treat to prevent clinical progression and the risks of long-term therapy (side effects, resistance, etc.) [17–22].

The main issue is when to start therapy.

Goals of first-line therapy

The goals of first-line therapy are to improve the clinical state, provide an improved quality of life, together with a CD4 cell increase/immune restoration,

and the avoidance of viral resistance as a consequence of optimal viral suppression (≤ 50 copies) within the initial 6 months of therapy, and to maintain such a response.

When to start treatment

Clinical signs and symptoms remain the main criteria for starting treatment. In the absence of HIV-related clinical conditions, the CD4 cell level is the criteria for commencing therapy. The risk of severe OI is linked to levels of CD4 cell count below 200 cells/ml. There is a consensus to initiate therapy below 350 cells/ml regardless of the plasma viral load.

The decision to commence treatment at a CD4 cell level above 350 cells/ml should be based on the plasma viral load, obtained on at least two consecutive occasions 2 (or more) weeks apart. (see Fig. 1).

How to prepare a patient for treatment

The British HIV Association adherence guidelines cover information to be provided (see Table 3).

What treatment to start with

With first-line therapy it is of vital importance to preserve further therapeutic options. Treatment should therefore be individualized. Suboptimal therapy that does not achieve viral load suppression could affect the efficacy of subsequent treatments because of the risk of cross resistance, creating a need later for more complicated and heavy regimens that may result in poor adherence, cumulative toxicity, and impaired quality of life [23–25].

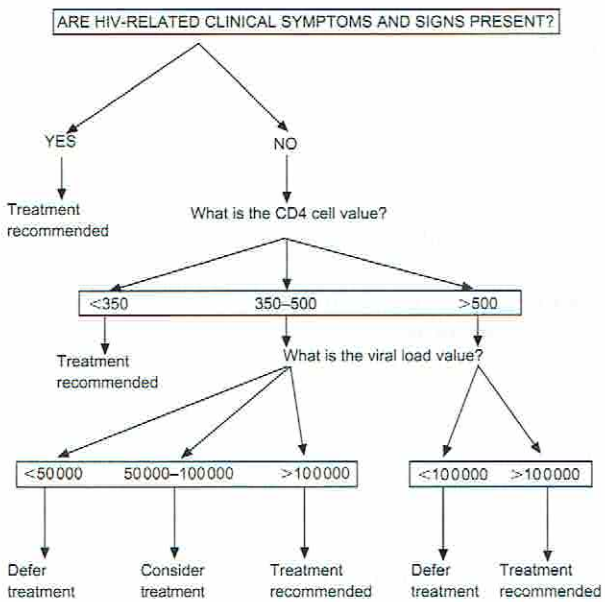

Fig. 1. Decision tree for starting therapy in chronic HIV infection.

So far, there is no specific drug regimen that has definitively been shown to be superior in the long term. Therefore, various combinations for first-line treatment may be considered (see Table 4).

A number of specific considerations should be taken into account before deciding between regimens: previous medical history, especially metabolic disorders such as diabetes, hyperuricemia, risk factor(s) for cardiovascular diseases, chronic liver disease, concomitant medications; a history of exposure to resistant virus or the results of resistance testing showing key mutations; HBV/HCV co-infection; studies are in progress to evaluate whether HIV non-B subtypes respond to treatment similarly to B subtypes. So far, there are no strong arguments for modifying first-line therapy according to the HIV subtype.

Of note is the fact that because of the complexity of drug regimens and pharmacological parameters, the advice of experienced clinicians or virologists is likely to be helpful [26].

Treatment simplification in patients with fully suppressed viral replication

Treatment simplification is possible in patients who have had viral loads below 50 copies for at least 6 months [27,28].

The objectives are: to improve long-term compliance and adherence to treatment, and thereby to reduce the likelihood of the emergence of drug resistance; to improve the quality of life; and possibly to reduce the side-effects or toxicity associated with PI-containing regimens, such as hypertriglyceridemia and hypercholesterolemia, insulin resistance, lipodystrophy and cardiovascular events.

Because of the potential existence of drug-resistance mutations in the reverse transcriptase (RT) gene, treatment simplification should be evaluated on a case by case basis taking into account compliance, quality of life, tolerance, metabolic disorders, and past treatment history. In patients who have initially been treated with two NRTI combined with a PI, switching to either a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) or abacavir maintains viral suppression for at least 2 years. Such simplification should be avoided in patients who may be expected to harbour virus strains resistant to thymidine analogue RT inhibitors as a result of previous suboptimal therapy with mono or dual therapy with NRTI.

In the case of the substitution of PI with efavirenz, there is no impact on cholesterol abnormalities. In most

Table 3. Information for patients starting highly active antiretroviral therapy.

Explanation of HAART	How HAART works
	Patient-specific rationale for starting HAART now, which takes account of the patient's own beliefs about treatment
	Goals of HAART
	Role of CD4 cell count and viral load testing
	How to monitor HAART
Adherence	Why it is important
	How drug resistance occurs
	The relationship between adherence and resistance, and treatment failure
	The impact of resistance on future options
	What to do if doses are missed, delayed, or vomited
	What to do if stopping therapy
Lifestyle assessment	Assessment of daily routine, e.g. eating, sleeping and working patterns; recreational activities; familial/social relationships and responsibilities
	Travel plans, etc.
Medication history	Prescription medicines
	Non-prescription (over the counter) medicines
	Herbal, homeopathic, traditional medicines
	Recreational drug and alcohol use
	Previous allergies or intolerances, adherence difficulties and strategies
	Swallowing difficulties, i.e. can the patient take a pill or are liquids preferred?
Side-effects	Acute
	Chronic/long-term
	Side-effect management, including in-hours, and out-of-hours contact
Regimen-specific	Drug names and what they look like
	Form of medication, i.e. tablet, capsule, liquid, etc.
	Dose, i.e. number of pills
	Dosing frequency and spacing
	Relationship between dosing and eating, i.e. dietary restrictions, examples of appropriate/inappropriate foods
	Storage of drugs, e.g. expiry dates, refrigeration
	Drug interactions

HAART, Highly active antiretroviral therapy.

patients, clinical manifestations of lipodystrophy have not or have only marginally improved after the switch to a PI-sparing regimen.

Changing therapy in the case of adverse event or toxicity

If an adverse event or biological toxicity can reasonably be attributed to one agent, it is recommended to replace this drug by another from the same class, which is not expected to induce the same kind of intolerance/toxicity [29–32].

Exposure to nucleoside analogues can lead to mitochondrial toxicity. Hyperlactatemia should be excluded if a patient develops a syndrome compatible with lactic acidosis (nausea, abdominal discomfort, weight loss, malaise, liver enlargement). If hyperlactatemia [venous lactate repeatedly > 5 mmol/l (45 mg/dl)] with or without acidosis is confirmed, treatment interruption is mandatory. Treatment may be continued with close monitoring, in the case of elevated venous lactate levels between 2 and 5 mmol/l (18–45 mg/dl) in the absence of symptoms. The role of carnitine and other oxidative phosphorylation supplements in the case of lactic acidosis is under evaluation.

The most prevalent side-effect of highly active antiretroviral therapy (HAART) is lipodystrophy. Its aetiology and pathogenesis remain unclear and the same applies to the management of this condition. The respective role of different classes of drugs or individual agents is not well established, although both PI and NRTI are thought to be involved. PI-sparing and NRTI-sparing regimens are under evaluation [33–35].

Physical exercise has been shown to reduce the incidence and severity of lipodystrophy, and may have some benefit on insulin resistance. In the case of increased blood levels of triglycerides or cholesterol, exercise and diet are strongly recommended.

The reduction of other cardiovascular risks factors (such as smoking) is essential.

The discontinuation of thymidine analogues, particularly stavudine, is advocated by many physicians.

Lipid-lowering agents may be used, but their long-term clinical efficacy in this setting has not been established (pharmacological interactions with PI and NNRTI must be considered in the choice of the lipid-lowering agent).

Plastic surgery may be considered, particularly for the correction of facial lipoatrophy and dorsocervical fat pad (buffalo hump).

Table 4. Which first-line combination? Pros and cons.

	Pro	Con	Comments
2 NRTI + 1 PI (or boosted PI, i.e. use of low-dose ritonavir to enhance blood drug levels of other PI)	• Most investigated regimen especially in patients with low CD4 cell count • Boosted PI regimens allow lower pill burden and costs, and greater convenience	• Associated with hyperlipidemia and insulin resistance • Risk of fat accumulation, possibly cardio-vascular disease • Interindividual variations of pharmacokinetics (in non-boosted PI regimens) • Higher pill burden and risk of poor drug adherence	• PI-containing regimens are the ones with the most available data for high VL (> 100 000 copies/ml) • Preferred for pregnant women • TDM could be useful for non-boosted PI-containing regimens • New PI with lower pill burden are under evaluation • 2 NRTI + 2 active PI: few comparative data on efficacy. Could increase the risk of poor drug adherence and toxicity
2 NRTI + 1 NNRTI	• Low pill burden • Lower risk of cardiovascular or metabolic disorders • Effective as maintenance after induction with PI-containing regimens	• Patients with liver disease treated with nevirapine should be closely monitored • Resistance to NNRTI as a class, if adherence is poor (low genetic barrier) • Efavirenz may induce hypercholesterolemia	• Might be preferred for patients with higher CD4 cells • Efavirenz shown to be effective in patients with high VL (> 100 000 copies/ml) • 2 NRTI + 2 NNRTI or 2 NRTI + 1 NNRTI + 1 PI: on trial
3 NRTI	• Low pill burden • Class-sparing regimens (PI and NNRTI) • Good alternative after induction with a PI-containing regimen	• Less effective than PI or NNRTI-containing regimens especially in patients with high VL	• To be considered if VL < 100 000 copies/ml or risk of poor adherence • Potential risk of increased mitochondrial toxicity

NNRTI, Non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TDM, therapeutic drug monitoring; VL, viral load.
Induction/maintenance strategy should be favoured whenever possible. Before switching from PI-containing regimen to PI-sparing regimen, a viral load of less than 50 copies/ml for at least 6 months is recommended, (see section on Treatment simplification).
The once daily administration of PI can be considered in specific situations: (methadone programmes, direct observed therapy).
Zalcitabine should be avoided.
Daily administration of lamivudine, nevirapine, and abacavir has been successfully tested.

As a therapeutic approach to metabolic disorders and lipodystrophy, compounds, such as metformin, glitazones and carnitine, are under investigation.

Specific comments

In the case of hypersensitivity to abacavir, do not rechallenge (fatal cases have occurred).

If abacavir has been stopped for reasons that are clearly distinguishable from hypersensitivity, abacavir could be re-initiated, but this should be done under close medical surveillance.

The role of the co-administration of antihistaminic agents during the first weeks of treatment to reduce the incidence of rash associated with nevirapine remains controversial. Corticosteroids have not been shown to be of any benefit.

In the case of rash caused by nevirapine, efavirenz may be used.

Changing therapy for failure

Virological failure is characterized by a persistent detectable plasma viral load in the presence of therapy. The reasons for failure are many and include problems of adherence, drug–drug interactions, pharmacokinetic issues, and the occurrence of resistance. These factors can accumulate sequentially. In the case of persistent viral replication under therapy, the accumulation of key resistance mutations will increase the level of resistance as well as the risk of cross-resistance, which is broad within each class of drugs, particularly within the NNRTI class. Resistance can be determined either genotypically or phenotypically; resistance testing is recommended in all patients failing on therapy (refer to the European guidelines on resistance) [1,36].

The determination of the optimal level of detectable HIV plasma viral load at which treatment should be changed in order to minimize the accumulation of key mutations is still unclear and under investigation.

Potential strategies to overcome resistance include: the combination of drugs with expected preserved activity as demonstrated by resistance testing; an improvement of pharmacokinetics to optimalize exposure to drugs; the incorporation of previously unused drug classes in a new regimen; and the cycling of drugs.

The probability of treatment success decreases as the number of key resistance mutations increases.

Management of failure on first-line therapy

Failure on first-line therapy is defined as the detection of a plasma HIV-RNA level (viral load) greater than 50 copies (confirmed by at least two consecutive tests) 6 months or more after the initiation of a first treatment regimen.

When failure of therapy is suspected, the patient's evaluation should include: an interview of the patient to evaluate adherence and compliance to therapy, with a focus on the evaluation and management of side-effects and psychosocial parameters; a re-explanation to the patient of the objectives and modalities of the treatment and the potential risks of poor adherence; the exclusion of potential drug–drug or drug–food interactions; and the exclusion of an intercurrent infection or recent vaccination.

After these interventions, a second viral load determination should be performed a few weeks later, and treatment adherence should be re-assessed. In the case of good treatment adherence and a persistent detectable plasma viral load, resistance testing should be performed and plasma drug measurement should be considered (see section on the Use of therapeutic drug monitoring).

It should be noted that a viral load of more than 500–1000 copies/ml is currently generally required to perform reliable genotypic resistance testing (for phenotypic testing a level above 10 000 copies/ml may be required).

For those patients whose viral load is below 500–1000 copies/ml, the options are: to wait and measure the viral load 1–2 months later; to improve pharmacokinetics by boosting PI with ritonavir (if applicable and feasible) or to intensify treatment. Intensification with abacavir or tenofovir has been shown to be effective in patients with suboptimal virological response. There are no data regarding intensification with other NRTI or PI. Intensification with NNRTI is not recommended because of the risk of the rapid emergence of resistance. It might be necessary to switch all drugs.

For those patients whose viral load is above 500–1000 copies/ml: resistance testing is recommended. If no resistance mutations are found, adherence should be checked once again and therapeutic drug monitoring (TDM) performed (if available and not performed before). If resistance mutations are found, two options are possible: to change only the drug(s) for which resistance is documented; to change the whole regimen (because minor resistant variants could be present that are not detected by most currently used assay systems) or because unknown resistance patterns may be present to stop all therapy (see section on Treatment interruption in patients with multiple failures).

The advantage of maintaining lamivudine with the

objective of maintaining a potentially less replication-competent virus, if a patient harbours the mutation M184V, is currently being investigated.

If resistance testing is not available, the options are to change the whole regimen or to interrupt therapy, (see section on Treatment interruption in patients with multiple failures).

Management of failure on second or subsequent therapy

In this situation, which is quite common, the general recommendations are the same as for the failure of first-line treatment. However, as treatment options tend to decrease with the number of previous failures, the decision to change a failing regimen in this setting should take into account the treatment options remaining, the level of failure as determined by the degree of increased plasma viral load and the decline of CD4 cell count, and the past treatment and resistance history, including tolerability and adherence issues.

Many patients who experience virological failure with their current anti-HIV regimen, but who do not have appropriate remaining treatment options, may derive clinical benefit from continuing their failing regimens. This may be particularly true if they are able to maintain a viral load that is lower than the one defining their set-point (before therapy) or if their CD4 cell count remains higher than their nadir CD4 cell count. Such benefits may be related to the decreased viral fitness of the dominant HIV species that is maintained during continued drug pressure.

These considerations emphasize the fact that patients failing multiple therapies should benefit from being managed by practitioners who have experience in the care of HIV patients.

Choice of antiviral therapy

The choice of subsequent therapeutic regimens will depend on the level of viral load (classified as low/intermediate: $< 50\,000$ copies/ml, or high: $> 50\,000$ copies/ml), the number of active drugs within each class based on resistance testing, including boosted PI combinations and previous intolerance to drugs.

Three common clinical situations predominate:

Situation 1: Resistance testing indicates that there is at least one active drug within each of the three drug classes. The following therapeutic options are possible: one NNRTI and two active NRTI (based on resistance testing); one boosted PI plus two active NRTI; one NNRTI plus two NRTI plus one boosted PI (increase boosted dosage when combined with efavirenz); two boosted PI plus two NRTI.

The first two options may be preferable in the case of low/intermediate viral load and the last two in the case of high viral load.

Situation 2: Resistance testing indicates that there is at least one active drug within two drug classes. The following therapeutic options are possible: one active NNRTI plus two active NRTI; one active NNRTI plus one or two active boosted PI; two active NRTI plus one or two boosted active PI.

Situation 3: Resistance testing indicates that there is only one drug class with at least one active drug or no class with active drug. The following therapeutic options are possible: two or three boosted PI combined with optimized reverse transcriptase inhibitors; consider treatment interruption; consider the use of new/experimental drugs.

Treatment interruption in patients with multiple failures

In heavily pretreated patients who have experienced multiple treatment failures carrying highly resistant viruses, treatment interruption may lead to a repopulation with wild-type, drug-sensitive virus that could respond to a new course of therapy. However, the long-term benefit from this approach is unclear, and treatment interruption has also been shown sometimes to be associated with the re-appearance of virus strains harbouring archived mutations after the re-institution of therapy because of the selective pressure of the salvage regimen on wild-type virus [36–38].

Treatment interruption in this setting may also be associated with a rapid decline in the CD4 cell count, resulting in levels of immunosuppression that put the patient at risk of potentially life-threatening opportunistic conditions [39].

Prophylaxis of OI during treatment interruption is mandatory and monthly clinical follow-up should be instituted, particularly in patients with a history of previous OI.

The optimal time for the re-initiation of therapy is not established. It could be defined by resistance testing, indicating that sensitivity of the isolated strain to a minimum of one class of drugs has re-appeared in the plasma. In any case, treatment should be re-initiated if clinical or immunological progression occurs.

Use of therapeutic drug monitoring

In prospective studies, a good correlation has been shown between the minimum plasma drug concentrations (C_{min}) of PI and the degree and duration of viral

suppression. However, the role of TDM in routine clinical practice has not yet been established.

TDM is not currently relevant for NRTI, whose activity depends on intracellular phosphorylation of the parent compound.

No standardized methods are yet available and the plasma drug determination of PI and NNRTI should be performed in specialized laboratories.

Determination of the minimal drug concentration (trough value C_{min}) sampled before the next drug intake is the most relevant parameter to check drug activity. Measurement of the maximal concentration (peak value C_{max}) is only relevant for the evaluation or prevention of potential drug-related toxicities.

C_{min} needs to be interpreted in relation to the resistance profile of the virus. A comparison with the IC_{50} or IC_{90} of the viral strain of the patient could provide a reasonable evaluation of treatment efficacy. However, there are currently no data showing that phenotypic determination is more accurate than the genotype in this setting. The use of the virtual phenotype, based on genotype findings could be an alternative [40,41].

Therapeutic drug monitoring may currently be indicated in three situations: to evaluate adherence or exclude drug malabsorption or interactions in patients with a suboptimal therapeutic response; to avoid or reduce side-effects or toxicity, while avoiding suboptimal therapy; and to optimalize drug efficacy in patients with resistant viruses, avoiding suboptimal minimum concentrations.

Future approaches

Supervised treatment interruption

There is presently no general consensus on the settings in which one could consider interrupting therapy. Supervised treatment interruption has been reported in a number of specific clinical situations such as severe toxicity, surgery, in pregnancy (although most advice is to continue) or in patients failing therapy.

The rationale for supervised treatment interruption is quite different in various circumstances.

In patients failing therapy, the goal is to allow a repopulation of the viral burden with drug-sensitive strains (see section on Treatment interruption in patients with multiple failures).

In patients who have started treatment in the earliest stages of a newly acquired HIV infection, supervised treatment interruption may boost the host's immune response to elicit HIV-specific cellular effector cells, especially cytotoxic cells, mimicking an auto-immunization during viral rebounds.

In chronically infected individuals whose infection is properly controlled with therapy, the benefit of supervised treatment interruption seems to be much less. Most of these patients show significant viral rebound after interrupting treatment. Fortunately, the re-institution of therapy is virtually universally followed by re-achieving complete viral suppression. Several ongoing clinical studies are evaluating supervised treatment interruption with or without additional immune-based therapy.

It must also be borne in mind that supervised treatment interruption may increase the risk of HIV transmission. Furthermore, both physicians and patients must be aware of the possible re-occurrence of clinical symptoms mimicking acute PHI during viral rebounds [42–49].

Immunotherapy

The use of immunotherapy for HIV infection is still under investigation. No data have so far suggested a clinical benefit for using this approach combined with antiretroviral drugs. The ultimate goal is to be able to consider the prolonged interruption of antiretroviral therapy. In order to achieve this goal, immune-based therapy should improve or reconstitute host immunity, especially HIV-specific T cells, and reduce the viral infectivity by reducing cellular activation.

Three major approaches are being investigated in trials: cytokines, mainly IL-2 and interferons, vaccines, including vectors such as DNA or various attenuated viruses and different adjuvants, and blockers of cell activation, such as hydroxyurea, cyclosporin A or mycophenolic acid [50–53].

Special considerations

Treatment of HIV-infected pregnant women

As a general recommendation, HIV-infected women wishing to become pregnant should be advised to do so when in the best possible conditions: undetectable viral load, high CD4 cell count, no other infection, no use of drugs that are prohibited during pregnancy.

Guidelines for antiretroviral therapy and for the initiation of treatment in HIV-infected pregnant women are the same as those proposed for non-pregnant women: the woman's clinical, immunological and virological

status are of primary importance in guiding treatment decisions.

Treatment of the HIV-infected pregnant woman has two objectives: treatment of the woman, irrespective of pregnancy; and the prevention of mother-to-child transmission.

The potential impact of antiretroviral therapy on the fetus and infant is currently poorly understood. It is generally recommended to avoid antiretroviral treatment during the first trimester to minimize the impact of these drugs on organogenesis. Some agents or combinations must be avoided during pregnancy because of the risk of teratogenicity or toxicity: efavirenz (documented teratogenicity in animals), stavudine plus didanosine (documented toxicity in neonates and mothers), indinavir (hyperbilirubinemia) (see Table 5 for further details).

The potential risk of mitochondrial toxicity to the fetus and infant as a result of exposure to NRTI during pregnancy has been suggested. The long-term follow-up of babies born to treated mothers is important [54–58].

The treatment of HIV-infected pregnant women falls under four headings.

Women becoming pregnant while already treated with highly active antiretroviral therapy
Current treatment should be maintained whenever feasible (with the exception of some agents and combinations mentioned above).

In the case of unacceptable drug intolerance as a result of pregnancy or in women who had started treatment very early in their HIV natural history (low viral load, high CD4 cell count at the start of therapy), treatment may be temporarily withheld during the first trimester.

Women becoming pregnant while treatment naive who fulfill the criteria for the initiation of highly active antiretroviral therapy
The initiation of therapy should be delayed until 12 weeks of gestation (end of organogenesis) if the clinical and immunological status allows for this delay in treatment.

Women becoming pregnant while treatment naive who do not fulfill the criteria for the initiation of highly active antiretroviral therapy
Treatment should be commenced 12 weeks before delivery.

Although zidovudine as monotherapy has been shown to be effective in reducing the risk of vertical transmission, because of the potential for developing resistance, combination therapy is recommended in order to preserve future therapeutic options.

Women whose follow-up starts very late during pregnancy
This is a difficult emergency situation that occurs most often in cases of poor psychosocial conditions.

It is recommended that anti-HIV therapy be started immediately (even if delivery is imminent). Nevirapine should be included in the regimen, zidovudine should be administered intravenously during labour and delivery, and Caesarean section is strongly recommended.

Prevention of mother-to-child transmission

Vertical transmission of HIV occurs mainly during the last part of pregnancy, and particularly during labour and delivery.

Breast feeding is associated with a significant risk of transmission and is therefore contraindicated.

Caesarean section has been shown to reduce HIV transmission, and should be advised, but its usefulness in women with fully suppressed viraemia, in good obstetric conditions, is unclear.

The risk of transmission is directly related to the maternal plasma viral load. It is therefore recommended to suppress HIV optimally during the last 8–12 weeks of pregnancy. Zidovudine is the only drug that has been shown to reduce transmission when given as monotherapy, and should be part of the regimen whenever possible. Intravenous zidovudine during labour and delivery remains current clinical practice; however, the benefit of this specific approach when viral load is fully suppressed is uncertain [59–63].

The use of nevirapine as a single dose at delivery has shown some benefit. It should be noted, however, that this approach has been associated with the emergence of nevirapine-resistant strains in a substantial proportion of women. This jeopardizes subsequent treatment options in the mother [64].

The HIV-2-infected patient

Specific considerations
The natural history of HIV-2 infection is characterized by a long asymptomatic phase, and HIV-2 is generally considered to be less pathogenic than HIV-1.

Most HIV-2-infected patients with a CD4 cell count above 500 cells have an undetectable HIV-2 plasma viral load. The rate of detectability slightly increases between 200 and 500 CD4 cell and becomes significant below 200 CD4 cells.

Table 5. Preclinical and clinical data relevant to use of antiretroviral drugs in pregnancy.

Antiretroviral drug	FDA pregnancy category	Placental passage (newborn : mother drug ratio)	Long-term animal carcinogenecity studies	Rodent teratogen
Zidovudine	C	Yes (human) (0.85)	Positive (rodent, thymic lymphomas)	Positive (near lethal dose)
Zalcitabine	C	Yes (rhesus) (0.30–0.50)	Negative (no tumours, lifetime rodent study)	Positive (hydrocephalus at high dose)
Didanosine	B	Yes (human) (0.5)	Positive (rodent, vaginal tumours)	Negative
Stavudine	C	Yes (rhesus) (0.76)	Positive (rodent, liver and bladder tumours)	Negative (but sternal bone calcium decreases)
Lamivudine	C	Yes (human) (≈1.0)	Negative (no tumours, lifetime rodent study)	Negative
Abacavir	C	Yes (rats)	Not completed	Positive (anasarca and skeletal malformations at 1000 mg/kg (35 × human exposure) during organogenesis)
Saquinavir	B	Unknown	Not completed	Negative
Indinavir	C	Yes (rats) ('Significant' in rats, low in rabbits)	Not completed	Negative (but extra ribs rats)
Ritonavir	B	Yes (rats) (mid-term fetus, 1.15–0.64)	Positive (rodent, liver tumours)	Negative (but cryptorchidism in rats)
Nelfinavir	B	Unknown	Not completed	Negative
Amprenavir	C	Unknown	Not completed	Positive (thymic elongation, incomplete ossification of bones, low body weight)
Lopinavir/ritonavir	C	Lopinavir – yes (rats) (0.08 at 6 h post-dose)	Lopinavir – not competed Ritonavir – see above	Negative (but delayed skeletal ossification and increase in skeletal varations in rats at maternally toxic doses)
Nevirapine	C	Yes (human) (≈1.0)	Not completed	Negative
Delavirdine	C	Yes (rats) (late-term fetus blood, 0.15; late-term fetus liver, 0.04)	Positive (rodent, liver and bladder tumours)	Ventricular septal effect
Efavirenz	C	Yes (cynomolgus monkeys, rats, rabbits)	Not completed	Anencephaly, anophthalmia, microphtalmia (cynomolgus monkeys)
Tenofovir	B	Unknown	Not completed	Negative

FDA, Food and Drug Administration (USA).
A, Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to fetus during the first semester of pregnancy (and there is no evidence during later trimesters).
B, Animal reproduction studies fail to demonstrate a risk to the fetus and adequate but well-controlled studies of pregnant women have not been conducted.
C, Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk for the fetus.
D, Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X, Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

The HIV-2 viral load is not detected by standard commercial HIV-1 kits.

HIV-2 viral load determination is not standardized and is not quantitative. However, a detectable viral load has been shown to be predictive of outcome. The HIV-2 viral load is available in selected laboratories [65–68].

Criteria for initiation of therapy

The validation of the criteria proposed here, which are mainly based on CD4 cell levels, await cohort studies. If the CD4 cell count is less than 200 cells/ml, the patient should be treated; if it is greater than 200 but less than 500 cells/ml, the patient should be treated if the viral load is detectable. If the CD4 cell count is greater than 500 cells/ml, the patient should not be treated.

Follow-up is the same as for HIV-1-infected patients. Resistance testing is currently unavailable.

Choice of treatment

HIV-2 is intrinsically resistant to currently available NNRTI and is probably less sensitive to PI than HIV-1. Treatment should include two NRTI and two PI (both PI used for their antiretroviral activity) or three NRTI (no data available). Amprenavir is not active against HIV-2.

The wild-type HIV-2 protease gene carries a mutation at position 77. Mutations at this position give resistance to nelfinavir, whose use against HIV-2 is thus questionnable [69–73].

There are no specific treatment guidelines for patients co-infected with HIV-1 and HIV-2.

Treatment of the HIV-infected patient with hepatitis B or hepatitis C virus co-infection

HIV-1, HBV and HCV share similar routes of transmission. Co-infection with HIV-1 and HBV or HCV is therefore common. Up to 80% of injecting drug users with HIV-1 infection and up to 77% of homosexual men with HIV-1 infection have markers of past or chronic HBV infection, and more than 70 and 7%, respectively, have markers of past or chronic HCV infection [74].

HIV and hepatitis B virus

HBV replication is increased in the case of HIV co-infection, and results in an increased risk of developing chronic infection (21% compared with 7% in HIV-seronegative patients). Patients with a low CD4 cell count clear hepatitis B serum antigen (HBsAg) significantly less frequently. Histological and biochemical studies have suggested that the severity of liver disease is reduced in case of HIV and HBV co-infection, whereas the expression of hepatitis B e antigen and HBV DNA are increased. In patients who have cleared HBsAg from plasma, HBsAg and HBV DNA may re-appear in connection with the development of advanced immunodeficiency [75].

Recommendations for management are: liver biopsy should be considered to evaluate the degree of liver damage. The treatment of HBV is currently based on interferon or lamivudine. The dosage of lamivudine for HBV infection is 100 mg/day. The anti-HIV dosage of 150 mg twice a day should be used in HIV-co-infected patients. The use of lamivudine as monotherapy (or as part of anti-HIV therapy) is associated with a significant risk of the emergence of lamivudine-resistant strains of HBV and should be avoided. Adefovir and tenofovir has been shown to be active against lamivudine-resistant HBV strains. Alcohol should be avoided in all cases.

HIV and hepatitis C virus

The effects of HCV infection on the course of HIV disease have yet to be clearly established. HCV could impair immune recovery after the initiation of anti-HIV treatment. On the other hand, there is mounting evidence to show that there is a faster progression of HCV-related liver disease in HIV-co-infected individuals. HIV-infected patients have a five- to 20-fold higher risk of developing cirrhosis and liver failure and a six-fold increased risk of liver carcinoma, when compared with HIV-negative individuals infected with HCV. Low CD4 cell counts (i.e. < 200 cells/ml) have been shown to be associated with a faster progression to liver fibrosis [76–78]. Liver biopsy is recommended before the initiation of therapy.

Treatment of HCV consists of a combination of interferon and ribavirin. Clinical studies are underway to evaluate the potential interaction between ribavirin and nucleoside analogues, as well as the cumulative risk of pancreatitis when ribavirin is used together with didanosine. Pegylated interferon in combination with ribavirin is currently being investigated in HIV/HCV co-infected patients [79–81].

Response to treatment depends on: age (lower response rate in older patients); race (response rate is lower among blacks when compared with caucasians); duration of HCV infection (response rate decreases as duration increases); histological findings (response rate decreases as liver damage increases); HCV genotype (genotype 1 response rate is low); CD4 cell level (lower response rate in case of low CD4 cell count). There are some suggestions to treat HCV in patients with higher CD4 cell counts before initiating therapy for HIV.

Initiation of anti-HIV treatment in patients with active opportunistic infections or malignant disease

There are three kinds of interactions between anti-HIV treatment and OI or cancers.

The initiation of anti-HIV treatment may exacerbate clinical manifestations of latent or mildly symptomatic infections. This has been mainly documented for mycobacterial infections, cytomegalovirus infection (presenting as anterior chamber vitritis), and viral hepatitis. Such phenomena have been less clearly established for other OI. The recommendations are: to exclude mycobacterial disease, before the initiation of anti-HIV treatment, in the case of suggestive signs or symptoms; if mycobacterial disease is diagnosed, to treat it for 2 months before starting anti-HIV treatment; if exacerbation of symptoms as a result of mycobacterial disease suggestive of an immunorestoration syndrome occurs after the initiation of anti-HIV treatment, to start mycobacterial therapy with or without corticosteroids and to consider interruption of anti-HIV treatment [82]; and to perform fundoscopy in all patients with CD4 cell counts of 100 cells/ml or less, in order to exclude asymptomatic cytomegalovirus retinitis.

The simultaneous initiation of anti-HIV treatment and specific treatment for certain OI may lead to cumulative toxicity or difficult to manage drug interractions. This is sometimes the case, for example, for cytomegalovirus disease. The recommendations are: to treat and stabilize cytomegalovirus disease if diagnosed before starting anti-HIV treatment in order to avoid unacceptable toxicity; and to measure quantitative cytomegalovirus viraemia by polymerase chain reaction and to treat if positive before initiating anti-HIV treatment. It must be noted that the efficacy of this pre-emptive approach has not been established.

Anti-HIV treatment is the cornerstone of the therapy for certain opportunistic diseases associated with profound immunosuppression. This is particularly the case for cryptosporidiosis, progressive multifocal leukoencephalopathy, Kaposi's sarcoma and lymphoma. The recommendations are: to initiate anti-HIV treatment and specific therapy (if available) as soon as possible; for Kaposi's sarcoma, specific chemotherapy should be initiated quickly only in cases of life-threatening clinical presentation (severe lung involvment) or if Kaposi's sarcoma fails to improve after 3–6 months of anti-HIV treatment; and for lymphoma, to start with specific chemotherapy and delay the initiation of anti-HIV treatment to a second or later cycle, to avoid cumulative toxicity.

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Appendix 1. Anti-HIV drugs and combinations

Table 6. Reverse transcriptase inhibitors: nucleoside analogues.

Table 7. Reverse transcriptase inhibitors: non-nucleosides.

Table 8. Protease inhibitors.

Table 9. Nucleotide analogue (tenofovir).

Table 10. Anti-HIV drug combinations.

Table 11. Interactions between protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Table 12. Use of anti-HIV drugs, in patients with renal insufficiency, in haemodialysed patients, in patients on peritoneal dialysis, and in patients with liver failure.

Appendix 2. Prevention of infectious complications in HIV-infected adult patients

Vaccination of the HIV-infected patient

The efficacy of vaccination depends on the level of CD4 cells. It is therefore recommended to immunize patients before their CD4 cell count drops below 200 cells/ml or to wait for immune restoration if CD4 cell levels are below 200 cells/ml at the start of anti-HIV therapy (in patients whose CD4 cell count does not increase above 200 cells/ml one should nevertheless consider vaccination against pneumococcal infection).

Any vaccination may lead to a transient increase of the HIV viral load. This rise is considered to be clinically not relevant (see Table 13).

Primary prophylaxis of opportunistic infections

The indications and modalities of primary prophylaxis of OI are summarized in Table 14.

The immune reconstitution that is observed in most patients in whom anti-HIV treatment is initiated allows the interruption of primary prophylaxis in selected situations. The decision to stop or re-initiate primary prophylaxis against OI should be based on CD4 cell levels.

The follow-up of the CD4 cell count after the interruption of primary prophylaxis is warranted in order to allow for the re-initiation of primary prophylaxis in the case of immune degradation. This is particularly indicated in the case of antiretroviral treatment failure or treatment interruption.

These same recommendations are valid for the interruption/re-initiation of long-term suppressive therapy for previous OI (Table 15) [85–95].

Table 6. Reverse transcriptase inhibitors: nucleoside analogues.

	Zidovudine[ab]	Didanosine	Zalcitabine	Stavudine	Lamivudine[ab]	Abacavir[b]
Trade name	Retrovir	Videx	Hivid	Zerit	Epivir, 3TC	Ziagen
Presentation	Capsules 100, 250, 300 mg Oral solution 10 mg/ml IV formulation 10 mg/ml	Tablets 25, 50, 100, 150, 200 mg Enteric-coated capsules 125, 200, 250, 400 mg	Tablets 0.375, 0.75 mg	Capsules 15, 20, 30, 40 mg Oral solution 1 mg/ml	Capsules 150 mg Oral solution 10 mg/ml	Capsules 300 mg Oral solution 20 mg/ml
Recommended doses	250–300 mg BID > 60 kg 400 mg QD or 200 mg BID	< 60 kg 250 mg QD or 125 mg BID	0.75 mg TID ⩾ 60 kg 40 mg BID	< 60 kg 30 mg BID	150 mg BID	300 mg BID
Oral bioavailability	60–70%	30–40%	85%	85%	85%	83%
Plasma half-life	1.1 h	1.6 h	1.2 h	1 h	3–6 h	1.5 h
Cellular half-life	3 h	25 h	3 h	3.5 h	12 h	3.3 h
IC_{50}[c]	0.003–0.061 μg/ml (0.01–0.23 μmol/l)	0.116–4.01 μg/ml (0.49–17 μmol/l)	0.0063–0.338 μg/ml (0.03–1.6 μmol/l)	0.0112–0.112 μg/ml (0.05–0.5 μmol/l)	0.00046–0.48 μg/ml (0.002–2.1 μmol/l)	0.074–1.144 μg/ml (0.26–4 μmol/l)
CSF concentration (% of plasma concentration)	50–85%	20%	20%	40%	10%	27–33%
Dietetical restrictions	No	Yes (fasting)	No	No	No	No
Metabolism	Hepatic (50–80%)	Hepatic (50%)	Hepatic (5–10%)	Hepatic (50%)	None	Hepatic
Excretion	Renal (15% unaltered)	Renal (50% unaltered)	Renal (70% unaltered) and fecal (< 10%)	Renal (50% unaltered)	Renal (70% unaltered)	Renal 83% (2% unaltered and 81% metabolized)
Side-effects[d]	Myelosuppression: anaemia and/or neutropenia, myalgia, myopathy, headache, GI intolerance	Pancreatitis, hyperuricemia, peripheral neuropathy, diarrhoea, nausea	Peripheral neuropathy, oral ulcers	Peripheral neuropathy, pancreatitis	Peripheral neuropathy	Hypersensitivity reaction (2–3%)
Resistance (codons with mutations selected at the RT gene[ef])	Major 69ss[e], 151[f], 215 Minor 41, 62, 67, 70, 75, 77, 116, 210, 219	Major 65, 69ss[e], 74, 151[f] Minor 62, 75, 77, 116, 184	Major 65, 69, 69ss[e], 74, 151[f] Minor 62, 75, 77, 116, 184	Major 69, 69ss[e], 75, 151[f], 184 Minor 41, 62, 67, 70, 77, 116, 210, 215, 219	Major 69ss[e], 151[f], 184 Minor 62, 65, 75, 77, 116	Major 69ss[e], 151[f] Minor 41, 62, 65, 67, 70, 74, 75, 77, 115, 116, 184, 210, 215, 219

BID, Twice a day; CSF, cerebrospinal fluid; GI, gastrointestinal; TID, three times a day; 3TC, lamivudine; QD, per day.
[a]Also available in combination as Combivir (zidovudine 300 mg + lamivudine 150 mg capsule).
[b]Also available in combination as Trizivir (zidovudine 300 mg + abacavir 300 mg capsule).
[c]In-vitro antiviral activity of the inhibitors against laboratory HIV-1 strains and clinical HIV-1 isolates, evaluated in cell lines and peripheral blood mononuclear cells.
[d]As a class, nucleoside analogues may induce lipodystrophy, lactic acidosis and liver steatosis, through some form of mitochondrial toxicity.
[e]An insertion at position 69 is a marker of multinucleoside resistance. High-level resistance towards the nucleoside analogues is obtained in association with zidovudine resistance-related mutations.
[f]A mutation at position 151 is a marker of multinucleoside resistance. High-level resistance towards the nucleoside analogues is obtained in association with mutations at positions 62, 70, 75, 77, or 116.
For further details refer to Schinazi *et al.* [83] and Shafer *et al.* [84].

Table 7. Reverse transcriptase inhibitors: non-nucleosides.

	Nevirapine	Efavirenz	Delavirdine
Trade name	Viramune	Sustiva, Stocrin	Rescriptor (not approved in Europe)
Presentation	Tablets 200 mg Oral suspension 50 mg/ml	Capsules 50, 100, 200, 600 mg	Tablets 100, 200 mg
Recommended doses	200 mg QD for 14 days then 200 mg BID or 400 mg QD	600 mg QD	400 mg TID or 600 mg BID
Oral bioavailability	> 90%	66%	> 85%
Plasma half-life	25–30 h	40–55 h	5–8 h
IC_{50}[a]	0.0026–0.026 μg/ml (0.01–0.1 μmol/l)	0.00014–0.0021 μg/ml (0.00046–0.0068 μmol/l)	0.00276–0.016 μg/ml (0.005–0.03 μmol/l)
CSF concentration (% of plasma concentration)	45%	0.4%	0.26–1.2%
Dietetical restrictions	No	No	No
Metabolism	Hepatic CYP3A4 (induction)	Hepatic CYP3A4 (induction–inhibition)	Hepatic CYP3A4 (inhibition)
Excretion	Renal 80%, fecal 10%	Renal 14–34%, fecal 16–61%	Renal 51%, fecal 44%
Side-effects	Rash, including rare cases of Stevens–Johnson, increase of transaminases and acute hepatitis	Dizziness, insomnia, somnolence, abnormal dreams, psychosis (1–2%), acute depression, rash	Rash, headaches, increase in transaminases
Resistance (codons with mutations selected at the RT gene)[b]	100, 101, 103, 106, 108, 181, 188, 190, 230	Major 103, 188, 190, 230 Minor 100, 101, 106, 108, 181, 225	100, 101, 103, 106, 108, 181, 188, 230, 236

BID, Twice a day; CSF, cerebrospinal fluid; TID, three times a day; QD, per day.
[a]In-vitro antiviral activity of the inhibitors against laboratory HIV-1 strains and clinical HIV-1 isolates, evaluted in cell or peripheral blood mononuclear cells.
[b]For further details refer to Schinazi *et al.* [83] and Shafer *et al.* [84].

Table 8. Protease inhibitors.

	Indinavir	Ritonavir	Saquinavir[a]	Nelfinavir	Amprenavir	Lopinavir/ritonavir[b]
Trade name	Crixivan	Norvir	Invirase Fortovase (SGC)	Viracept	Agenerase	Kaletra
Presentation	Capsules 200–400 mg	Capsules 100 mg Oral solution 600 mg/7.5ml	HGC 200 mg SGC 200 g	Tablets 250 mg Oral powder 50 mg/1 g	Capsules 50/150 mg Oral solution 15 mg/ml	Capsules 133.3 + 33.3 mg Oral solution 80 mg + 20 mg/ml
Doses[c]	800 mg TID	600 mg BID	HGC 600 mg TID SGC 1200 mg TID	750 mg TID or 1250 mg BID	1200 mg BID	400/100 mg BID
Oral bioavailability	30–60%	80%	HGC 4–8% SGC 16–32%	20–80%	⩾ 70% (capsules) Oral solution 14% less than capsule	?
IC_{50}[d]	0.0098–0.031 µg/ml (0.016–0.044 µmol/l)	2.7–108 µg/ml (3.8–153 µmol/l)	0.67–20 µg/ml (0.001–0.03 µmol/l)	6.6–40 µg/ml (0.01–0.06 µmol/l)	0.007–0.25 µg/l (0.012–0.41 µmol/l)	0.0025–0.017 µg/l (0.004–0.027 µmol/l)
CSF concentration (% of plasma concentration)	14.7% (for AUC)	< 1%	< 1%	< 1%	< 1%	No data
Diet restrictions	Fasting if not boosted	With food	With food	With food	No restrictions	With food
Plasma half-life	1.5–2 h	3–5 h	1–2 h	3.5–5 h	9 h	5–6 h
Metabolism	Hepatic CYP3A4 (inhibition)	Hepatic CYP3A4 (potent inhibition)	Hepatic CYP3A4 (weak inhibition)	Hepatic CYP3A4 (inhibition)	Hepatic CYP3A4 (inhibition)	Hepatic CYP3A4 (inhibition)
Excretion	Biliary	Biliary	Biliary	Biliary	Biliary	Biliary (< 3% urinary)
Side-effects[e]	Nephrolithiasis GI intolerance Hyperbilirubinemia	GI intolerance Oral paresthesia Increase in transaminases	GI intolerance (diarrhoea) Headaches	Diarrhoea	GI intolerance Rash	Digestive intolerance Rash
Resistance	Major 46, 82, 84 Minor 10, 20, 36, 54, 63, 71, 73, 90	Major 46, 82, 84 Minor 10, 20, 36, 54, 63, 71, 90	Major 48, 90 Minor 10, 36, 54, 63, 71, 73, 82, 84	Major 30, 82, 90 Minor 10, 36, 46, 63, 71, 77, 84, 88	Major 50 Minor 10, 20, 46, 47, 54, 63, 82, 84	Minor 10, 46, 47, 50, 63, 71, 84, 90

AUC, Area under the curve; BID, twice a day; CSF, cerebrospinal fluid; GI, gastrointestinal; HGC, hard gel capsule; PI, protease inhibitors; SGC, soft gel capsule; TID, three times a day.
[a]In view of its poor bioavailability saquinavir-HGC should only be used in association with another PI, either as double therapy, or in a ritonavir-boosted combination.
[b]It is generally considered that no single mutation leads to resistance to lopinavir (boosted with ritovanir), which is a cumulative process.
[c]See next chapter for doses in boosted PI combinations.
[d]In-vitro antiviral activity of the inhibitors against laboratory HIV-1 strains and clinical HIV-1 isolates, evaluated in cell lines or peripheral blood mononuclear cells.
[e]As a class, PI may induce significant increase in blood levels of triglycerides and cholesterol, as well as the development of resistance to insulin, which may lead to diabetes. They may also induce retinoid-like effects such as dry mouth and lips, erythema, and periungueal oedema. PI contribute to the lipodystrophy syndrome although their role is not unequivocal, particularly for lipoatrophy, which has been described in patients who had never been exposed to PI. Data suggest that there might be differences in the incidence of side-effects induced by each of the different PI.

Table 9. Reverse transciptase inhibitors: nucleotide analogues (tenofovir).

Generic name	Tenofovir
Trade name	Viread
Presentation	Tablets 300 mg
Recommended doses	300 mg QD
Oral bioavailability	39%
Plasma half-life	16 h
Cellular half-life	10–50 h
IC_{50}	1.1 μM
CSF concentration	Unknown
Dietetical restrictions	With food
Metabolization	Hepatic
Excretion	Renal
Side-effects	GI disturbances
Resistance	Major 69 ss, 65 Minor 41, 210

CSF, Cerebrospinal; GI, gastrointestinal; QD, per day.
The concomittant administration of tenofovir and didanosine leads to a significant increase in didanosine plasma concentration. It is thus recommended to reduce the dose of didanosine from 400 to 250 mg a day and to take both drugs with food.

Table 10. Anti-HIV drug combinations.

1. Combinations of nucleoside analogues:
   A few combinations should not be used, because of:
   Cumulative toxicity: stavudine + zalcitabine, didanosine + zalcitabine
   Antagonism: zalcitabine + lamivudine, zidovudine + stavudine
2. Combinations of NNRTI
   Studies are underway to evaluate the safety and efficacy of combining two NNRTI. Pending the results of these studies no recommendations can be made regarding such combinations.
3. Combinations of PI
   PI can be combined in two different settings:
   Combinations in which both PI are used for their antiretroviral activity
   Boosted combinations in which ritonavir is used as a pharmacological booster; in this case ritonavir dosages are usually 100 or 200 mg BID, well below its antiviral effective dosage, which is at least 400 mg BID
   There are currently no data to support the use of three PI, used for their anti-HIV activity. However this approach may be used in the setting of salvage therapy if resistance testing supports its use and provided the combination is tolerated.

BID, Twice a day; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 11. Interactions between protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Affecting drug	Amprenavir	Indinavir	Lopinavir (+ ritonavir)	Nelfinavir	Ritonavir	Saquinavir	Delavirdine	Efavirenz	Nevirapine
Amprenavir		↓ AUC by 38% ↓ C_{min} by 27% Dosages not established	No significant effect	↑ AUC by 15% No need for dose adjustment	No effect Use 100–200 mg BID ritonavir + 600 mg BID amprenavir	No effect Use 800 mg TID saquinavir + 600 mg TID amprenavir or 600 mg BID amprenavir +100 mg BID ritonavir + 800 mg BID saquinavir	No effect	↑ AUC by 15% Do not use amprenavir as single PI in combination with efavirenz Use a combination of ritonavir (100 mg BID) + amprenavir (900 mg BID) + efavirenz (600 mg QD)	No data available
Indinavir	↑ AUC by 22–64% No need for dose adjustment		No effect ↑ C_{min} Data available for 600 mg BID indinavir + lopinavir/r 400/100 mg BID	No effect of multiple doses [data available with nelfinavir (1.25 g BID) + indinavir (1.2 g BID)]	No effect but allows to administer indinavir BID (non-fasting state) Regimens include [ritonavir (400 mg BID) + indinavir (400 mg BID)] or [ritonavir (200 mg BID) + indinavir (600 mg BID)] or [ritonavir (100 mg BID) + indinavir (600 mg BID)] or [ritonavir (100 mg BID) + indinavir (800 mg BID)]	↑ AUC by 364–620% In-vitro data suggest antagonism. Dosages not established	No effect Adapt dosages of indinavir (1 g TID) or add ritonavir	No effect Adapt dosages of indinavir (1 g TID) or add ritonavir	No effect
Lopinavir (+ ritonavir)	↓ AUC by 50–420% Use of this combination is questionnable	↑ C_{min} Data available for 600 mg BID indinavir + lopinavir/r 400/100 mg BID		No effect on AUC ↑ C_{min} [Data available with 750 mg BID nelfinavir + 400/100 mg BID lopinavir/r]		↑ AUC, C_{min} [Data available with 800 mg BID saquinavir + 400/100 mg BID lopinavir/r]	No effect	No effect	No effect
Nelfinavir	No effect Use 1.2 g BID or 800 mg TID amprenavir + 1.25 g BID or 750 mg TID nelfinavir	↑ AUC by 12–50% [limited data available with indinavir 1.2 g BID + nelfinavir 1.25 g BID]	No effect ↑ C_{min} [Data available with 750 mg BID nelfinavir + 400/100 mg BID lopinavir/r]		No effect Use 400 mg BID ritonavir + 500–750 mg TID nelfinavir [limited data available with ritonavir (100–200 mg BID) + nelfinavir (1.25 g BID) or ritonavir (200 mg QD) + nelfinavir (2000 mg QD)]	↑ AUC by 392% Adapt dosages and use 800 mg TID saquinavir + 750 mg BID nelfinavir or 1200 mg BID saquinavir + 1250 mg BID nelfinavir	↓ AUC by 30–40% Dosages not established	No effect	No effect

Table 11. (*continued*).

Affecting drug	Amprenavir	Indinavir	Lopinavir (+ ritonavir)	Nelfinavir	Ritonavir	Saquinavir	Delavirdine	Efavirenz	Nevirapine
Ritonavir	↑ AUC significantly Use 600 mg BID amprenavir + 100–200 mg BID ritonavir. Data available for 1200 mg amprenavir + 200 mg QD ritonavir	↑ AUC by 480% Allows to administer indinavir BID (non-fasting state). Regimens are [indinavir (400 mg BID) + ritonavir (400 mg BID)] or [indinavir (600 mg BID) + ritonavir (200 mg BID)] or [indinavir (600 mg BID) + ritonavir (100 mg BID)] or [indinavir (800 mg BID) + ritonavir (100 mg BID)]		↑ AUC by 152% Variable effect on metabolite Adapt dosages and use 500–750 mg BID nelfinavir + 400 mg BID ritonavir [limited data available with nelfinavir (1.25 g BID) + ritonavir (100–200 mg BID)]		↑ AUC by 121% Adapt dosages and use 400 mg BID saquinavir + 400 mg BID ritonavir + or 600 mg to 1 g BID saquinavir + 100–200 mg BID ritonavir or 1.2–1.6 g QD saquinavir + 100 mg QD ritonavir	No effect	↑ AUC by 21% No need for dose adjustment	No effect
Saquinavir	↓ AUC by 36% Use 600 mg TID amprenavir + 800 mg TID saquinavir or 600 mg BID amprenavir +100 mg BID ritonavir + 800 mg BID saquinavir	No effect (in-vitro data suggest antagonism)	No effect ↑ AUC, C_{min} [Data available with 800 mg BID saquinavir + 400/100 mg BID lopinavir/r]	↑ AUC by 18% Adapt dosages and use 750 mg TID nelfinavir + 800 mg TID saquinavir or 1200 mg BID saquinavir + 1250 mg BID nelfinavir	No effect Regimens include 400 mg BID ritonavir + 400 mg BID saquinavir or 100–200 mg BID ritonavir + 600 mg to 1 g BID saquinavir or 100 mg QD ritonavir + 1.2–1.6 g QD saquinavir		No effect	↓ AUC by 12% Do not use saquinavir HCG as single PI in combination with efavirenz	No effect Do not use saquinavir HCG as single PI in combination with nevirapine
Delavirdine	No data available	↑ AUC by 40–100% Adapt dosages and use 600 mg TID indinavir + 400 mg TID delavirdine	No data	↑ AUC by 100% ↓ AUC of active metabolite Dosages not established	↑ AUC by 70% Dosages not established	↑ AUC by 500% Adapt dosages and use 800 mg TID saquinavir + 600 mg TID delavirdine		No data available	No data available
Efavirenz	↓ AUC by 39% Do not use as single PI in combination with efavirenz. Addition of ritonavir (100 mg BID) to amprenavir (900 mg q12 h po) corrects the impact of efavirenz	↓ AUC by 35% Use 1 g TID indinavir or add ritonavir	↓ AUC by 25% Use 533 mg + 133 mg lopinavir/r	↑ AUC by 20% ↓ AUC of metabolite. No need for dose adjustment	↑ AUC by 18% No need for dose adjustment	↓ AUC by 62% Dosages not established Do not use as single PI in combination with efavirenz. No need for dose adjustment if ritonavir is added	No data available		No data available
Nevirapine	No data available See comments on efavirenz	↓ AUC by 30% Adapt dosages of indinavir (1 g TID) or add ritonavir	↓ AUC by 25% Use 533 + 133 mg lopinavir/r	↑ AUC by 8% No need for dose adjustment	No effect Do not use as single PI in combination with nevirapine	↓ AUC by 27% Dosages not established	No data available	No data available	

AUC, Area under the curve; BID, twice a day; HGC, hard gel capsule; PI, protease inhibitor; po, by mouth; SGC, soft gel capsule; TID, three times a day; QD, per day.

Table 12. Use of anti-HIV drugs in renal insufficiency, dialysis and liver failure.

	Dosing in renal insufficiency					
	Creatinine clearance					
	50–80 ml/min	10–50 ml/min	< 10 ml/min	Dosing in case of haemodialysis	Dosing in case of peritoneal dialysis	Dosing in case of liver failure
Abacavir	UD	UD	UD	UD	UD	Avoid or reduce dose in severe cases. No formal recommendation available
Didanosine	250 mg QD	150–250 mg QD	> 60 kg 100 mg QD	> 60 kg 200 mg QD < 60 kg/50 mg QD	Same as haemodialysis < 60 kg 125 mg QD after dialysis	Avoid or reduce dose in severe cases. No formal recommendation available
Lamivudine	UD	150 mg QD	25–50 mg QD	25–50 mg QD after dialysis	Same as haemodialysis	UD
Stavudine	UD	20 mg QD or BID	20 mg QD	> 60 kg 20 mg QD < 60 kg 15 mg QD after dialysis	Same as haemodialysis	UD
Zalcitabine	UD	0.75 mg QD or BID	Avoid or 0.75 mg QD	0.75 mg after dialysis	Same as haemodialysis	Avoid or reduce dose in severe cases. No formal recommendation available
Zidovudine	UD	100–200 mg q12 h	100 mg q12 h	UD	UD	Reduce dose by 50% or double the interval between doses
Nevirapine	UD	200 mg QD if creatinine clearance < 25 ml/min	200 mg QD	200 mg QD after dialysis	Same as haemodialysis	Avoid or reduce dose in severe cases. No formal recommendation available
Efavirenz	UD	UD	UD	UD	UD	No data
Nelfinavir	UD	UD	UD	Contradictory data. TDM should be performed	UD	Reduce dose in severe cases. No formal recommendation available. TDM may be useful
Indinavir	Avoid	Avoid	Avoid	UD	UD	Reduce dose in severe cases. No formal recommendation available. TDM may be useful
Saquinavir	UD	UD	UD	UD	UD	Reduce dose in severe cases. No formal recommendation available. TDM may be useful
Ritonavir	UD	UD	UD	UD	UD	Avoid or use as pharmacological booster only
Amprenavir	UD	UD	UD	UD	UD	Reduced dose in severe cases to 300–450 mg BID
Lopinavir	UD	UD	UD	UD	UD	Reduce dose in severe cases. No formal recommendation available. TDM may be useful

BID, Twice a day; TDM, therapeutic drug monitoring; QD, per day; UD, unchanged dosage (no need for dose adjustment).

Table 13. Vaccination of the HIV-infected patient.

Recommendations have been divided into three categories:

	Vaccine	Eligibility	Frequency	Comment
1.	Vaccines that should be administered to all HIV patients			
	Tetanus	All patients	Every 10 years	
2.	Vaccines that are recommended in selected groups of HIV patients			
	Pneumococcus	Same categories as with HIV-negative population including splenectomized patients and patients with past pneumococcal infection	Every 5 years	
	Influenza	Same categories of patients as in HIV-negative population	Yearly	Vaccination before influenza epidemic
	Hepatitis A	Patients at risk (travel) HCV co-infected patients Homosexual men	Every 10 years	Check for antibodies before vaccination (if IgG positive, vaccine is not necessary)
	Hepatitis B	Patients with multiple sexual partners HIV-infected healthcare workers HCV-co-infected patients	Follow level of antibodies	Check for anti-HBs antibodies before vaccination (if positive, vaccine is not necessary). Response to vaccine is lower than in HIV-negative patients. Re-vaccination may be considered in case of failure
3.	Vaccines whose indications are limited to selected cases/circumstances (travel) This category includes all other vaccines with the exception of: Oral live vaccines, which are contraindicated BCG, which is contraindicated Yellow fever vaccine, which should be considered only for HIV patients with CD4 cell counts above 300 cells who are exposed to substantial risk			

BCG, Bacillus Calmette-Guérin; HBs, hepatitis B serum; HCV, hepatitis C virus.

Table 14. Criteria for initiating and stopping primary prophylaxis against opportunistic infections.

Opportunistic infections	Criteria for initiation of primary prophylaxis	Drug regimen	Criteria for interruption of primary prophylaxis
PCP	CD4 cell count < 200 or symptomatic HIV disease	Cotrimoxazole 1 DS tablet thrice weekly or 1 regular tablet QD Dapsone 100 mg daily Pentamidine aerosol 300 mg once monthly	CD4 cell count > 200 for > 3–6 months on anti-HIV treatment
Toxoplasmosis	CD4 cell count < 100 and positive IgG for toxoplasmosis	Cotrimoxazole 1 DS tablet daily Dapsone 100 mg QD + pyrimethamine 25 mg twice weekly Atovaquone 3 × 750 mg QD + pyrimethamine 25 mg twice weekly	CD4 cell count > 200 for > 3–6 months on anti-HIV treatment
Tuberculosis	Positive PPD – no active TB or contact with a patient with active pulmonary TB and no history of BCG	Rifampicin/rifabutin + pyrazinamide for 2 months[a] or isoniazide + pyridoxine for 6–9 months	NA
Atypical mycobacteria	CD4 cell count < 50	Azythromycin 1–1.25 g weekly Clarithromycin 500 mg BID (rifabutin 300 mg daily)	CD4 cell count > 100 for > 6 months on anti-HIV treatment

BID, twice a day; DS, double strength; PCP, *Pneumocystis carinii* pneumonia; PPD, purified protein derivative; QD, per day.
[a]If possible, primary prophylaxis with rifampicine or rifabutine should be given before the initiation of protease inhibitors.

Table 15. Recommendations for interruption of long-term suppressive therapy of opportunistic infections.

Pneumocystis carinii pneumonia	Same as primary prophylaxis, i.e. CD4 cell count > 200 for ≥ 6 months on anti-HIV treatment
Toxoplasmosis	Provisional recommendations: CD4 cell count > 200 for ≥ 6 months on anti-HIV treatment
Mycobacterium avium complex	Provisional recommendations: CD4 cell count > 100 for > 6 months on anti-HIV treatment
Cytomegalovirus	CD4 cell count > 100 for ≥ 6 months on anti-HIV treatment. No active lesion