Italian Consensus Statement on Management of HIV-Infected Individuals with Advanced Disease Naïve to Antiretroviral Therapy

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Abstract

Background: Individuals with advanced HIV infection naïve to antiretroviral therapy represent a special population of patients frequently encountered in clinical practice. They are at high risk of disease progression and death, and their viro-immunologic response following the initiation of highly active antiretroviral therapy may be more incomplete or slower than that of other patients. Infection management in such patients can also be complicated by underlying conditions, comorbidities, and the need for concomitant medications.
Aim: To provide practical guidelines to those clinicians providing care to HIV-infected patients in terms of diagnostic assessment, monitoring, and treatment.
Conclusions: The principals of antiretroviral treatment in asymptomatic naïve patients with advanced HIV infection are the same as those applicable to the general population with asymptomatic HIV infection. Naïve patients with advanced HIV infection and a history of AIDS-defining illnesses urgently need antiretroviral treatment, with the choice of antiretroviral regimen and timetable based on such factors as concomitant treatment and prophylaxis, drug interactions, and potential concomitant drug toxicity. Finally, an adequate counseling program – both before and after HIV-testing – that includes aspects other than treatment adherence monitoring is a crucial step in disease management.

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Introduction

Despite a general awareness of the fact that early HIV screening is advisable, a considerable proportion of individuals in developed countries receive a new diagnosis of HIV infection at an advanced disease stage, when AIDS-related diseases or symptoms are already present [1–3]. High plasma HIV-RNA levels and low CD4+ cell counts, typically found in advanced stages of HIV disease, are both associated with an increased risk of mortality, even after the initiation of combination antiretroviral therapy (cART) [4, 5]. In addition, even after cART has been initiated, early viro-immunologic response may be incomplete or slower in patients with more advanced HIV infection at baseline [6, 7], and it is also strongly associated with subsequent disease progression [8].

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Proper clinical management of antiretroviral therapy in patients with advanced HIV infection by appropriate, timely, and efficacious prescriptions is therefore crucial to an improved prognosis [9, 10]. When treating special patient populations, clinicians also need to take into account co-morbidities, concomitant treatments, and medical problems specific to that particular patient population.

This document is a consensus statement resulting from a consensus conference of experts and clinicians active in the field of HIV infection and treatment. This aim of this conference was to outline our current understanding of advanced HIV infection clinical management and develop recommendations for clinicians.

Methods

The recommendations presented here are the result of a consensus workshop which took place in Rome, Italy, on December 2006. The 2-day workshop started with two introductory plenary lectures held by international experts on the issues covered by the consensus conference. Thereafter, a draft of the statements and a grading system classifying the strength of the recommendations and the quality of evidence were presented by 27 Italian experts in the field, who had previously searched, reviewed, and synthesized the literature specifically pertaining to the topics. The strength of the recommendations was graded as strong (A), moderate (B), and optional (C); the quality of the evidence was classified as I, indicating properly randomized controlled trials with clinical and/or laboratory results; II, indicating other published studies with clinical and/or laboratory results; III, indicating expert opinion. Four main topics were covered:

1. diagnostic assessments and monitoring of naïve patients with advanced HIV infection;
2. principles of antiretroviral treatment in naïve patients with asymptomatic advanced HIV infection;
3. principles of antiretroviral treatment and monitoring of naïve patients with advanced HIV infection and opportunistic disorders, and at high risk of death (AIDS presenter);
4. principles of antiretroviral treatment and monitoring of naïve patients with advanced HIV infection and special conditions or co-morbidities.

Four working groups, each comprising 10–15 Italian HIV-treating physicians, reviewed and modified these preliminary statements according to the current literature and their personal clinical experiences. The revised statements were presented in a plenary session and voted by all consensus participants: they were then either accepted or re-discussed and re-voted according to the degree of agreement reached.

Diagnostic Assessments and Monitoring in Naïve Patients with Advanced HIV Infection

Introduction

The early and correct identification of patients with an advanced naïve HIV infection is addressed here. A correct definition of the laboratory tests recommended for these patients at baseline and follow-up visits is essential to disease staging, monitoring of eventual therapy-related toxicities, and risk assessment of opportunistic infections. Initial clinical management is crucial for these patients, since it will represent the basis for a trusting relationship with the health care staff.

Definition of Advanced Naïve HIV-Infection

Patients with advanced HIV infection naïve to antiretrovirals are individuals presenting with one or both of the following two conditions at HIV diagnosis: (1) stage C according to 1993 Revised Classification System for HIV infection [11] (A-II); (b) CD4+ T cell count $\leq$ 200/mm^3 on two consecutive determinations (B-II). However, this definition should be viewed in a larger context. Older age ($\geq$ 60 years) or coexisting illnesses at diagnosis of HIV infection could also be included in the definition of advanced naïve patients, if the negative effects of these conditions on quality of life, disease progression, immunologic response to treatment, and cART-related toxicities are taken into account [12] (B-II).

As a result of the clinical complexity of naïve patients with advanced HIV infection [2], clinicians should make every possible effort to facilitate early detection of HIV infection (A-II).

Patient Support

Special care and psychological support of patients with advanced naïve HIV infection during the initial clinical assessment are necessary. Patients may have to receive many different pieces of information at the same time: positive test for HIV antibody, urgency of promptly starting cART and, perhaps, the need for treatment of opportunistic infections. Therefore, adequate counseling both before and after HIV-testing is crucial (A-II). Depending on the patients' desire to conceal or disclose their HIV status to trusted family members, partners, and friends, the latter may become involved in the patient support counseling.

HIV-Surrogate Markers and Resistance Testing

On a routine basis, blood examinations, such as complete blood cell count and chemistry profile (A-III), lymphocyte cell count (absolute and percentage value of both CD4+ and CD8+ T cells) (A-I) [13], and plasma HIV-RNA levels (viral load) [4] (A-I), need to be assessed at the first and all follow-up visits (Table 1). Two distinct baseline measurements of CD4+ T cell count should be obtained – at least 1 week apart if possible – because of a possible variation in results (C-III). Although the absolute CD4+ T cell count is the most commonly used parameter in clinical practice, the percentage of CD4+ T cells is somewhat less variable than the absolute count, and the latter may provide additional information when immune function is assessed (C-III). Other lymphocytic subpopulations, such as CD8/CD38+ T cells, are measurable and may be considered a marker of both disease progression and response to treatment regardless of other viro-immunologic parameters (C-III). During opportunistic

Table 1
Laboratory examinations that should be performed in patients with advanced naïve HIV infection at baseline and/or on a routine basis.

Hematology	Complete blood count
	Lymphocyte subpopulations
Serum chemistry	Fasting blood glucose
	Electrolytes (Na/K/Ca/P), creatinine
	Transaminase levels, bilirubin, γGT, LDH, CK
	Albumin
	Alkaline phosphatase, amylase
	Fasting triglycerides, cholesterol (total, HDL, LDL)
	Urinalysis
	C-reactive protein
Virological tests	Plasma HIV RNA
	Viral subtype
	Genotypic resistance test
Serological tests	RPR or VDRL (confirmatory test FTA-ABS)
	CMV Ag and IgG/M, EBV IgG/M
	Toxoplasma gondii IgG
	Cryptococcal antigen
	HBsAg, HBsAb, HBcAb, HCV IgG, HAV IgG
Cytology	Papanicolaou smear test of the cervix
Microbiology	Search for pathogens responsible of other sexually transmitted diseases (such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HPV-PCR and genotyping)

γGT: γ-Glutamyl transferase; LDH: lactate dehydrogenase; CK: creatine kinase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RPR: rapid plasma reagin; VDRL: venereal disease research laboratory; FTA-ABS: fluorescent treponemal antibody absorption; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HBsAg: surface antigen of the Hepatitis B virus; HbsAb: hepatitis B surface antibody; HBcAb: hepatitis B core antibody; HCV: hepatitis C virus; HAV: hepatitis A virus; HPV: human papillomavirus

infections (e.g., tuberculosis, cytomegalovirus [CMV]), virologic and immunologic parameters may be less helpful than usual in evaluating the risk of disease progression in single patients since they may be wrongly reduced or elevated [14]. Viro-immunologic parameters should be repeated in these cases (A-II).

Genotypic resistance testing should be carried out [15] (A-II) and viral subtype determination performed (B-III) in all naïve patients with advanced HIV infection. Regardless of the imminent necessity to start cART, the genotypic assay is helpful in guiding the selection of treatment strategies [15]. Nevertheless, there is no reason for delaying the initiation of cART while awaiting the results of the test in patients at a high risk of disease progression: in these cases, treatment should be started promptly using drugs with a high genetic barrier and eventually modified thereafter on the basis of the result of the genotypic test (A-III). In terms of research applied to genotypic resistance testing, it could be interesting to consider innovative methodologies to identify specific mutations as minority quasi-species (e.g., single genome assay or allele-specific PCR for detecting the K103N mutation) [16] (B-III).

In the future, the determination of HIV-1 cell receptor (CCR5, CXCR4, or mixed/dual CXCR4/CCR5) tropism may be appropriate to design innovative strategies by using entry inhibitors in early phases of treatment. Nevertheless, this test currently does not seem to provide additional information since no significant differences in mean CD4+ T cell count increases in patients with either CXCR4- or CCR5-tropic HIV-1 have been observed [17]. Although an investigation of other virologic markers, such as proviral DNA, appears to be interesting in terms of gaining a better understanding of the pathogenetic mechanism of HIV and being able to better evaluate the response to cART, it should not yet be considered a part of standard monitoring procedures (B-III).

Other Laboratory Assessments

The hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele and, therefore, pharmacogenetic testing should be used to prevent the specific toxic effect of the drug [10, 18] (A-I).

Adequate screening of the hepatitis viruses (HV) determining chronic disease (HCV, HBV, HDV) needs to be carried out (Table 1) (A-III). False negative results of some diagnostic tests may occur in patients with advanced HIV infection, particularly in patients with strong immunosuppression; such results generally concern antibodies against hepatitis B surface antigen, HCV, and *Toxoplasma gondii* [19]. Based on this fact, despite HCV-antibody negativity, determination of plasma HCV-RNA should be performed in all patients with advanced HIV infection having unexplained high levels of serum transaminases (B-II).

The tuberculin skin test is yet another test whose result may be affected by the loss of cellular immune function. A chest radiograph should be performed in the presence of respiratory symptoms – even if no skin induration ≥ 5 mm is evident – and three sputum samples should be collected to investigate the presence of acid-fast bacilli as well as to culture for mycobacteria (A-II). A low sensitivity to the skin tuberculin test will be overcome, in part, by the introduction of two blood tests (T-SPOT.TB and Quantiferon-TB Gold), which are based on the detection of IFN-gamma released by T lymphocytes in response to *Mycobacterium tuberculosis*-specific antigens. Clinical studies examining these new tests in the HIV patient population are in progress [20].

Additional Tests

A baseline chest radiograph should be reserved for all patients with advanced HIV infection and naïve to antiretroviral therapy, particularly if they have a prior history of pulmonary disease or active pulmonary problems (A-III). An electrocardiogram should be considered as a

component of the initial assessment if clinically indicated (B-III). Finally, routine screening for health-maintenance issues, particularly those defined by age-appropriate standard-of-care, should be included (e.g., prostate-specific antigen determination, mammography, test for occult blood in stool) (B-III).

Opportunistic Diseases and Concomitant Conditions

Patients with advanced naïve HIV infection carry a substantially increased risk of the following concomitant conditions that may complicate clinical management by worsening disease prognosis and response to treatment [3, 12]:

- presence of opportunistic infections [1];
- co-morbidities, such as chronic liver diseases, malignancies, etc. [12];
- older age [13, 21];
- immune reconstitution inflammatory syndrome (IRIS) [22, 23];
- need for concomitant medications (e.g., concomitant prevention/treatment of opportunistic infections);
- psychological distress.

In particular, the presence of concomitant opportunistic diseases should be evaluated by assessing the following (A-II):

– medical history and complete physical examination;
– routine blood tests (hematology and chemistry);
– instrumental examinations based on specific signs and symptoms (chest X-ray, brain CT scan, endoscopy, etc.);
– biopsy samples (e.g., lymph node, liver);
– serological and virological tests as well as cultures (where appropriate) to detect specific opportunistic pathogens (CMV, *Pneumocystis jiroveci*, mycobacteria, *T. gondii*, *Cryptococcus neoformans*, etc.).

A funduscopic examination in patients having a CD4+ T cell count < 100/mmc may be appropriate (B-II).

Advanced naïve patients should receive an intensive follow-up program, especially during the initial treatment phase (B-II) because the risk of opportunistic infections during the first 12 months is reduced, but not eliminated by cART [24–27].

Monitoring Antiretroviral Therapy Efficacy and cART-Related Toxicities

One month after initiating cART, treatment efficacy should be evaluated by determining lymphocyte subpopulations (absolute and percentage value of CD4+ T cells) (A-I), and plasma HIV-RNA levels (A-I). Once an antiretroviral treatment has begun, patients should be carefully monitored by means of blood tests in order to guard against the risk of different cART-related toxicities (A-II). It may also be advisable to store a blood sample for future diagnostic procedures (C-III).

Advanced naïve HIV patients are generally older than early HIV presenters: both advanced age and HIV infection are associated with an increase in cardiovascular risks. Moreover, prolonged exposure to cART, in particular to regimens containing protease inhibitors, induces metabolic alterations that represent an additional risk factor for cardiovascular events. Hence, the assessment, monitoring, and correction of likely cardiovascular risk factors should be implemented [28] (A-II).

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome is a clinical condition observed in some AIDS patients, in which the immune system begins to recover and to respond to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically worsens the symptoms of infection. Since the onset of IRIS highly complicates the management of naïve patients with advanced HIV infection, strategies to prevent IRIS by identifying patients with possible ongoing opportunistic infections during the initial phase of cART treatment should be developed [22, 23] (B-II). As IRIS has been associated with the reactivation of the organism's response to almost all opportunistic infections, a well-established diagnostic procedure should be elaborated (B-II).

Principles of Antiretroviral Treatment in Naïve Patients with Asymptomatic Advanced HIV Infection

Introduction

The principal objectives of cART are to reduce HIV-related morbidity and mortality, to restore immune system, to suppress viral replication as long as possible, and to improve quality of life. The decision of when to initiate antiretroviral treatment in asymptomatic patients should be based on their prognosis, as determined by the CD4+ T cell count and plasma HIV-RNA values at the baseline visit, possible drug-related toxicity, and adherence issues [4, 8, 21].

In general, the principles of antiretroviral treatment in this sub-group of patients are the same as those applicable to the general population with asymptomatic HIV infection. Therefore, only special concepts of advanced naïve patients with respect to the general HIV population will be highlighted in the present guidelines.

General Recommendations

Based on the results of randomized trials and observational cohorts which focused on the high risk of disease progression, the initiation of antiretroviral treatment is strongly recommended in all patients with a CD4+ T cell count < 200/mm^3 [4, 8, 21, 29] (A-I). In these patients antiretroviral treatment should be started as soon as possible (A-II) and be coupled with both a previous comprehensive clinical as well as pharmacological evaluation and an accurate counseling program on adherence to treatment [30] (A-III).

Taking into consideration both the risk of clinical progression and the relevance of achieving a prompt suppression of viral replication, the panel strongly recommends that initial antiretroviral regimen be selected on the basis of HIV genotypic test results [15] (A-II).

Choice of Antiretroviral Treatment

Randomized prospective trials comparing treatment strategies in exclusively advanced patients are few and therefore desirable. Preliminary data on the short-medium efficacy and safety of first-line antiretroviral regimens are derived from observational studies as well as randomized trials, including asymptomatic patients without CD4+ T cells count restriction.

A virologic, but not immunologic, superiority has been documented for non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens when these are compared to mostly unboosted protease inhibitor (PI)-based cART in randomized trials and retrospective cohort studies [31, 32]. One randomized comparative trial performed in a naïve patient population containing a relevant proportion (about 40%) of patients with advanced HIV infection showed that lopinavir/ritonavir (LPV/r)-containing regimens were associated with a better CD4+ T cell count increase as well as with a reduced risk of resistance mutation development at treatment failure, while efavirenz-containing regimens showed more likely virologic success [33]. Data from prospective observational studies did not show substantial differences between NNRTI-based and PI/r-based regimens with reference to virologic efficacy and/or clinical outcome [34, 35]. However, in prospective non-randomized studies and in non-comparative randomized trials, LPV/r-containing regimens had a persistent immunologic efficacy, a better immunologic recovery, and no primary resistance-associated mutation development in patients with suppressed viral load [36, 37].

Based on the finding that regimens including other boosted-PIs showed non-inferior results, as evidenced in comparative trials at short-term follow-up, these can be considered for regimen building [38–40] (B-I).

While numerous data are available on the potency of regimens containing efavirenz [32, 34], empirical evidence for using regimens containing nevirapine in this population is limited (B-I). Even if specific studies on a direct comparison are lacking, regimens containing non-thymidine nucleoside analogues seem to be more desirable since they are associated with a better CD4+ cells recovery (B-I).

Antiretroviral regimens containing four drugs, based either on a combination of drugs belonging to all three antiretroviral drug classes (NRTI–NNRTI–PI) or on the association of three nucleoside analogues and an NNRTI drug, did not show an advantage relative to the standard of care [41]. Based on available data, antiretroviral treatment with PI/r monotherapy is not advisable in this patient population [42] (A-I). To date, data are inadequate for supporting the introduction of fusion inhibitors [43] or immunomodulators (e.g. IL-2) in the first antiretroviral regimens (A-II).

Concomitant Treatments

The risk of opportunistic infections in patients with advanced naïve HIV infection persists throughout the entire phase of immunosuppression and even lasts several months following the start of cART [25, 26]. For this reason, patients with low CD4+ T cell counts should receive primary prophylaxis for opportunistic infections (A-II). The drug regimens used for specific opportunistic infections and the CD4+ T cell count below which prophylaxis is indicated are summarized in table 2.

Table 2
Type of regimen for primary prophylaxis of opportunistic infections and timing.

	PCP	Toxoplasmic encephalitis	MAC infection
CD4+ T cell count below which prophylaxis should be started	< 200 cells/mm^3	< 100 cells/mm^3	< 50 cells/mm^3
Preferred regimen	Trimethoprim-sulfamethoxazole double-strength (DS) tablet 1 tablet by mouth daily (A-I) 1 tablet by mouth three times weekly (B-II)	Trimethoprim-sulfamethoxazole DS 1 tablet by mouth daily (A-I)	Clarithromycin 500 mg by mouth twice daily (A-I) Azithromycin 1,200 mg by mouth weekly (A-I)
Alternative regimen	Aerosolized pentamidine 300 mg monthly via aerosol Dapsone 100 mg by mouth daily Atovaquone 1,500 mg by mouth daily	Dapsone 50 mg by mouth daily plus pyrimethamine 50 mg by mouth weekly plus leucovorin 25 mg by mouth weekly Atovaquone 1,500 mg by mouth daily	Rifabutin 300 mg by mouth daily
CD4+ T cell count above which prophylaxis should be discontinued	> 200 cells/mm^3 for ≥ 3 months		> 100 cells/mm^3 for ≥ 3 months

MAC: *Mycobacterium avium* complex; PCP: *P. jiroveci* pneumonia

Since there are no documented interactions between drugs used for primary prophylaxis of either *P. jiroveci* pneumonia (PCP) or toxoplasmic encephalitis (trimethoprim/sulphamethoxazole, dapsone, pentamidine) and currently available antiretrovirals, these can be used without concern (A-III).

PIs and NNRTIs are metabolized in the liver by the cytochrome P450 system, particularly by CYP3A4, so that drug–drug interaction should be checked in the presence of concomitant medications (A-III). Since rifamycins in general (rifabutin to a lesser extent) are CYP3A4 inducers, they should be used with caution when administered in association with other drugs inducing or inhibiting the same cytochrome enzyme (A-III). In fact, they can significantly reduce plasma concentrations of most PIs and NNRTIs.

Since interactions between macrolides and antiretroviral drugs do not seem to be clinically significant, dosage modifications are not necessary (A-III).

Adherence

Adherence to antiretroviral treatment is crucial to obtain and maintain virological suppression, to avoid the occurrence of HIV resistance, and to prolong survival [44–46]. Patient-reported non-adherence is a valid tool for assessing suboptimal antiretroviral intake and correlates with major treatment outcomes [44, 45, 47]. Clinicians should be able to reassure the patient while emphasizing the importance of adherence and the risks associated with an incorrect intake of the prescribed treatments (A-II).

Interaction between patients and their health care providers should be close and constant in order that the latter be able to carefully evaluate treatment adherence and to promptly monitor the onset of side effects possibly related to cART or, eventually, to other concomitant treatments. Adequate counseling to reinforce adherence (A-I), provide psychological support, and treat potential psychiatric disorders and drug dependence (A-II) should be considered both before and during the administration of cART.

Principles of Antiretroviral Treatment and Monitoring in Naïve Patients with Advanced HIV Infection, Opportunistic Disorders and High Risk of Death (Aids Presenter)

Introduction

Advanced naïve HIV-positive patients presenting with AIDS-defining illnesses or severe symptoms are at an extremely high risk of developing other opportunistic conditions or dying [3, 23] and, therefore, urgently need antiretroviral treatment. This topic focuses on issues concerning the timing of cART initiation and the type of treatment regimen to be used.

Timing of cART During Opportunistic Infections and Malignancies

Antiretroviral treatment must be started in all HIV-infected patients with a diagnosis of AIDS and should be initiated, in the absence of contraindications, during the early stages of acute opportunistic infections [10, 48] (A-I). cART per se should be considered a therapeutic strategy for all opportunistic disorders for which an etiologic treatment against a specific agent is lacking: cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), and localized cutaneous and mucosal Kaposi's sarcoma [3] (A-III). In these cases, cART should be started immediately, without awaiting the results of an HIV genotypic resistance test, preferably using high-genetic barrier drugs (A-III).

In the case of opportunistic infection for which an etiologic treatment is available (*M. avium*-complex infection [MAC], PCP, cryptococcal meningitis, CMV infection, toxoplasmic encephalitis, esophageal candidiasis), cART may be deferred until stabilization of the clinical condition of the patient [3]. It is advisable, however, not to postpone the initiation of cART beyond 14 days from disease diagnosis, considering that immediate cART is associated with reduced death and AIDS progression and a shorter time to immune recovery [48–50] (C-I).

The following factors should be considered in the decision-making process on when to start cART:

- degree of immunosuppression;
- toxicity related to concomitant treatments;
- risk of IRIS;
- type of pathogen.

cART has been shown to improve outcome in ventilator-supported patients hospitalized in the intensive care unit with severe PCP and to be an independent predictor of decreased mortality [51]. Thus, in patients with PCP, cART needs to be started before completion of the acute phase of anti-*P. jiroveci* treatment to avoid any possible complication of the clinical picture [52] (B-III). It is important that if there is either evidence of clinical worsening or a lack of response to etiologic treatment, cART should be started during the first 14 days (C-III).

Patients who receive the combination of cancer chemotherapy and cART may achieve better response rates than patients who receive antineoplastic therapy alone [53]. Some studies have reported that patients with Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL) who started cART at the same time as chemotherapy showed increased survival [54–56], reduced toxicity (especially bone marrow toxicity), and a decreased risk of developing opportunistic infections. Therefore, cART should be started before or at the same time as chemotherapy in patients diagnosed with HL, NHL, or Kaposis's sarcoma (A-I).

In patients with a diagnosis of non-AIDS-defining malignancies, antiretroviral treatment should be considered before or at the same time as chemotherapy treatment (C-III). While the benefit of cART in patients with

Table 3
Type of antitubercular therapy and timing of cART based on immuno-suppression at diagnosis of tuberculosis.

CD4+ T cell count	Antitubercular treatment[a]	cART	Recommendation[b]
< 100 cells/mm^3	Rifampicin-based	Add after the first 15 days	C-III
100, 200 cells/mm^3	Rifampicin-based	Add at completion of the initial phase of antitubercular therapy or at least after the first month	C-III
200–350 cells/mm^3	Rifampicin-based	Evaluate cART indication every 2 months	C-III
> 350 cells/mm^3	Rifampicin-based	Evaluate cART indication after 2 months and thereafter every 3 months	C-III

cART: Combination antiretroviral therapy; [a] If a protease-inhibitor-containing regimen is adopted, rifampicin should be replaced by rifabutin; [b] The strength of the recommendations was graded: C, optional; the quality of the evidence was classified: III, expert opinion

HL is supported by clinical evidence [57], there is no evidence of such an advantage in other malignancies. However, the unreliability of close immunologic monitoring, the clinical advantages observed in patients with HL and NHL, and the strong scientific rationale regarding anti-tumoral immunity support the starting of cART in this group of patients as well.

Choice of Antiretroviral Drugs

In terms of treatment efficacy, there is at yet no clear evidence of which is the best initial regimen (e.g. PI/r- or NNRTI-based cART) to be used to treat patients with ongoing HIV-related malignancies and opportunistic infections (C-III). Combinations of cART and treatments against opportunistic infections should be carefully selected in order not to overlap bone marrow, renal, or hepatic toxicities (A-II). In particular, NNRTIs should be avoided when therapy-induced hepatic toxicity is expected, zidovudine should not be used in case of possible mielotoxicity, tenofovir should not be considered in the presence of renal impairment, and didanosine/stavudine/zidovudine should not be included in the case of possible peripheral neurological toxicity (B-III).

It is likely that PIs should be preferred as part of an initial cART in the presence of a number of opportunistic infections, such as Candida spp, *P. jiroveci*, and *Cryptococcus* spp, since these drugs have shown a direct *in vitro* activity on these pathogens (C-III).

Optimal initial antiretroviral treatment options have not yet been established in patients with Kaposi's sarcoma. Both PI/r- and NNRTI-containing regimens have been shown to have comparable antiviral activity in reducing Kaposi's sarcoma-associated herpesvirus (KSHV) viremia. Nevertheless, based on *in vitro* experimental data, clinical evidence, and single case reports, several experts suggest the initial use of PI/r-containing regimens (C-III).

The start of antiretroviral therapy during tuberculosis treatment in naïve patients with advanced HIV infection may be safe and effective [58]. Tuberculosis treatment should preferably include rifampicin (A-II) and, due to drug–drug interactions, cART should be based on efavirenz together with two NRTI drugs (A-II). When a PI-containing regimen is adopted, rifampicin should be replaced by rifabutin (A-I). When rifabutin is prescribed in association with PI/r or NNRTI, the dosage of the former drug should be modified (A-III). The regimens of tuberculosis therapy and timing of cART are summarized in table 3 based on the degree of immune-suppression at the diagnosis of tuberculosis.

Immune Reconstitution Inflammatory Syndrome

For all patients with tuberculosis, MAC, CMV retinitis, cryptococcal meningitis, and PML, the starting antiretroviral treatment should be accurately evaluated for the onset of IRIS [22, 23] (A-II). Studies have shown that the risk of IRIS is associated with baseline CD4 cell count as well as early initiation of cART and that severe, life-threatening manifestations are uncommon [48, 59, 60].

IRIS should be treated with anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids, to control symptoms, and antiretroviral treatment should be continued. It may be necessary to stop antiretroviral treatment if the clinical picture of IRIS is severe (C-III).

Prophylaxis Against Opportunistic Infections

In all patients with symptomatic advanced naïve HIV infection, primary prophylaxis against opportunistic infections other than those already diagnosed should be initiated as soon as possible (A-I). Drugs for primary prophylaxis can be prescribed at the same time as cART and other treatments for concomitant opportunistic infections (Table 2).

Secondary prophylaxis for opportunistic infections may be stopped once a stable immune recovery is reached by cART [61–66] (A-I). CD4+ T cell levels at which secondary prophylaxis can be withdrawn are shown in table 4.

Principles of Antiretroviral Treatment and Monitoring in Naïve Patients with Advanced HIV Infection and Special Conditions or Co-morbidities

Introduction

This section examines the issues pertinent to naïve patients with advanced HIV infection and special conditions or co-morbidities. Attention will focus on special populations, such as the elderly, who show a slower immune recovery,

Table 4
CD4+ T cell levels at which secondary prophylaxis may be withdrawn.

Opportunistic infection	CD4+ T cell count	Recommendation[a]
P. jiroveci pneumonia	> 200 cells/mm^3 ≥ 3 months	A-I
Cytomegalovirus infection	> 100 cells/mm^3 ≥ 6 months	A-II
Toxoplasmic encephalitis	> 200 cells/mm^3 ≥ 6 months	A-I
Cryptococcosis	> 100 cells/mm^3 ≥ 6 months	B–I
MAC infection	> 100 cells/mm^3 ≥ 6 months	B-II

[a] The strength of the recommendations was graded: A, strong; B, moderate; the quality of the evidence was classified: I, properly randomized controlled trials with clinical and/or laboratory results; II, other published studies with clinical and/or laboratory results

patients with neurocognitive disorders, who are frequently observed during severe immunosuppression [67, 68], and those co-infected with hepatitis viruses [69, 70].

Older Age

After starting cART, older patients show a reduced recovery of CD4+ T cells and an increased risk of progression to AIDS diagnosis, neurocognitive disorders, and death with respect to younger patients having comparable levels of CD4+ T cells and HIV viral loads [67, 68]. Therefore, in this patient population, the initiation of cART could be indicated at an earlier stage of disease. At the present time, cART must to be started at least when the CD4+ T cell level < 350/mmc (A-III) and may be considered in patients with CD4+ T cells between 350 and 500/mm^3 and plasma HIV-1 RNA levels > 30,000 cp/ml (A-III). Specific studies on this topic are warranted.

Neurocognitive Impairment

In advanced naïve HIV patients or in patients with neurocognitive impairment not taking antiretroviral treatment, HIV-1 viral load level in the CSF correlates with the severity of HIV-related dementia and, therefore, may predict subsequent onset of neurocognitive impairments [68, 69]. In all patients presenting with neurological signs and symptoms in whom a diagnostic lumbar puncture is indicated, the measurement of HIV-RNA in CSF should be added to all specific tests being performed to diagnose opportunistic infections (A-II).

All patients with advanced naïve HIV infection should undergo an accurate assessment of neuropsychological status using a validated cognitive test battery or a standardized scale for clinical measurements [71, 72]. This assessment should be repeated during follow-up in patients having a cognitive impairment and an abnormal baseline test result (A-II).

Patients with neurocognitive disorders and/or detectable HIV-1 RNA levels in the CSF before cART has been started should be prescribed antiretroviral regimens containing neuroactive drugs with a high penetration score in CSF [68, 73, 74] (A-II). In the case of worsening clinical conditions and/or of neurocognitive tests, these patients should undergo lumbar puncture both to assess HIV-1 RNA levels in the CSF and to perform genotypic resistance test on the CSF virus in order to choose the most appropriate therapeutic option (B-III).

Co-Infection with Hepatic Viruses

Liver disease is one of the major causes of morbidity and mortality in HIV-infected patients [75, 76], and its severity has been associated with more advanced immunosuppression. HCV/HIV co-infection may accelerate HIV-related neurocognitive decline [69]. Further, HCV viremia seems to play a role in impairing the CD4+ T cell count response to cART [70]. On the other hand, effective antiretroviral drugs use may contribute to worsening the liver disease [77]. Reversal or prevention of immunosuppression with cART will slow the progression of HCV disease.

The analyses to be performed in advanced naïve patients having abnormal liver function tests are summarized in table 5.

In advanced naïve patients with chronic HCV infection, therapy with peg-IFN plus ribavirin is indicated:

- in all subjects achieving an adequate immune reconstitution and a stabilization of antiretroviral therapy, in the absence of contraindications, and following specific guidelines (A-II);
- when hepatopathy related to HCV co-infection represents a major obstacle to proper antiretroviral treatment (C-III).

All HBsAg-positive patients having HBV DNA levels > 2,000 IU/ml and/or cirrhosis should receive an antiretroviral regimen containing tenofovir (TDF) (possibly associated with 3TC/FTC) as part of the NRTI backbone (A-III). In patients in which TDF use is contraindicated or must be stopped, adefovir or entecavir should be used (B-II). It should be noted that entecavir is a potent partial inhibitor of HIV replication *in vivo* and *in vitro* and that it may select for viruses bearing the M184V mutation [78]. Therefore in HBV/HIV-coinfected patients, entecavir should not be used for the treatment of HBV infection without concomitant suppressive treatment for HIV (B-II). In subjects diagnosed with HBV-related cirrhosis, especially if the continuous performance test (CPT) score is > 5, a pre-emptive treatment with entecavir or adefovir before starting cART may be considered in order to reduce the risk of decompensation during the phase of immune reconstitution (C-III). Before starting or modifying treatment against chronic HBV infection, it may be useful to have a HBV genotype test performed in order to identify mutational patterns that confer resistance to drugs against HBV (B-III).

Patients who are HBsAg- and/or HBcAb-positive and undergoing a period of severe immunodepression fol-

Table 5
Tests in advanced naïve patients having abnormal liver function tests.

	Recommendation	Comments
Markers of viral hepatitis		
HBsAg, HBsAb, HBcAb, HCV IgG, HAV IgG	A-II	
In HBsAg-positive patients:		
HBV-DNA, HBcAb IgM, HBeAg, HBeAb	A-II	
IgM and IgG anti-HDV	A-II	
HDV-RNA	B-II	
In HCV IgG-positive patients:		
Qualitative HCV-RNA	A-II	In all patients with CD4+ T cells < 200/mm^3 having negative test results for HBsAg and HCV IgG
HCV genotypic test	C-III	
Exams for opportunistic infections possibly involving the liver	A-II	Depending on CD4+ T cells
Evaluation for non-infectious liver disorders:	B-II	
Non-alcoholic steatohepatitis (NASH)		
Alcoholic steatohepatitis (ASH)		
Metabolic diseases		
Other		
Assessment of daily alcohol consumption	A-II	Measured in mean number of daily drinks
Hepatic ultrasound	A-II	
Identification of patients with liver cirrhosis		
Abdominal ultrasonography	B-II	
Indirect scores (FIB-4 and APRI scores)	B-II	
Fibroscan technology	B-III	
Liver biopsy	A-II	If results of previous examinations are not conclusive
Further investigations in patients with live cirrhosis		
Child-Turcotte Pugh (CTP) and model for end-stage liver disease (MELD) scores	A-II	
Gastroscopy to identify possible esophageal varices at risk of bleeding	A-II	
Six-monthly ultrasound screening for early detection of hepatocarcinoma	A-II	

HBeAg: Hepatitis e antigen

lowing chemotherapy for neoplasms should receive prophylaxis against hepatitis B reactivation (A-I) with cART containing TDF associated with or without 3TC/FTC, or alternatively entecavir (A-III).

No antiretroviral drug is contraindicated at the early stages of hepatopathy. In patients with advanced hepatopathy, antiretroviral regimens containing either TPV/RTV (A-II), nevirapine (A-II), d-drugs (A-II), or abacavir (C-III) should be avoided [79].

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